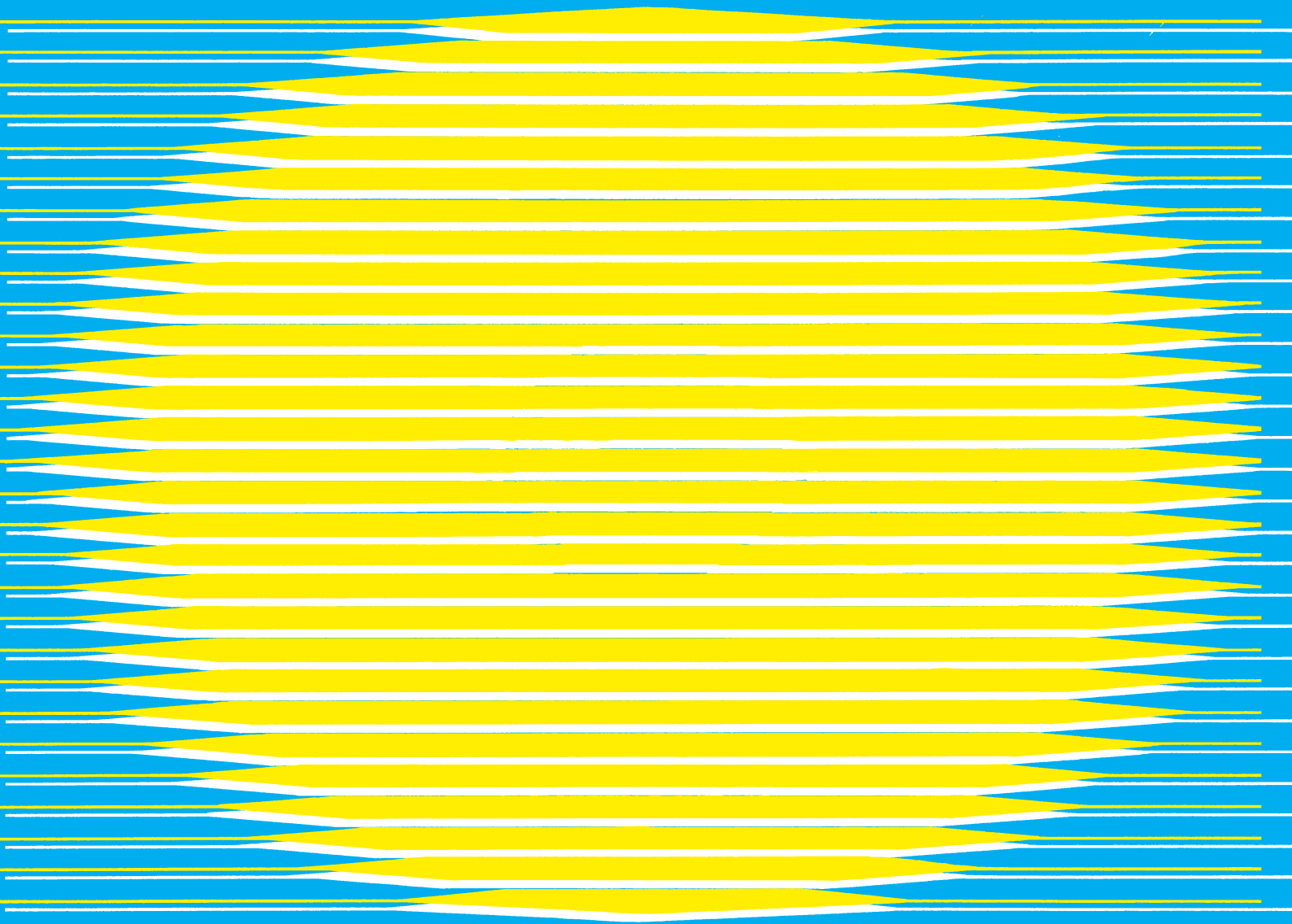
SOURCES AND EFFECTS OF IONIZING RADIATION

United Nations Scientific Committee on the Effects of Atomic Radiation
1977 report to the General Assembly, with annexes



UNITED NATIONS

UNITED NATIONS SCIENTIFIC COMMITTEE
ON THE EFFECTS OF ATOMIC RADIATION

1977 REPORT

1977年報告

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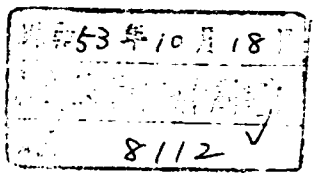

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NOTE

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In the text of each annex, Arabic numbers in parentheses are references listed at the end.

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I. INTRODUCTION

1. The preparation of the present report of the United Nations Scientific Committee on the Effects of Atomic Radiation[1] took place at the twenty-third to the twenty-sixth sessions of the Committee. Professor L. R. Caldas (Brazil), Professor F. H. Sobels (Belgium) and Dr. C. B. Guzmán Acevedo (Peru) served as Chairman, Vice-Chairman and Rapporteur, respectively, at the twenty-third session. Professor F. H. Sobels (Belgium), Dr. M. Klímek (Czechoslovakia) and Professor Z. Jaworowski (Poland) served as Chairman, Vice-Chairman and Rapporteur, respectively, at the twenty-fourth and twenty-fifth sessions; and Dr. M. Klímek (Czechoslovakia), Professor F. E. Stieve (Federal Republic of Germany) and Dr. K. Sundaram (India) served in the same capacity, respectively, at the twenty-sixth session.

2. As in the case of previous substantive reports,[2] most of the work of the Committee was done in meetings of groups of specialist scientists who considered working papers prepared by the Secretariat on the basis of the Committee's request. The names of those specialists who attended one or more of the sessions of the Committee during the preparation of the report as members of national delegations are listed in appendix I below.

3. The Committee was assisted by a small scientific staff and by consultants appointed by the Secretary-General. Although the Committee itself assumes full responsibility for the report, it wishes to acknowledge the assistance given by those scientists who were responsible for the preliminary review and analysis of the technical information received by the Committee or published in the scientific literature and whose names are listed in appendix II.

4. The technical reports received between 18 April 1972 and 22 April 1977 by the Committee from States Members of the United Nations and members of the specialized agencies and of the International Atomic Energy Agency (IAEA), as well as from these agencies themselves, are listed in appendix III. Reports received before 18 April 1972 were listed in earlier reports of the Committee to the General Assembly. The information received officially by the Committee was supplemented by information available in the scientific literature or obtained from unpublished communications of individual scientists. The Committee wishes to acknowledge with appreciation the information on exposures from various radioactive sources received in response to the Committee's request.

5. Representatives of IAEA, the Food and Agriculture Organization of the United Nations (FAO), the World Health Organization (WHO) and of the United Nations Environment Programme (UNEP), as well as of the International Commission on Radiological Protection (ICRP) and the International Commission on Radiation Units and Measurements (ICRU), attended the twenty-third to the twenty-sixth sessions of the Committee.

6. The Committee has formulated plans to continue to keep under review and to assess the levels of radiation to which the world population is or may become exposed, and to improve the assessments of risk entailed by exposure to radiation. Such activities can contribute significantly to UNEP and the Committee has established an active co-operation with the Programme in the preparation of criteria documents for selected radionuclides.

7. The present report, as the previous comprehensive reports, consists of a main text, which outlines the conclusions of the Committee's discussions, and scientific annexes reviewing in detail the available scientific information and the analytical procedures on which rest the Committee's conclusions. Following the practice of the 1972 report, only the main text of the present report is submitted to the General Assembly. The full report, however, including the scientific annexes, is being made available in a separate publication[3] and the Committee wishes to draw the attention of the General Assembly to the fact that the separation of the submitted main text from its annexes is for convenience only, and that the major importance attaches to the scientific analysis presented in the annexes.

8. The Committee summarizes the biological effects of radiation in the following section (paras. 9-51) and describes the radiation exposures received from the various sources and practices in the ensuing section (paras. 52-106), including some general conclusions based on this information.

[1] The terms of reference of the Scientific Committee, which was established by the General Assembly at its tenth session in 1955, are set out in resolution 913 (X). It was originally composed of the following Member States: Argentina, Australia, Belgium, Brazil, Canada, Czechoslovakia, Egypt, France, India, Japan, Mexico, Sweden, Union of Soviet Socialist Republics, United Kingdom of Great Britain and Northern Ireland and United States of America. By resolution 3154 C (XXVIII), the General Assembly decided to increase the Committee's membership by up to five additional members, and the following Member States were appointed members of the Committee by the President of the General Assembly in consultation with the Chairmen of the regional groups: Federal Republic of Germany, Indonesia, Peru, Poland and Sudan.

[2] For the previous substantive reports of the Committee see *Official Records of the General Assembly, Thirteenth Session, Supplement No. 17* (A/3838); *ibid., Seventeenth Session, Supplement No. 16* (A/5216); *ibid., Nineteenth Session, Supplement No. 14* (A/5814); *ibid., Twenty-first Session, Supplement No. 14* (A/6314 and Corr.1); and *ibid., Twenty-fourth Session, Supplement No. 13* (A/7613 and Corr.1). They will be referred to as the 1958, 1962, 1964, 1966 and 1969 reports, respectively. See also *Ionizing Radiation: Levels and Effects. A Report of the United Nations Scientific Committee on the Effects of Atomic Radiation to the General Assembly, with annexes*, vols. I and II (United Nations publication, Sales Nos. E.72.IX.17 and 18), which will be referred to as the 1972 report. The report without its appendices and annexes appeared as *Official Records of the General Assembly, Twenty-seventh Session, Supplement No. 25* (A/8725 and Corr.1).

[3] United Nations publication, Sales No. E.77.IX.1.

II. EFFECTS OF RADIATION

A. GENERAL ASPECTS

9. In the five years that have elapsed since the publication of the Committee's last comprehensive report,[4] a considerable amount of new information has become available not only on the frequency with which certain harmful effects may be induced by ionizing radiation, but also on the amounts of radiation exposure that are involved in various circumstances. It has become possible, therefore, to estimate with rather more confidence than previously the types and frequencies of detrimental effects that are likely to result from various procedures as a consequence of the radiation exposure of people that they involve.

10. The present report therefore deals in some detail with the most important effects of radiation on man, concentrating upon those effects which are liable to be caused by low doses of radiation and which may appear, or continue to appear, at long intervals of time after exposure in the individual irradiated (the so-called somatic effects) or in his progeny (the genetic effects). In respect of both classes of effect, the Committee has reviewed in detail the evidence from which estimates can be derived of the frequency with which such effects are likely to occur in man, per unit radiation dose. The effects of heavy irradiation of the whole body are not discussed in the present report.

11. Both for somatic and for genetic effects, it is important to estimate the likely frequency with which harmful effects may follow the low doses of radiation to which people may be exposed from fallout from nuclear explosions, from radioactive consumer products, from many medical uses of radiation and from the environmental or occupational exposures involved in power production from nuclear sources, as well as from natural sources and from human activities resulting in enhanced exposures to natural sources, as discussed below. In most cases, however, the available evidence as to the frequency with which harmful effects are induced by radiation is only obtained following exposure to substantially higher radiation doses.

12. Particular attention is paid, therefore, to the uncertainties involved in inferring the frequency of harmful effects to be expected following low doses from those actually observed following higher doses, and to the guidance that can be obtained in making this inference from research into the mechanism by which radiation causes harmful effects. For this purpose, investigations of the effects of radiation on animals or, in some cases, on plant material, may be informative and considerable advances have been made in analysing the mechanisms of radiation damage and repair in biological systems.

[4] 1972 report of the Committee.

13. In general, however, the only secure basis for quantitative estimates of the frequency with which harmful effects may be produced in man must depend upon surveys of human populations who have been exposed to known doses of radiation, and in whom the effects of these exposures have been adequately studied.

14. The risks of developmental defects associated with pre-natal exposure or of genetic defects, however, cannot be derived, or derived solely, from human epidemiological information and use must be made of the results of experiments on animals to estimate the radiation-induced frequency of forms of developmental or genetic defects. For the somatic effects developing in the exposed individuals, several such sources of information are now available for estimating the risks of radiation exposure, both of the body as a whole and of many of the body organs if exposed individually. In such cases, the corresponding risk estimates are of considerable importance, even though they are not of high precision and apply at higher dose levels than are likely to be encountered in the working or in the general environment. For these quantitative purposes, epidemiological studies are of greater value than estimates of the frequencies with which malignancies are induced experimentally in animals, since the frequency of a given type of somatic effect may vary in different species of animals and may therefore give limited guidance as to the frequency to be expected in man.

15. In addition, human epidemiological studies on radiation-induced cancer have commonly involved much larger populations and better ascertainment of the types of harmful effects produced than has been practicable in most experimental studies on animals. In principle, therefore, the effects of lower doses may be detectable by studies on human populations, provided that a number of conditions are satisfied. It is necessary that the total frequency of harmful effects should be fully ascertained, if necessary by observation over periods of several decades in the case of most somatic effects, and compared with their frequency in an unirradiated but otherwise similar population. The initial radiation exposure should be known, and should be of a type and distribution in the body that is relevant to the risk estimate required. Furthermore, the frequency of the effect observed, relative to that in the comparison populations, should be sufficiently high for a statistically valid estimate of the effect of radiation to be determined. As discussed below, most of these conditions are not adequately satisfied in various surveys of the frequency with which radiation induces malignant diseases in man.

16. For most types of harm that may be induced by radiation, the frequency with which the effect is induced varies with the quantity of radiation absorbed in the body tissues concerned. All the various types of

"ionizing" radiation dealt with in the present report cause harm as a consequence of the ionization which they cause in the chemical constituents of the body tissues, and of the energy delivered to important molecular structures of the tissues, particularly the desoxyribonucleic acid (DNA). To a large extent, therefore, the likely harmful effect of any particular exposure to radiation can be related to the energy delivered in this way per unit mass of tissue. The unit of this absorbed dose of ionizing radiation is named the "rad", one rad corresponding to the absorption of 0.01 joule of energy per kilogram of the tissue concerned.

17. The same relationships between the likely frequency of a given type of effect and the absorbed dose in a given tissue apply for most types of radiation with which the present report is concerned (for example, x rays, beta or gamma radiation), regardless of whether the energy is delivered to the tissue from radiation sources outside the body or from radioactive materials deposited within the body tissues. For certain types of radiation, however, e.g., for neutrons and for the alpha radiation emitted by some radioactive materials, the likely frequency of effects for a given absorbed dose is greater—often by a factor of 5-20—than that from the same dose of other, and more common, forms of radiation. This is believed to be due to the fact that dose is delivered over short tracks in tissue along which ionization is dense. When references are made in the present report to the estimated frequency of effects per rad, it should be noted that, where the estimates relate to neutrons or to alpha radiation, the frequencies per rad of other forms of radiation are likely to be lower by a substantial factor. The size of this factor, the relative biological effectiveness (or RBE) of the neutron or alpha radiation under the particular condition of the exposure, is discussed in the report.

B. CARCINOGENIC EFFECTS OF RADIATION[5]

18. It has become clear that the most important late somatic effect of low doses of radiation is the occasional induction of malignant diseases, as shown by their increased incidence in the exposed populations. The extensive and careful studies of A-bomb survivors in Hiroshima and Nagasaki, which have now been continued to over about 30 years from exposure, still show no excess in mortality rate from conditions other than malignant disease in those who were irradiated. The Committee has therefore studied all available information on the carcinogenic effects of radiation on which valid estimates can be based. The word "carcinogenic" is used to include the induction of all forms of malignancy—whether of leukaemia or of the solid, or focal, types of cancer developing in the different body organs or tissues.

19. In the present study, it has been of the greatest importance to examine the results of experimental work on animals, on the types of tumour induced by irradiation in different species and the way in which the frequency of tumours varies with the absorbed dose of radiation in the body organ in which the tumours develop. In some of the studies of the effects of radiation in man, it is possible to obtain some indication of the way in which the frequency of cancers varies with the size of the absorbed dose. In general, however, the human epidemiological evidence is too limited, either in the range of radiation exposures or in the precision of estimated cancer induction at each dose, to establish clearly the mathematical form of this dose-effect relationship. The animal studies, therefore, are of great value in showing the way in which the frequency of induced cancers may vary with the dose, under conditions in which reliable estimates are made of the frequencies at different defined dose levels, and when the type and conditions of radiation exposure and the numbers and strain of animals exposed are accurately controlled and known. Under these conditions, it is commonly found that tumours become detectable at varying periods of time, up to some years, after exposure, and that the total number of tumours which finally develop varies consistently with the size of the dose which each group of animals had received. In some instances the frequency becomes larger with progressively larger doses up to a dose of a few hundred to a few thousand rad, higher doses causing in these cases no greater—and often smaller—frequency of tumours. Following doses substantially lower than that causing this maximum yield, and in the region of a few tens of rad, the frequency is sometimes found directly proportional to the size of the dose, but more commonly the frequency per rad is greater at higher doses than at lower ones.

20. Experimental studies in animals have been of great value also in establishing the greater carcinogenic effect per rad of alpha radiation or of neutrons, than of other types of radiation, and in suggesting that the form of the dose-effect relationship differs in these two groups of radiation. For alpha radiation and for neutrons, which cause dense ionization along a path of short length in tissues, the frequency of cancer induction often appears to be more strictly proportional to the size of the dose than in the case of other types of radiation. Studies in animals have been of value also in assessing the significance of the rate at which a given dose is delivered, or of the way in which its delivery is made in separate fractions rather than continuously.

21. In many cases it has also been easier to study systematically in animals, rather than in irradiated human populations, the influence that certain biological variables may have on radiation carcinogenesis. Thus the sex, the age of the animal at the time of irradiation, the associated effects of other carcinogenic agents or the genetic characteristics of an inbred strain of animals may have an important influence on the frequency with which tumours are induced at a given dose, and these variables may be adequately studied by experimental methods.

22. For assessing risks it is necessary not only to evaluate the total frequency of malignancies that may be induced by irradiation of the whole body at any given dose. In many circumstances, single organs or groups of

[5] This subject is treated in detail in Annex G (Radiation carcinogenesis in man) and in Annex I (Experimental radiation carcinogenesis).

organs are selectively irradiated, for example following medical exposures or the inhalation or ingestion of a radioactive nuclide, which becomes selectively concentrated only in certain tissues or organs. It is thus necessary also to evaluate the frequency with which malignant changes are induced in the various body organs individually, and where possible to examine and assess the influence of age, sex and other biological factors on the organ sensitivity.

23. It is of importance, therefore, that several surveys have now been made and continued for prolonged periods of time on the frequency with which cancers of various types develop in certain irradiated human populations in excess of that observed in comparison populations who have not been similarly irradiated. The most important of these surveys is that of the A-bomb survivors at Hiroshima and Nagasaki, in which a large group have been closely examined in regard both to the development of malignant diseases and to death from all diseases, including different types of malignant disease. Comparisons can be made between those who were exposed at various dose levels and those who were unexposed to any significant radiation. From the point of view of risk estimation, this study has the great advantage of being based on substantially uniform "whole-body" irradiation of large numbers of people of all ages, who have now been closely followed for almost 30 years. The irradiation at Hiroshima included a substantial contribution from neutrons, of which the biological effectiveness relative to that from other radiations is hard to determine, but approximate estimates of the carcinogenic risk of irradiation of many body organs can now be determined from these surveys. Some evidence on the risk for one organ, the thyroid gland, can also be derived from the occurrence of cancers of this gland in populations of two Pacific islands, who were exposed to irradiation and radioiodine concentration in the gland from fallout from a weapon test in 1954. Extensive information on lung cancer induction is also obtainable in a number of countries from the increased mortality from this disease in uranium miners who inhale radioactive gases in the course of their work. Here, however, the relevant exposure is from alpha radiation, for which the relative biological effectiveness is not known with certainty.

24. A number of other carcinogenic risk estimates are obtainable from studies made on groups of patients who have been irradiated, either in the course of frequently repeated diagnostic examinations or during treatment of their diseases by radiotherapy. In the former group, patients treated for pulmonary tuberculosis by injections of air into the chest to maintain collapse of the diseased lung have sometimes received substantial radiation exposures to the chest from the examinations required to control the degree of collapse: female patients have been found to develop breast cancer in excess of normal expectation. Increased numbers of cancers in locally irradiated organs have been observed in a substantial number of surveys following x-ray treatment to the spine for ankylosing spondylitis, to the pelvis for diseases of the uterus, to the breast for diseases of these glands, or to the head and neck region, for ringworm of the scalp, for pharyngeal infections or for supposed enlargement of the thymus gland. In some instances radium preparations have been administered for the treatment of spinal or other conditions, or thorium compounds as radiological contrast media, and have given rise to increased frequencies of malignancies in irradiated tissues. It has also been found that exposure of the foetus in the course of diagnostic x-ray examinations of the mother's pelvis during pregnancy has been followed by increased frequencies of certain malignant diseases during childhood.

25. From these extensive and varied surveys, it has been possible to derive approximate estimates of the carcinogenic risk of radiation for a substantial number of important body tissues, and to exclude any high risk for others. Reasonably consistent estimates are obtainable from several different sources for certain organs or tissues, such as the thyroid, the breast in females, the lung, the bone and the bone marrow (as regards induction of leukaemia). For some others, including the brain, the salivary glands, the stomach and other parts of the gastro-intestinal tract, the bladder, the lymphoid tissues and probably the liver, the estimates are more tentative, often because the risk appears to be lower and therefore less easily detected or evaluated in human surveys. For one type of leukaemia (the chronic lymphatic type), no induction has been detected in any survey, and for malignant diseases of muscle, adipose tissue, the prostate gland or many other tissues, the risk must be very low since no unequivocal evidence of such a risk has been found.

26. In general it appears that relatively high cancer induction rates apply to the breast in females and to the thyroid, although the mortality rate from induced thyroid cancers is low. The induction rates for lung and for leukaemia are somewhat lower, and those for other organs for which estimates are obtainable appear to be lower again.

27. In evaluating the somatic risks of radiation, however, an estimate is required for the total risk of all malignancies, and particularly of all fatal malignancies, from irradiation of the whole body at low doses. This estimate cannot be derived with confidence by adding the risks for all body organs, since some, and particularly those with low values, are not known with any precision. Several sources of information, however, indicate that the total risk for all fatal malignancies as an average for both sexes and all ages is likely to be in the region of five times that for leukaemia alone, and that the corresponding risk for leukaemia is about $2\ 10^{-5}$ rad^{-1} (that is, 2 per 100 000 persons, per rad of absorbed dose) for moderately low doses of most types of radiation (that is of x rays and gamma radiation, rather than of neutron and alpha radiation) (see paragraph 15). The average risk of inducing a fatal malignancy is thus taken as being in the region of 10^{-4} rad^{-1} and that of inducing a non-fatal malignancy is probably of about the same magnitude. The estimated risks for individual organs and tissues appear consistent with this total, and indicate that no organ with a high induction rate is likely to have been omitted from these estimates. It must be emphasized, however, that such estimates are derived predominantly from rates observed following absorbed doses of over 100 rad. While the rate per rad from doses of a few rad is unlikely to be higher than this value, it

might be substantially lower. In particular, at low doses in the region of those received annually from natural sources, no direct information is available as to the level of induction of malignancies that might apply. When body tissues are subject to "internal radiation" from radioactive nuclides within the body, no evidence has been obtained of rates of tumour induction differing from those from external radiation, when account is taken of the absorbed dose to tissues from the internal radiation.

28. Many aspects of this subject require fuller investigation, particularly the variations of risk for many organs with the age and sex of those exposed, and the relationship between risk from low dose and that inferred at higher dose. However, for doses of over 100 rad, the total risk of induction of malignancies and the average risks for many body organs appear to be determined with sufficient consistency from different sources to give guidance as to the radiation protection precautions that should be taken in occupations that involve radiation exposure, for which the doses received are discussed later in the present report.

C. RADIATION EFFECTS ON PRE-NATAL DEVELOPMENT[6]

29. It has been shown repeatedly in experiments on animals that irradiation of the embryo or foetus may cause defects of a wide range of severity. Some are so profound that they cause death of the animal while still within the uterus. Others cause structural changes which are recognizable at birth. Still others are only manifested after birth as functional deficiencies. It has been shown also that the types of changes produced and the sensitivity to the induction of these effects differ considerably at different stages of pre-natal development, and vary according to whether the exposure to radiation occurs before the implantation of the conceptus in the uterine wall, or during the main phase of "organogenesis", when body organs or tissues are becoming differentiated in the embryo, or during subsequent foetal growth.

30. It is evident also that similar types of injury may be caused in man by pre-natal exposure to radiation at corresponding stages in development. Very few human data are available, however, on which to base any quantitative estimate of risks from radiation at these stages, and it is clear that values derived from animal studies cannot be directly applied to man. The Committee has, however, reviewed the effects produced in a number of mammalian species at various stages of development and has attempted to correlate them with changes observed in man at corresponding stages, where known. The present section of the report is thus concerned with the developmental effects produced by radiation on the embryo or foetus. Those effects caused by irradiation of the germ cells before conception, but expressed during subsequent development, will be discussed in section D on genetic effects of radiation, while the induction of malignant change by irradiation of the foetus has been dealt with in paragraphs 18-28.

[6] This subject is treated in detail in Annex J (Developmental effects of irradiation *in utero*).

31. The effects of radiation before the implantation of the conceptus in the uterus have been examined in the mouse, rat, hamster, rabbit and dog. Exposure to radiation at this stage may cause the death of the embryo and failure of implantation, with variable frequency in the different species. Those embryos which survive the exposure and become implanted would appear, however, to develop normally, with little evidence of an increased frequency of intra-uterine death or of induced abnormality shown at birth or subsequently.

32. Irradiation after implantation, and during the period in which body structures are becoming differentiated and organs are developing, causes broadly similar types of malformation or harm in a number of different mammalian species if they are irradiated at comparable stages of development. It appears, from collected reports of the rare cases of therapeutic pelvic irradiation of pregnant women, that the same applied in humans if irradiation took place during the period from about 9 to 40 days following conception.

33. Studies on irradiated animals, largely on rats and mice but with some observations on a number of other species, show that three main types of effect may occur. From relatively high doses, especially if delivered early in this period, death of the conceptus may result either in the uterus or soon after birth, the doses causing 50 per cent lethality in these conditions being about 100 rad or higher. Alternatively, growth of the embryo may be impaired at these or lower doses, and this impairment of normal growth may persist during post-natal life. And thirdly, more localized defects in development may result, causing malformations in particular body structures or metabolic functions.

34. From studies on animals, it is found that malformations of the eye, the brain and nervous system, or the head, skeleton and extremities may typically result from irradiation during the period of organogenesis, and that the particular malformation which is most likely to occur depends very critically upon the time within this period at which radiation exposure occurs. Not much information is available as to the way in which the frequency of any particular malformation, or of all malformations, varies with dose. An increased incidence of some malformations has, however, been observed at doses as low as 5 rad in the mouse, and at 5-10 rad in the rat, for exposures at times appropriate to induce these malformations. At absorbed doses of 10-100 rad of sparsely ionizing radiation several types of malformations may be induced, each with a frequency of about 10^{-3} rad^{-1} or more, but adequate data are not available in general to show what these frequencies may be at lower doses.

35. While it is evident that radiation-induced malformations occur in man, of types depending upon the stage of development at which the exposure occurs, there is little information indicating the likely frequency, particularly at low dose. In its 1969 report, the Committee estimated a possible incidence of mental retardation, associated with small head size (microcephaly), in the region of 10^{-3} rad^{-1} for doses over 50 rad delivered at high dose rate. Recent data have shown an increased incidence of microcephaly and mental

retardation as a function of dose at Nagasaki following exposures within 3-17 weeks of gestation. At Hiroshima, where the neutron component was appreciably higher, a comparable incidence was observed at lower doses. However, various studies of the effects of embryonic exposure during radiological procedures, usually in the region of a few rad, have failed to show a significantly increased incidence of malformations.

36. In animals, irradiation during the foetal stage of development, as in earlier stages of intra-uterine life, may cause death of the foetus, impairment of growth or malformations. In this stage, however, the likelihood of death decreases progressively and the induction of malformations becomes considerably less likely, at least as regards the defects in major anatomical structures which result in important functional disabilities. Some major defects continue to be caused, particularly after high doses. Such malformations as occur at lower doses, however, are largely confined to lesions detectable microscopically. The body size and weight at birth, however, are commonly found to be decreased following irradiation during this foetal stage of development.

37. In man the foetal period extends over the last 33 weeks of gestation. Irradiation during this period has been shown to be associated with defects in growth and with some mortality at high dose levels. The induction of microcephaly may still occur if doses are high, but substantial malformations are less likely to be induced at this stage than during organogenesis, although heterochromia (irregular coloration of the iris) has been shown to have been induced by diagnostic radiological exposure during the fourth and fifth months of gestation.

38. Japanese children who had been exposed *in utero* as a result of A-bomb explosions in Hiroshima and Nagasaki at doses exceeding 50 rad have shown, at the age of 17 years, clear evidence of reduction in body size.

39. From experimental studies in animals it may be concluded that the developing embryo and foetus show a pronounced sensitivity to the induction of malformations by radiation, particularly during the main phases of organogenesis. The pattern of response in various species is so similar that man may not be expected to be an exception in this respect. However, no satisfactory data are yet available for deriving reliable quantitative estimates of the risk from pre-natal human irradiation at comparable developmental stages, particularly at the low doses and dose rates. The Committee emphasizes therefore the importance of further studies on a number of special aspects of this subject.

D. GENETIC EFFECTS OF RADIATION[7]

40. When cells are exposed to ionizing radiation, the chromosomes of the cell nuclei may be damaged by the production of gene mutations, involving alterations in the elementary units of heredity which are localized within the chromosomes, or by the induction of chromosome aberrations, consisting of changes in the structure or number of the chromosomes. When such changes are induced in the germ cells, they may be transmitted to descendants of the irradiated persons. The gene mutations and chromosome aberrations which occur spontaneously in man are a source of considerable hardship, being responsible for a substantial fraction of all spontaneous miscarriages and congenital malformations, causing mental and physical defects. It is of importance therefore to estimate the amount by which radiation exposure may increase the frequency of these genetic defects. The Committee has reviewed the frequency estimates obtainable for different types of gene mutations and chromosome aberrations, particularly as applicable to the two germ cell stages which have been found to be of the major importance. These are the spermatogonia and the oocytes, which constitute the permanent germ cell population in the male and female, respectively.

41. Gene mutations are classified for convenience as dominant or recessive, according to the extent to which the effect of the mutation is expressed in a descendant inheriting the mutated gene from one parent only. A fully dominant mutation has a maximal effect in the descendant even if only transmitted from one parent. A fully recessive mutation has no effect in a descendant unless he has received genes with the same abnormality from both parents (or unless it is received in the X-chromosome). The effects of many mutations in man and experimental mammals are intermediate between the fully dominant and the fully recessive.

42. Chromosome aberrations are of two kinds: *(a)* structural aberrations arising from breakage and rejoining of chromosomes, which may involve decreases (deletions) or increases (duplications) in the number of certain genes within a chromosome or changes in the sequence of arrangement of genes (inversions or translocations); *(b)* numerical aberrations, involving the addition or loss of chromosomes.

43. The Committee has reviewed in detail recent work on the processes of radiation damage and repair of DNA, since it is evident that the genetic effects of radiation are likely to be due predominantly to damage induced in this molecular structure.

44. In estimating the genetic risks of radiation, particularly for low doses, very little quantitative information is available from observations of the effects of human exposure. To a large extent, therefore, these estimates need to be based upon the effects observed in studies on animals, and particularly on the mouse, in which the genetic effects of radiation have been extensively investigated. In using such data, it has to be assumed that the amount of genetic damage induced by radiation under a given set of conditions is equal in mouse and human germ cells, and that physical and biological variables affect the magnitude of the damage in similar ways and to similar extents. In some instances these assumptions can be checked by data obtained in man or in other primates.

45. Two methods have been used in the present report to estimate the genetic risk of radiation in man. By the first, or "direct" method, the risks are expressed in

[7] This subject is treated in detail in Annex H (Genetic effects of radiation).

terms of the expected frequencies of various types of genetic change induced per unit dose. By the second, or "doubling-dose" method, estimates are made of the radiation doses that double the natural frequencies of various types of genetic abnormality. The expected effect of a given dose is then estimated, on a proportional basis, from the known natural frequencies of the various forms of genetic abnormality in man and from the value assumed for the doubling dose.

46. Using the direct method, the total rate of induction of recessive mutations is estimated as 60 10^{-6} per gamete per rad. The value is derived from the rate with which autosomal recessive lethal mutations are induced by irradiation at high dose rate in mouse spermatogonia, with corrections for mutations that are not likely to have been detected and for radiation conditions applicable to man. For evaluation of the risk in the first-generation progeny of the exposed parents, it is the degree of dominance of these mutations that is of importance.

47. An overall estimate of the risk from the induction of mutations causing dominant effects (and this includes the recessives with partial dominance referred to in paragraph 46, as well as dominant visibles) can be derived from the rate of induction of mutations causing skeletal abnormalities in the mouse, which have been studied in detail. The induction rate for skeletal mutations in mice has been used to estimate the rate of induction of dominants affecting all body systems in man. A study of the nature of the skeletal effects has also permitted an evaluation of the proportion of these mutations that would, in man, entail serious handicaps. The overall estimate thus obtained is 20 10^{-6} rad^{-1} for irradiation of males. For irradiation of females at low doses and low dose rates, the mutational risk is expected to be very low, provided that the human ovary responds to irradiation as does that of the mouse.

48. In estimating the risk of induction of chromosomal aberrations by the direct method, some data are available from observations on man and also on certain primate species. The data from primates show considerable variability, but those indicating the higher risk (in the marmoset rather than in the rhesus monkey) have been used in conjunction with those from man. On these bases, the risks from induction of reciprocal translocations are taken to be of from 2 to 10 congenitally malformed liveborn children per million conceptuses, per rad of paternal irradiation, with about five times this number of recognizable abortions and about 10 times the number of losses at the early embryonic stage. The corresponding risk from maternal irradiation is likely to be small, as are those from other structural aberrations and from sex-chromosome losses, while those from chromosome gains cannot at present be estimated quantitatively. Direct methods thus suggest that the genetic risk in the first generation following irradiation of parents with 1 rad is likely to be of the order of 20-30 seriously affected cases per million liveborn (20 by mutations with dominant effects and 2-10 resulting from structural chromosome aberrations). This estimate excludes the risk from the induction of numerical chromosome abnormalities for which no reliable figure is yet available.

49. The doubling-dose method involves the assumption that the radiation-induced mutation rate is for each kind of genetic defect proportional to the rate with which it originates spontaneously. It has been observed in the mouse that the dose required to double the natural frequency of several different forms of genetic abnormality is of roughly the same magnitude and can be taken as about 100 rad for radiations such as x rays, beta or gamma radiation delivered at low dose rate. In this connection it is of considerable importance that data on the mortality of children born to survivors of the atomic bombs at Hiroshima and Nagasaki indicate that for man, in both sexes, the doubling-dose is unlikely to be lower than this value. The increase of genetically determined diseases per rad is thus unlikely to exceed 1 per cent of the corresponding natural rates.

50. By this method, the Committee estimates that, in a million liveborn children in the first generation of offspring of a population exposed to 1 rad at low dose rate during the generation, there would be 20 cases suffering from dominant or X-linked diseases, 38 with chromosomally determined diseases and 5 with diseases of complex aetiology, induced by the radiation. The total genetic damage expressed over all generations (or the value in each generation reached after prolonged continuous exposure) is estimated to be 185 10^{-6} rad^{-1} by the doubling-dose method.

51. The kinds of genetic damage discussed and the risk estimates derived do not take full account of the class of mutational events which lead to minor deleterious effects and which, by their large number, might impose a greater total genetic burden on the population than that from a smaller number of relatively more serious conditions.

III. RADIATION SOURCES AND EXPOSURES TO RADIATION

A. GENERAL ASPECTS[8]

52. The Committee has collected and assessed data on human radiation exposures for two main purposes. The first purpose is to present individual exposure data which would indicate the possible levels of risk to which individuals are subjected under various circumstances. The second purpose is to present data which could be used to indicate the total consequences in radiation harm from given sources of radiation. The two types of assessment, the individual-related assessment and the source-related assessment, therefore, serve different purposes.

53. The basic quantity in all assessments is the absorbed dose, which for certain types of radiation needs to be weighted for an enhanced biological effectiveness (para. 17). In the present report, the shorter term "dose", unless otherwise qualified, refers to the mean absorbed dose over an organ or tissue. In presenting dose data, the period of time over which the dose is accumulated is always stated in the individual-related presentations, while the period of time over which the dose is delivered is of less importance in the source-related assessments.

1. Individual-related assessments

54. Depending upon the purpose of the assessment, the time period to which the individual dose is related may be one year, a lifetime, the limited time of a single exposure or some other time of relevance. Continued practices inevitably give rise to accumulations of radioactivity in the human body or in the environment until a steady-state situation is reached. This would be the case, for example, if the practice caused releases of long-lived radionuclides which remained in the environment for a long time. For such situations, the "dose commitment" from, for example, one year of practice is assessed as the sum of the individual's future annual doses. This summation is also applied for an average individual and, in the general case, extended over future generations. It can be shown that the annual dose, when it reaches its maximum value in the future, will not exceed the dose commitment from one year of practice. Dose commitments to various populations, such as the groups of most highly exposed individuals, or the whole world population, are assessed in order to account for those future dose contributions to which human populations are committed from present practices and which would give rise to higher annual doses than at present if these practices were continued.

[8] Concepts used in the assessment of radiation exposures are treated in detail in Annex A (Concepts and quantities in the assessment of human exposures).

2. Source-related assessments

55. For the source-related assessments it is necessary to derive a quantity which would be related to the detriment from the practice. On the assumption of proportionality between radiation dose and individual risk within the range of doses encountered, the "collective dose" is a quantity which is proportional to the radiation detriment. The collective dose is the product of the number of people in the exposed population and their average dose. If the purpose is to assess the total detriment of a given practice, all individuals must be included in the assessment, that is, the global collective dose should be calculated. For the assessment of the total radiation detriment, future dose contributions committed by the practice should also be included. Therefore, "collective dose commitments" have been calculated as the sum of the annual global collective doses over all future years. The collective dose commitment is always related to a limited amount of practice, the release of a certain quantity of a radioactive substance into the environment, the production of a certain amount of electric energy or the result of any single decision.

56. The values of the collective dose commitment may be used for the assessment of the radiation detriment, provided that the radiation detriment per unit of collective dose (man rad) is known. Even without this provision, collective doses from various practices may be compared for relative detriment assessments. This could provide a useful input for cost-effectiveness decisions on various alternative applications of radiation protection measures, under the assumption that the likelihood of harm is proportional to dose.

B. SOURCES OF HUMAN RADIATION EXPOSURES

57. In the previous reports of the Committee, data on human radiation exposures have been presented separately for various classes of exposure, such as occupational exposures, medical exposures of patients, exposures from environmental contamination and miscellaneous exposures. Basically, the same procedure has been followed in the scientific annexes to the present report.[9] In the following paragraphs, however, a number of *sources* and *practices* are reviewed with regard to the total resulting exposures, including all

[9] More detailed information on these exposures, as well as on others, is presented in the relevant annexes to the present report: Annex B (Natural sources of radiation), Annex C (Radioactive contamination due to nuclear explosions), Annex D (Radioactive contamination due to nuclear power production), Annex E (Doses from occupational exposure) and Annex F (Medical irradiation).

contributions whether occupational or environmental, with the aim of providing data for source-related assessments.

58. Radiation exposure due to natural sources is a result of both terrestrial and cosmic irradiation and varies somewhat with geographic location, primarily owing to differences in altitude and radionuclide distributions in the terrestrial environment. For illustrative purposes, the collective dose commitment from other sources of radiation exposure is sometimes given in the present report in terms of the equivalent duration of exposure to natural sources which would cause the same global collective dose commitment (see table 3).

59. Exposure to natural radiation may be enhanced by human activities such as high-altitude flights, construction of buildings using materials of high radium content, reduction of ventilation rate in homes and boring deep wells into radon-rich water. Enhanced exposures to natural radiation are also variable, ranging from slight increases to those of orders of magnitude. These enhanced exposures may well be subject to source-related assessments when they result from human decisions to which a collective dose commitment may be related as a measure of the consequent detriment. Other sources or practices for which the Committee provides estimates of exposures are medical uses of radiation (including the exposure of patients and other exposures), electric-power generation from nuclear fission, nuclear explosions and radiation-emitting consumer products.

1. Normal exposures to natural radiation sources[10]

60. Man has always been exposed to ionizing radiation from various natural sources. A distinguishing characteristic of this natural irradiation is that it involves the entire population of the world and that it has been experienced at a relatively constant rate over a very long period of time. On the other hand, even the normal natural exposure varies substantially from place to place, as well as locally, for example even within one building.

61. The assessment of the radiation doses in man from natural sources is of particular importance because natural irradiation is the largest contributor to the collective dose of the world population. Furthermore, the extent of variation of natural exposures with location and habits is of practical interest.

62. The various natural radiation sources include *external* sources, such as cosmic rays and radioactive substances in the ground and in building materials, and *internal* sources in the form of naturally occurring radioactive substances in the human body, particularly potassium-40.

63. Table 1 below summarizes the average contribution of natural sources to the radiation exposure of human populations living in areas of normal radiation background. The annual *per capita* dose has been assessed for four tissues: the gonads, the whole lung, the cells lining the bone surfaces and the red bone marrow, with the contributions from all types of radiation included. In those tissues the annual dose from normal exposure to natural sources is estimated to be of the order of 100 mrad (1 mrad = 0.001 rad). For purposes of comparison, the estimates of the 1972 report are given in parentheses in table 1. The new estimates are a few per cent lower than the previous ones for the gonads and the bone-lining cells and a few per cent higher for the red bone marrow. The difference is mainly due to better knowledge of the doses from "terrestrial" radiation (taken here as including gamma radiation from the ground and that from building materials), which are now estimated to be about 30 per cent lower than indicated in the 1972 report. The increase in the estimate of the dose in the red bone marrow is caused by a higher estimate of the contribution from potassium-40 than previously.

TABLE 1. ANNUAL *PER CAPITA* DOSES FROM NORMAL EXPOSURE TO NATURAL SOURCES OF RADIATION

(in mrad)[a]

	Gonads		*Whole lung*	*Bone-lining cells*		*Red bone marrow*	
External irradiation							
Cosmic rays	28	(28)	28	28	(28)	28	(28)
Terrestrial radiation	32	(44)	32	32	(44)	32	(44)
Internal irradiation							
Potassium-40	15	(19)	17	15	(15)	27	(15)
Radon-222 (with daughters)	0.2	(0.07)	30	0.3	(0.08)	0.3	(0.08)
Other nuclides	2	(1.4)	5.5	9.1	(4.3)	4	(1.9)
Total	78	(93)	110	84	(92)	92	(89)

[a] Figures in parentheses refer to estimates made in the 1972 report. All values and the totals are rounded to two significant figures.

64. As the result of inhalation of radon-222 and its daughter products, the dose in the entire lung—which is now being assessed for the first time by the Committee—is between 20 and 45 per cent higher than the dose in the other tissues. Moreover, a substantial fraction (31 per cent) of this dose is caused by alpha radiation, which is expected to have a higher relative biological effectiveness than do the beta and gamma radiations, which cause more than 90 per cent of the dose in the other tissues. It may be mentioned that an annual dose of the order of 200 mrad is received by the epithelial cells of the tracheo-bronchial tree, mainly from alpha particles.

65. The variability of individual doses from potassium-40 in the body is small. The individual lung doses, however, are subject to rather large variations because of the varying concentrations of radon and its daughter products in indoor air. The normal variation of the dose contributions from these sources ranges from 4 to 400 mrad in a year.

[10] This subject is treated in detail in Annex B (Natural sources of radiation).

66. Much higher external doses are received by population groups living at high altitudes or in regions of high natural radiation. Some population groups are also exposed to elevated internal doses. Such population groups are, for example, the caribou or reindeer eaters in the northern regions, or those people living in houses with low rate of ventilation, as may be the case in the colder climates. The ventilation rate determines the average concentration of radon in indoor air at a given emanation rate (from the building material, from the basement floor or from radon-rich tap water).

67. In relative risk assessments, the total exposure due to a limited amount of a practice involving radiation (para. 55) may be expressed in terms of the duration of an exposure at a constant rate of a specified population which would be expected to cause the same detriment. This comparison is particularly illustrative if the practice gives a relative uniform exposure and the reference is made to the equivalent duration of exposure of the world population to natural radiation sources. As in previous reports, therefore, the Committee has indicated the equivalent durations of exposure to natural sources which would cause the same collective dose commitments as the practices discussed in the present report. The annual collective dose from natural sources to the world population is of the order of $3\ 10^8$ man rad for most of the body tissues but is about 30 per cent higher for the whole lung.

2. Technologically enhanced exposures to natural sources[11]

68. In some situations the exposure to natural radiation sources is enhanced as a result of technological developments. Some examples of such exposures are the irradiation by cosmic rays in aircraft, the irradiation resulting from the phosphate industry or the irradiation due to the release of natural radionuclides from coal-fired power plants.

69. *Building materials.* The use of some building materials leads to substantially elevated exposure levels indoors. These building materials may be of natural origin, as is the case of pumice stone, granite or light concrete derived from alum shale. They may also be made from by-products from industrial processes, such as slag or phosphogypsum. If all the phosphogypsum derived from one tonne of marketable phosphate ore were used in the building industry, the resulting collective dose commitment might be a few man rad per tonne of rock. The dose rates in air from gamma radiation in buildings constructed of such materials may be substantially higher than the average normal dose rate from terrestrial radiation. The radon levels will also be considerably enhanced, for a given ventilation rate.

70. *Reduced ventilation.* Changes in the ventilation in a poorly ventilated room influence the radon level considerably. The ventilation rate in houses varies in different countries owing to climate, heating systems and building standards. Between two and five exchanges of air per hour are not unusual in many countries. In countries with cold climates, however, the ventilation rate may sometimes be as low as 0.1 to 0.2 exchanges per hour, and this could result in annual doses of several rad in the lung from alpha radiation. Radon in water will cause exposures not only after ingestion, but also after inhalation of radon emanating from the water. When the radon concentration in tap water is large, the lung dose due to inhalation indoors is larger than the dose in the stomach resulting from the ingestion of normal quantities of water.

71. *Passengers in aircraft.* A total of about 10^9 passenger hours are spent travelling by air each year. Under average solar conditions, the annual collective dose contributed by air travel is about $3\ 10^5$ man rad. This risk of high dose rates from cosmic radiation at high altitudes due to large solar flares has made it necessary to equip supersonic aircraft with radiation monitors in order to warn the pilot when a solar flare is developing. The aircraft will then be moved to lower altitudes if the dose rate reaches a predetermined level. High radiation levels at high altitudes during solar flares are infrequent events which will not add significantly to the collective dose to the world population.

72. *Use of phosphate fertilizers.* Mineral phosphate deposits usually contain relatively high concentrations of radioactive nuclides of the uranium-238 decay series. Very large quantities of phosphate rock are mined. Some of the material is converted to fertilizers and some is disposed of as waste. Both practices may lead to exposure of the public. In addition, one by-product is chemical gypsum, which may be used as a building material and is therefore a radiation source of particular interest. The assessment of the collective dose commitment per tonne of marketable rock shows that the contribution from phosphate fertilizers is small, of the order of $3\ 10^{-4}$ man rad per tonne of fertilizer. For a world-wide annual use of 10^8 tonnes of phosphate fertilizers, the collective dose commitment from a year's use of these fertilizers is of the order of $3\ 10^4$ man rad.

73. *Coal-fired power plants.* Burning of coal is one source of enhanced radiation exposure to naturally occurring elements, particularly radium, thorium and uranium. The concentrations of the significant radionuclides have been measured both in coal of various origins and in slag and fly-ash. The Committee has assessed the collective dose commitment per megawatt year production of electric energy due to the deposition of fly-ash but has found that this is a small contribution, being between 0.002 and 0.02 man rad per MW(e)y in the various body tissues from discharged material deposited on the ground and also between 0.002 and 0.02 man rad per MW(e)y from the material inhaled.

74. *Use of natural gas.* Natural gas used for kitchen ranges and space heaters is a source of radon in buildings. The radon, which is produced in the ground, diffuses from the geological formations into the wells for natural gas. This source of radon, however, is found to be insignificant in comparison with the other sources of radon.

[11] This subject is treated in detail in Annex B (Natural sources of radiation).

3. Radiation-emitting consumer products[12]

75. A variety of consumer products contain radionuclides which have been deliberately incorporated to satisfy a specific purpose. In addition, some electronic products, such as television sets, may emit x rays. The most widespread radiation-emitting consumer products are radioluminescent time-pieces, compasses, luminous signs, smoke detectors, antistatic devices and television sets. The extent to which exposures from these products are permitted by national regulations varies from country to country. The most commonly used radionuclides in consumer products are tritium, krypton-85 and promethium-147, the use of which involves trivial amounts of penetrating radiation.

76. Until the 1960s, radium-226 was the most common nuclide in radioluminescent paint and therefore also in watches and alarm clocks. The wearer of an average radium-activated wristwatch receives a gonad dose of few mrad in a year. Although this external irradiation is eliminated by the present use of tritium for the same purpose, some tritium may escape from watches and cause internal irradiation producing a whole-body dose of about 0.5 mrad per year. The present use of radioluminescent paint in the watch industry may cause a collective dose to the world population of the order of 10^6 man rad in a year. It also causes some occupational exposure.

77. Luminizers have traditionally been among the groups of workers receiving higher than average doses. The marked improvement which could be brought about by an energetic programme of radiation protection was demonstrated in the 1972 report. The collective doses from the occupational exposures are small in comparison with those from the exposure of the public, but high individual doses may still occur.

78. Household colour television receivers are the most common consumer product with the potential of exposing the public to x rays. In the 1972 report, some cases of leakage of x rays from certain types of television sets were reported. Since then, however, solid-state circuitry has been widely adopted. It is therefore likely that the x-ray emission from recently-built colour television receivers is negligible under conditions of normal operation and proper servicing.

79. The assessment of dose from the use of radiation-emitting consumer products is rendered difficult by the lack of extensive information on the number of such products on the market and the amount of activity involved. Owing, however, to international recommendations and some national regulations, there is a gradual improvement of control, and it is likely that the annual *per capita* gonad dose from the use of radiation-emitting consumer products is less than 1 mrad at present.

[12] This subject is treated in detail in the appendix to chapter IV of Annex B, and in Annex E (Doses from occupational exposures).

4. Power generation from nuclear fission[13]

80. The use of nuclear reactors in the production of electrical power has continued to increase, although not at the rate predicted, since the Committee's first attempt to assess the releases of radioactive material from the nuclear fuel industry and the resulting global dose commitment. The total installed nuclear generating capacity in the world in 1976 was about 80 GW(e) from 187 power reactors operating in 19 countries. The projected capacity by the year 2000 is about 2000 GW(e).

81. Nuclear power production involves a series of steps, comprising the processes of mining and milling of uranium, conversion to fuel material (in most cases including enrichment in the isotope uranium-235), fabrication of fuel elements, utilization of the fuel in nuclear reactors, storage of the spent fuel, reprocessing of this fuel with a view to recycling, transportation of materials between the various installations and ultimate disposal of radioactive waste.

82. Almost all the radioactive material associated with the nuclear industry is present in the reactors and in spent fuel or in well-contained fractions separated from the fuel during the reprocessing operations. However, at most steps of the operations, releases of small quantities of radioactive material into the environment occur. Most of the radionuclides released are only of local or regional concern, because their half-lives are short compared to the time required for dispersion to greater distances. Some radionuclides, however, having longer half-lives or being more rapidly dispersed, can become globally distributed.

83. The Committee is interested in assessing the collective dose commitments due to releases of radioactive substances from all operations in the present nuclear industry. As the scale of each step is related to the nuclear capacity it serves, it seems reasonable to express such assessments in terms of collective dose commitments per unit energy generated, that is, per MW(e)y. These collective doses to the world population from nuclear power production comprise the contributions from four components, namely, the occupationally exposed groups, the local populations, the regional or intermediate populations and the world population.

84. A special presentation problem arises in the case of a few radionuclides which have very long half-lives. The most important examples are uranium-238 ($4.5\ 10^9$ y) and iodine-129 ($1.6\ 10^7$ y). Although these nuclides will not accumulate in sufficient quantities in the biosphere to cause more than one mrad per year, even if nuclear power production were continued for 500 years at a rate of 2000 GW(e) with the present technology, the exposure periods of many million years may make the dose commitments high.

85. Since the exposure periods involved in these cases are so extremely long in human perspectives, the collective dose commitments are not realistic. For

[13] This subject is treated in detail in Annex D (Radioactive contamination due to nuclear power production) and in Annex E (Doses from occupational exposures).

example, in order to accumulate a collective dose of 1 man rad per MW(e)y, a world population of 10^{10} persons would need to be exposed to uranium-238 over a period of the order of 10 million years or to iodine-129 over a period of 10 000 years. Because of the small annual doses, as indicated in paragraph 84, the exposures from these nuclides are not included in the following considerations.

86. Carbon-14 is a nuclide which presents similar problems, although it has a much shorter half-life (5730 y). The collective dose commitment from carbon-14 released from light-water reactors and related reprocessing plants is estimated to be about 5 man rad per MW(e)y in soft tissues and 14 man rad per MW(e)y in bone-lining cells and red bone marrow. One half of this collective dose will be delivered within 5700 years. However, because it takes some time for carbon-14 to become dispersed in the oceans, as much as one fourth of the collective dose will be delivered within 500 years. This means that if the nuclear industry were operating at a constant rate for 500 years, the maximum future annual collective dose would be about 1 man rad per MW(e)y in soft tissues and 3 man rad per MW(e)y following comparison of collective dose contributions.

87. In reviewing the dose contributions from the various steps in the nuclear power production, it must be kept in mind that the individual exposures are limited by national regulations, often based on the recommendations of the International Commission on Radiological Protection. This means that the annual whole-body dose to those who are occupationally exposed is limited at a maximum of 5 rad of the most frequent types of radiation. National authorities usually make provisions to ensure that the annual doses to the most highly exposed individual members of the public amount to a small fraction of the dose limit of 0.5 rad in a year recommended by ICRP for the sum of all exposures in addition to those from natural sources and medical exposures of patients. Present radiation protection policies also include the principle of eliminating any exposures which are not necessary and of keeping all doses as low as is reasonably achievable. The effect of these precautions is that exposure at the limits is rare and that the dose distributions are usually such that the average dose in each group of persons to which a limit applies is much lower than the limit. It is the source-related assessment of collective dose commitments that is of primary interest for the present report.

88. In reviewing the various steps of nuclear energy production, the Committee has found the following contributions to the exposure of the personnel and the public:

(a) *Mining, milling and fuel fabrication.* These steps involve mainly occupational exposures. The whole-body collective dose commitment to the workers is 0.05 man rad per MW(e)y in the mining and 0.15 man rad per MW(e)y in the milling and fuel fabrication industry. In addition, mining will cause lung exposure from radon daughter products, adding 0.1 man rad per MW(e)y. The exposure of the public is small (see, however, paragraphs 84 and 85).

(b) *Reactor operation.* The local and regional exposures of the public will cause a collective dose commitment of 0.2 to 0.3 man rad per MW(e)y due to releases into the air and 0.03 to 0.06 man rad per MW(e)y due to releases into water. The global exposures from reactor operations are small in comparison with those from the reprocessing industry, in circumstances in which all the spent fuel is reprocessed using present technology. The occupational collective dose commitment is in the vicinity of 1 man rad per MW(e)y.

(c) *Fuel reprocessing.* The local and regional collective doses from reprocessing are by necessity low because each plant serves a large nuclear energy production expressed in MW(e)y and it is the dose limits to the most highly exposed individuals in the neighbourhood that is the limiting factor. Global collective dose commitments from tritium (0.05 man rad per MW(e)y), carbon-14 (1-3 man rad per MW(e)y, see paragraph 86) and krypton-85 (0.09-0.25 man rad per MW(e)y) would contribute significantly to the total from the nuclear industry if all spent fuel were reprocessed and if these nuclides, as at present, were released. The occupational contribution from the relatively small amounts of fuel from the nuclear power industry that have yet been reprocessed is estimated to have been 1.2 man rad per MW(e)y. This contribution, however, is not expected to apply to a nuclear industry as a whole because fewer workers would be involved per MW(e)y than in the case quoted above, while the individual occupational doses would continue to be limited by regulation. For example, with the present occupational whole-body dose limit, it would be unlikely to exceed a collective dose commitment to the workers of the order of 1 man rad per MW(e)y if, as seems likely, a reprocessing plant could serve a nuclear capacity of 20 000 MW(e)y per year and have an operating staff of several thousand persons.

(d) *Transportation.* External exposures from all transportation is estimated to give only 0.003 man rad per MW(e)y.

(e) *Waste storage.* The Committee is satisfied that the collective dose contribution from present waste storage practices is very small compared to the contributions from other parts of the nuclear fuel cycle. The occupational contribution may be considered to be included in the contribution mentioned above for reprocessing.

(f) *Waste disposal.* Because high-level wastes from nuclear power production continue to be maintained in storage by national authorities, with the precise method of disposal at present undecided, the Committee feels that it is unable at this stage to make an adequate assessment of collective dose commitment for the world population from disposal of these wastes.

(g) *Research and development.* A part of the exposures incurred in research and development establishments are attributable to support for continued operation or future development of the nuclear power industry. It is estimated that about 1.4 man rad per MW(e)y is contributed by these occupational exposures. The collective dose commitment to the public is at least one order of magnitude lower.

89. The total of the exposures mentioned in the previous paragraph is near 7 man rad per MW(e)y, with a variation between different tissues of less than 30 per

cent from that value (the thyroid and lungs are organs which receive the highest doses, while the gonads are in the lower range). The major contibutions are shown in table 2.

TABLE 2

Step in fuel cycle	*Collective dose commitment (man rad/ MW(e)y)*
Mining, milling and fuel fabrication	
(a) Occupational exposure	0.2-0.3
Reactor operation	
(a) Occupational exposure	1.0
(b) Local and regional population exposure	0.2-0.4
Reprocessing	
(a) Occupational exposure	1.2
(b) Local and regional population exposure	0.1-0.6
(c) Global population exposure	1.1-3.3
Research and development	
(a) Occupational exposure	1.4
Whole industry	5.2-8.2

In this summation the occupational contributions dominate. For the reasons given in paragraph 88, however, the contribution of 1.2 man rad per MW(e)y from reprocessing would not be representative for a closed fuel cycle involving the whole nuclear industry. Neither would research and development be expected to give high contributions in the developed industry. Therefore, the total collective dose commitment in the future, with existing technology, would not be expected to exceed 3-6 man rad per MW(e)y. Because of the age distribution of those exposed, only about 30 per cent of the lower value of the range of collective doses for the whole industry in table 2 is of genetic significance.

5. Nuclear explosions[14]

90. Since the publication of the Committee's 1972 report, several nuclear tests have taken place, including 20 atmospheric tests, six of which were in the northern hemisphere and 14 in the southern hemisphere. The Committee's 1972 report contained estimates of dose commitments to populations from all atmospheric tests up to the end of 1970. In the present report, the Committee has evaluated dose commitments from atmospheric tests up to the end of 1975. From increases in the world inventory of strontium-90 and caesium-137, the Committee estimates that dose commitments in the northern and southern hemisphere have increased by about 2 and 6 per cent, respectively, owing to tests carried out from 1971 through 1975.

91. The total global dose commitment from all nuclear explosions carried out before 1976 ranges from about 100 mrad (in the gonads) to about 200 mrad (in bone-lining cells). In the northern temperate zone the values are about 50 per cent higher, and in the southern temperate zone about 50 per cent lower, than these estimates. External exposures contributed by caesium-137 and short-lived gamma-emitting nuclides account for about 70 mrad of the global dose commitment for all tissues. Internal exposures are dominated by contributions from the long-lived nuclides caesium-137 and strontium-90 (in the skeleton). Their half-lives of about 30 years will determine the length of time over which the doses will be delivered. The more short-lived ruthenium-106 and cerium-144 are significant contributors to the exposure of the lung.

92. As in the case of the nuclear power industry, carbon-14 gives the highest dose commitments. Its contribution is about 120 mrad for the gonads and the lung and 450 mrad for the bone-lining cells and the red bone marrow. These doses will be delivered over a period of many thousand years. For reasons given in paragraph 86, they are not included in the estimate of the dose commitment of the previous paragraph.

93. The total global collective dose commitment in different tissues from nuclear test explosions is $4\ 10^8$-$8\ 10^8$ man rad if the carbon-14 contribution is not included, and this commitment is equivalent to between 16 and 24 months of exposure of these tissues to radiation from normal natural sources. If the carbon-14 contribution is included, the collective dose commitment is twice as high.

94. Short-lived iodine-131 is an important contributor to the exposure of the thyroid for a few weeks after nuclear explosions. The highest doses are incurred by infants in some populations consuming fresh milk, and annual thyroid doses from a few mrad to about 200 mrad have been estimated since 1972 for those periods with atmospheric nuclear tests. The thyroid dose in adults is about one tenth of that in infants.

6. Medical uses of radiation[15]

95. The Committee has previously presented data on the medical irradiation of patients in its reports of 1958, 1962 and 1972 and of the related occupational exposures in the same reports. The medical exposures are of particular interest, since they contribute the highest man-made *per capita* doses in the population, are given with high instantaneous dose rates and cause the highest individual organ doses short of accidental exposures. From the radiation-protection point of view, they also offer the largest potential possibilities of dose reduction without loss of the information required. They differ from many other types of exposure in that they usually only involve irradiation of limited regions of the body. They also differ in the sense that the individuals who are irradiated are those who may expect to benefit directly from the particular treatment or examination.

96. In the previous reports, special emphasis was put on assessments of the annual genetically significant dose (GSD). The presentation of such data has encouraged further studies, so that it is now relatively clear to what extent medical exposures contribute to the total genetic dose both in developing countries and in countries which

[14] This subject is treated in detail in Annex C (Radioactive contamination due to nuclear explosions).

[15] This subject is treated in detail in Annex E (Doses from occupational exposures) and Annex F (Medical irradiation).

have already reached a high degree of technological development (see paragraph 99). In the developing countries the level of the annual genetically significant dose (GSD) will usually reflect the availability of x-ray facilities. Such services may need to be expanded, with appropriate emphasis on good practice, in order to meet the medical need. This is likely to increase the genetic dose in these countries.

97. The emphasis on the GSD may have distracted attention from exposure of other organs than the gonads and may therefore have led to an underestimation of the overall risk from certain types of examination which usually cause very low gonad doses. One example is chest examinations, which involve irradiation of such radiosensitive tissues as lung, breast, marrow and sometimes also thyroid. The 1972 report, accordingly, gave more information on the dose in the active marrow. A number of groups of patients were also reported who had been identified as receiving high doses, and some had been shown to have an incidence of certain diseases higher than in comparable but non-irradiated groups. In the present report further attention has been given to identifying examinations in which particular organs may receive high doses. An attempt has also been made to give a fuller picture of the dose distribution in the patients, including data on doses in radiosensitive tissues, such as bone marrow, thyroid, lung and breast.

98. In presenting data on dose levels in medical procedures, the Committee has three different purposes in mind. Firstly, it is of interest to know individual organ doses in various types of medical irradiation, and particularly the extent of variation of such doses, as a basis for any attempt to weigh the radiation risks against the expectation of benefit to the individual patient and for differential cost-benefit analyses of protective measures. Secondly, it may be of interest to know both the individual and the collective organ doses from various medical practices as part of the presentation of man's total radiation exposure. The third purpose is the identification of some highly exposed groups which may be of interest in epidemiological studies. For that purpose, the collective dose is of interest.

99. The individual doses to the patients must be judged by the medical practitioners on the basis of the patient's best interest and the need for diagnosis or treatment. This means that the patient's dose in various organs and tissues may vary from entirely insignificant doses up to high doses, which cause local tissue damage near treatment areas when the purpose is to destroy a tumour with radiation. The *per capita* doses from medical irradiations are therefore composed of a large variety of dose levels and dose distributions in the individual cases. However, the largest contributions to the *per capita* doses come from types of exposures which involve large numbers of individuals, as is the case in some diagnostic x-ray examinations. In these cases, the *per capita* annual doses to the tissues of interest to the Committee are roughly similar in magnitude and in many technologically developed countries are in the range of 50-100 mrad, the genetically significant dose often being about half of the *per capita* gonad dose. This means that the annual collective dose from medical practices is in the range of $5\ 10^4$-10^5 man rad per million of population in countries with developed radiological facilities, while it is estimated to be 10^3 man rad per million of population in countries with limited facilities.

100. In all countries which have reported to the Committee, monitoring of doses to workers involved with medical uses of radiation or radioactive substances is carried out by a number of establishments ranging from individual hospitals to large personnel monitoring services. In general, the results are reported back to the employer but are usually not collated on a systematic basis. It is therefore difficult to ensure that the dose data collected by the Committee are comprehensive and representative. It is estimated that the occupational exposure of workers in the medical field gives an annual collective dose of the order of 10^2 man rad per million of population.

101. The occupational contribution to the collective dose from the medical uses of radiation is therefore insignificant compared to that from the irradiation of patients. The annual global collective dose from medical procedures may be estimated to be of the order of $5\ 10^7$ man rad for the contribution made by those countries with developed radiological facilities and $2\ 10^6$ man rad for the contribution of those countries with limited facilities.

7. Summary of global dose commitments from the various radiation sources

102. Table 3 summarizes the estimated global whole-body dose commitments for the different sources and practices discussed in the report. It is expressed as the duration of exposure of the world population to natural radiation which would cause the same dose commitment.[16]

TABLE 3. GLOBAL DOSE COMMITMENTS FROM VARIOUS RADIATION SOURCES

Source of exposure	*Global dose commitment (days)*[a]
One-year exposure to natural sources	365
One year of commercial air travel	0.4
Use of one year's production of phosphate fertilizers at the present production rate	0.04
One-year global production of electric energy by coal-fired power plants at the present global installed capacity (10^6 MW(e))	0.02
One-year exposure to radiation-emitting consumer products	3
One-year production of nuclear power at the present global installed capacity ($8\ 10^4$ MW(e))	0.6
One year of nuclear explosions averaged over the period 1951-1976	30
One year's use of radiation in medical diagnosis	70

[a] The global dose commitment is expressed as the duration of exposure of the world population to natural radiation which would cause the same dose commitment. The occupational contribution is included.

[16] The time periods over which doses should be evaluated in the assessments of dose commitments are discussed in Annex A, and the detailed qualifications related to each entry in the table are given in the corresponding annexes where the calculations are presented.

103. Under the assumption of proportionality between increments in dose and risk, the relative contributions to the total radiation detriment from each of the various sources would be in proportion to the global dose commitments listed in table 3. However, the Committee stresses that comparisons based on the values given in table 3 would be misleading if the qualifications discussed in previous paragraphs of the present report were not taken into account. In particular, the dose commitments from future practices are dependent on technological developments and on the evolution of relevant regulations, both of which are difficult to predict.

104. The highest man-made contribution to the global collective dose is caused by the medical uses of radiation, and in particular by diagnostic x-ray procedures. It is important in many countries that facilities for the medical uses of radiation should be increased, and such increases would be associated with the increases in dose commitment in these countries. It is also important, however, that the exposure of patients involved in the course of radiological procedures should be kept to the minimum required for the medical purposes concerned (paras. 95-101).

105. The production of nuclear power is subject to national regulations usually based on internationally agreed principles. The global dose commitment corresponds to 0.6 days of natural radiation exposure for one year of energy production at the present installed capacity of 80 000 MW(e). Assuming that the present nuclear technology remains the same, one year of energy production at the projected nuclear installed capacity in the year 2000 ($2\ 10^6$ MW(e)) would lead to a global dose commitment equivalent to about 15 days of natural radiation exposure.

106. The collective dose commitment from nuclear explosions carried out to 1976 is equivalent to about two years of natural radiation exposures, if the contribution from carbon-14 is not included. If this contribution is included, the collective dose commitment is twice as high. The contributions from atmospheric explosions since 1970, that is, after the period covered by the Committee's previous report, have increased the dose commitments from strontium-90 and caesium-137 in the northern hemisphere by about 2 per cent and in the southern hemisphere by about 6 per cent.

Appendix I

LIST OF SPECIALIST SCIENTISTS, MEMBERS OF NATIONAL DELEGATIONS

The specialist scientists who took part in the preparation of the present report while attending Committee sessions as members of national delegations are listed below.

ARGENTINA

Dr. D. Cancio (Representative)
Dr. A. E. Placer (Representative)
Mr. C. A. Menossi

AUSTRALIA

Mr. J. R. Moroney (Representative)
Dr. D. J. Stevens (Representative)
Professor R. J. Walsh
Professor C. N. Watson-Munro

BELGIUM

Professor F. H. Sobels (Representative)
Dr. J. B. T. Aten

BRAZIL

Professor L. R. Caldas (Representative)
Dr. E. Penna-Franca

CANADA

Dr. G. C. Butler (Representative)
Mr. A. H. Booth
Mr. W. R. Bush
Dr. H. C. Rothschild
Dr. B. K. Trimble

CZECHOSLOVAKIA

Dr. M. Klímek (Representative)

EGYPT

Professor M. E. A. El-Kharadly (Representative)

FRANCE

Dr. H. Jammet (Representative)
Dr. R. Coulon
Dr. B. H. Dutrillaux
Dr. C. Lafuma
Professor P. Pellerin

GERMANY, FEDERAL REPUBLIC OF

Professor F. E. Stieve (Representative)
Professor U. H. Ehling
Professor W. Jacobi
Professor H. Kriegel
Professor L. Rausch

INDIA

Dr. A. R. Gopal-Ayengar (Representative)
Dr. K. Sundaram (Representative)

INDONESIA

Professor A. Baiquni (Representative)
Mr. M. K. Tadjudin (Representative)

JAPAN

Dr. K. Misono (Representative)
Dr. R. Ichikawa
Dr. N. Ito
Dr. S. Nakai
Dr. Y. Tazima

MEXICO

Dr. M. Martinez-Baez (Representative)
Mr. J. R. Ortiz-Magaña (Representative)
Dr. A. L. de Garay
Dr. Rebeca Magidin de Nulman

PERU

Dr. C. Guzman-Acevedo (Representative)

POLAND

Professor Z. Jaworowski (Representative)

SUDAN

Dr. A. Hidayatalla (Representative)

SWEDEN

Professor B. Lindell (Representative)
Dr. S. Bergström
Dr. K. Edvarson
Professor K. G. Lüning
Mr. J. O. Snihs
Dr. Evelyn Sokolowski
Dr. G. Walinder

UNION OF SOVIET SOCIALIST REPUBLICS

Professor A. M. Kuzin (Representative)
Dr. R. Alexakhin
Dr. Angelina Gouskowa
Dr. L. Ilyin
Dr. A. Moiseev
Dr. M. M. Saurov

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

Sir Edward Pochin (Representative)
Professor D. Carter
Mr. H. J. Dunster
Mr. F. Morley
Dr. A. G. Searle

UNITED STATES OF AMERICA

Dr. R. H. Chamberlain (Representative)
Dr. R. D. Moseley (Representative)
Dr. R. Baker
Dr. A. M. Brues
Dr. H. D. Bruner
Dr. J. H. Harley
Dr. F. Lowman
Professor H. Rossi
Dr. W. L. Russell
Dr. W. K. Sinclair
Professor A. C. Upton
Dr. H. O. Wyckoff

Appendix II

LIST OF SCIENTIFIC STAFF AND CONSULTANTS WHO HAVE CO-OPERATED WITH THE COMMITTEE IN THE PREPARATION OF THE REPORT

Dr. D. Beninson
Mr. B. G. Bennett
Dr. A. Bouville
Miss Pamela M. Bryant
Professor R. E. Ellis
Professor B. Lindell
Professor J. Liniecki
Dr. W. M. Lowder
Dr. V. Lyscov
Dr. B. J. O'Brien
Sir Edward Pochin
Dr. K. Sankaranarayanan
Professor Dr. W. Schüttmann
Dr. G. Silini
Mr. J. O. Snihs
Mr. G. A. M. Webb

Appendix III

LIST OF REPORTS RECEIVED BY THE COMMITTEE

1. Listed below are reports received by the Committee from Governments and agencies of the United Nations between 25 March 1972 and 12 April 1977.

2. Reports received by the Committee before 24 March 1972 were listed in annexes to earlier reports of the Committee to the General Assembly.

Document No.	*Country and title*
A/AC.82/G/L.	
	United States of America
1411	Global inventory and distribution of Pu-238 from SNAP-9A, 1 March 1972, HASL-250.
	Argentina
1412	Radium-226 in man.
1413	Compilation of results of monitoring Sr-90 and Cs-137 due to fall-out in the Argentine Republic.
1414	Study of a case of accidental human irradiation.
	United States of America
1415	Fall-out program quarterly summary report, 1 April 1972, HASL-249.
1415/Add.1	Appendix to HASL-249.
	New Zealand
1416	Annual report for the year 1969.
1417	Annual report for the year 1970.
1418	Environmental radio-activity in New Zealand: quarterly report July-September 1971 and Pacific Area Monitoring 31 August-31 October 1971.
	Sweden
1419	Radiostrontium-induced carcinomas of the external ear.
1420	Effect of different doses of ^{90}Sr on the ovaries of the foetal mouse.
1421	Pathologic effects of different doses of radiostrontium in mice development and incidence of leukaemia.
1422	Protective effect of cysteamine at fractionated irradiation. III. Histopathologic diagnoses at death.
	Australia
1423	Fall-out over Australia from nuclear weapons tested by France in Polynesia from June to August 1971.
	United States of America
1424	Fall-out program quarterly summary report, 1 July 1972 HASL-257.
1424/Add.1	Appendix to HASL-257.
	Switzerland
1425	Fifteenth report to the Federal Council by the Federal Commission on Radioactivity, for 1971.
	United States of America
1426	HASL-300 "HASL Procedures Manual".
1426/Add.1	Supplement to HASL-300 "HASL Procedures Manual".
1426/Add.2	Supplement to HASL-300 "HASL Procedures Manual".
	New Zealand
1427	Environmental radio-activity in New Zealand quarterly report, April-June 1971, and Pacific Area Monitoring 4 June-31 August 1971. (NRL-F/45).
	United Kingdom of Great Britain and Northern Ireland
1428	Agricultural Research Council–Letcombe Laboratory. Annual report 1971.
	United States of America
1429	Studies of the mortality of A-bomb survivors.
	Switzerland
1430	Twelfth report to the Federal Council by the Federal Commission on Radioactivity, for 1968.
	United States of America
1431	Fall-out program quarterly summary report, 1 October 1972, HASL-259.
1431/Add.1	Appendix to HASL-259.
1432	Index to fall-out program quarterly summary reports, 1 October 1972, HASL-266.

Document No.	*Country and title*
	New Zealand
1433	Fall-out from nuclear weapons tests conducted by France in the South Pacific from June to August 1971. (NRL-F/47).
1434	Annual report for the year 1971. (NRL-AR/22).
	Japan
1435	Radio-activity survey data in Japan. No. 34. February 1972.
	New Zealand
1436	Environmental radio-activity. Annual report 1971. (NRL-F/48).
	United States of America
1437	Fall-out program quarterly summary report, 1 January 1973. HASL-268.
1437/Add.1	Appendix to HASL-268.
	Italy
1438	Data on environmental radio-activity collected in Italy (January-December 1969).
	United Kingdom of Great Britain and Northern Ireland
1439	Radio-active fall-out in air and rain. Results to the middle of 1972.
	United States of America
1440	Fall-out program quarterly summary report, 1 April 1973, HASL-273.
1440/Add.1	Appendix to HASL-273.
	Japan
1441	Radio-activity survey data in Japan. No. 36. August 1972.
	Australia
1442	Strontium-90 and caesium-137 in the Australian environment during 1970 and some results for 1971.
1443	Fall-out over Australia from nuclear weapons tested by France in Polynesia during June and July 1972.
	France
1444	Radio-activity monitoring in 1972.
	United Kingdom of Great Britain and Northern Ireland
1445	Radio-activity in human diet in the United Kingdom, 1972.
1446	Assay of strontium-90 in human bone in the United Kingdom. Results for 1970.

Document No.	*Country and title*
	United States of America
1447	Fall-out program quarterly summary report, 1 July 1973, HASL-274.
1447/Add.1	Appendix to HASL-274.
	Japan
1448	Radio-activity survey data in Japan. No. 37. November 1972.
	United States of America
1449	Fall-out program quarterly summary report, 1 October 1973, HASL-276.
1449/Add.1	Appendix to HASL-276.
	Switzerland
1450	Sixteenth report to the Federal Council by the Federal Commission on Radioactivity, for 1972.
	Australia
1451	Data on levels of radio-activity in Australia, 1971-1973.
	United States of America
1452	Fall-out program quarterly summary report, 1 January 1974. HASL-278.
1452/Add.1	Appendix to HASL-278.
	Union of Soviet Socialist Republics
1453	On the possibility of using hair analysis to determine the level of polonium-210 in human bone tissue and liver.
1454	On the behaviour of caesium-137 in the turf-podzol soils of the Ukrainian polessie.
1455	Weight indicators for the development of the human foetus skeleton and its strontium and calcium content.
1456	Interaction of radio-active isotopes with organic soil materials.
1457	Strontium-90 and caesium-137 migration in the soil-vegetation cover of terminal-moraine areas.
1458	Rate of fall-out of caesium-137 and strontium-90 aerosols from the atmosphere.
1459	Migration of global caesium-137 and strontium-90 in the food chains of the population of various regions of the Ukrainian polessie.
1460	Radio-activity in the external environment, food-stuffs and the human organism in the Ukraine, 1962-1969.
1461	Lead-210, polonium-210, radium-226, thorium-228 and plutonium-239 in the lichen-reindeer-human chain in the far northern USSR.
1462	Relative mobility, state and forms of occurrence of strontium-90, stable strontium and calcium in soils.
1463	Artificial and natural radioisotopes with long half-lives in the seeds of crops in the Moscow region.

Document No.	Country and title
1464	State and forms of occurrence of radioisotopes in global fall-out.
1465	Strontium-90 content in adult bone tissue and the teeth of humans of different ages.
1466	The relation between strontium-90 and various organic soil material fractions.
1467	Lead-210 and polonium-210 absorption into the gastro-intestinal tract in rats and humans.
1468	Natural radio-active isotopes in marine fishes and sea water.
1469	Strontium-90 and caesium-137 migration in soils.
1470	Ecological and geochemical aspects of strontium-90 behaviour in forest and flood-plain ecosystems of polessies.
1471	Strontium-90 migration in water.
1472	Evaluation of the population dose of internal irradiation from global caesium-137 for some peoples inhabiting the far north of the Soviet Union.
1473	The concentration of strontium-90 in foodstuffs and its occurrence in the food consumed by the population of the Georgian SSR as a result of stratospheric fall-out.
1474	Distribution of radio-active isotopes in a reservoir system.
	United Kingdom of Great Britain and Northern Ireland
1475	Radio-active fall-out in air and rain. Results to the middle of 1973.
	New Zealand
1476	Environmental radio-activity. Fall-out from nuclear weapons tests conducted by France in the South Pacific during July and August 1973 and comparisons with previous test series.
	United States of America
1477	Serum immunoglobulin levels in atomic bomb survivors in Hiroshima, Japan.
1478	Spleen index in atomic bomb survivors.
1479	The health of atomic bomb survivors: a decade of examinations in a fixed population.
1480	Fall-out program quarterly summary report, 1 April 1974, HASL-281.
1480/Add.1	Appendix to HASL-281.
	United Kingdom of Great Britain and Northern Ireland
1481	Radio-activity in human diet in the United Kingdom, 1973.
	International Atomic Energy Agency
1482	Extracts from the Agency's programme for 1975-1980 and Budget for 1975. (GC(XVIII)/526).
1483	Annual report 1 July 1973-30 June 1974. (GC(XVIII)/525).
	New Zealand
1484	Monitoring of radio-active fall-out from the 1974 French South Pacific nuclear tests.
	France
1485	Radio-activity monitoring in 1973.
	New Zealand
1486	Fall-out from nuclear weapons tests conducted by France in the South Pacific during June and July 1972 and comparisons with previous test series.
1487	Environmental radio-activity. Annual report 1972.
1488	Environmental radio-activity. Annual report 1973.
	Argentina
1489	Radio-active fall-out due to explosions in the South Pacific in the period January-October 1973.
1490	Radio-active fall-out due to explosions in the South Pacific in the period 1971-1972.
1491	Monitoring SR-90 and Cs-137 due to fall-out in the Argentine Republic.
1492	Comparative study of the metabolism of lead-120 and polonium-120 in rats.
1493	Absorption of radiostrontium by marine organisms.
	Czechoslovakia
1494	Values of ^{90}Sr in vertebrae and femoral diaphysis of adults in Czechoslovakia in 1971.
1495	The values of the ratio ^{90}Sr in vertebrae/^{90}Sr in diaphysis in different age groups (Czechoslovakia 1969, 1970, 1971).
	New Zealand
1496	Fall-out from French nuclear tests in the South Pacific, 1974.
	Australia
1497	Data from the Australian fall-out monitoring programmes.
	Union of Soviet Socialist Republics
1498	Coefficients of the distribution of radioisotopes between the solid and liquid phases in bodies of water.
1499	Optimal interpretation of ocean radio-activity measurements.
1500	Dose commitment in mouse-like rodents living in areas of high natural radio-activity.
1501	Effect of an unseparated mixture of nuclear-fission products upon immune reactions.

Document No.	Country and title
	Union of Soviet Socialist Republics *(continued)*
1502	Strontium-90 and caesium-137 content of the food consumed by the population of the Soviet Union in 1967-1969.
1503	Determination of genetically significant doses resulting from the medical use of x-rays at Irkutsk.
1504	Immunological reactions in experimental animals under the combined effects of external irradiation and absorbed radioisotopes.
	United States of America
1505	Fall-out program quarterly summary report, 1 July 1974, HASL-284.
1505/Add.1	Appendix to HASL-284.
1506	Fall-out program quarterly summary report, 1 October 1974, HASL-286.
1506/Add.1	Appendix to HASL-286.
	United Kingdom of Great Britain and Northern Ireland
1507	Radio-active fall-out in air and rain: results to the middle of 1974.
	Japan
1508	Radio-activity survey data in Japan. No. 38. November 1973
1509	Radio-activity survey data in Japan. No. 39. September 1974.
	France
1510	Statistical study on 17,000 workers exposed to ionizing radiation during 1973.
	Belgium
1511	Radio-activity measured at Mol, 1970.
1512	Radio-activity measured at Mol, 1971.
	New Zealand
1513	Environmental radio-activity: fall-out from nuclear weapon tests conducted by France in the South Pacific from June to September 1974 and comparisons with previous test series.
	United States of America
1514	Autopsy study of blast crisis in patients with chronic granulocytic leukaemia, Hiroshima and Nagasaki, 1949-1969.
1515	Mortality in children of atomic bomb survivors and controls.
1516	Fall-out program quarterly summary report, 1 January 1975, HASL-288.
1516/Add.1	Appendix to HASL-288.
1517	Environmental quarterly, 1 April 1975, HASL-291.

Document No.	Country and title
1517/Add.1	Appendix to HASL-291.
1518	Index to fall-out program quarterly summary reports, 1 April 1975, HASL-292.
1519	Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: demographic, physical, dietary and biochemical characteristics.
1520	Environmental quarterly, 1 July 1975, HASL-294.
1520/Add.1	Appendix to HASL-294.
	France
1521	Radio-activity monitoring in 1974.
	Germany, Federal Republic of
1522	Environmental radio-activity and radiation levels, annual report 1973.
	United Kingdom of Great Britain and Northern Ireland
1523	Radio-activity in human diet in the United Kingdom, 1974.
	United States of America
1524	Environmental quarterly, 1 October 1975, HASL-297.
1524/Add.1	Appendix to HASL-297.
1525	Environmental quarterly, 1 January 1976, HASL-298.
1525/Add.1	Appendix to HASL-298.
	New Zealand
1526	Environmental radio-activity: annual report 1974.
	United States of America
1527	A review of 30 years of study of Hiroshima and Nagasaki atomic bomb survivors.
1528	Environmental quarterly, 1 April 1976, HASL-302.
	Japan
1529	cancelled
1530	cancelled
1531	Estimation of population doses from diagnostic medical examinations in Japan, 1974 (1 to 4).
1532	Estimation of population doses from brachytherapy in Japan.
	Switzerland
1533	Eighteenth report to the Federal Council by the Federal Commission on Radioactivity, for 1974.
	United Kingdom of Great Britain and Northern Ireland
1534	Radio-active fall-out in air and rain: results to the end of 1975.

Document No.	Country and title
	Union of Soviet Socialist Republics
1535	A methodical approach to the evaluation of dose commitments from osteotropic isotopes, taking into consideration changes in metabolism parameters with organism growth.
1536	Investigation and standardization of radioactivity in building materials.
1537	Materials for the standardization and norms of maximum permissible levels of radio-active isotopes of iodine in the human organism.
	United States of America
1538	Environmental quarterly, 1 July 1976, HASL-306.
1538/Add.1	Appendix to HASL-306.
	United Kingdom of Great Britain and Northern Ireland
1539	Radio-activity in human diet in the United Kingdom, 1975
	France
1540	Radio-activity monitoring in 1975.
	Japan
1541	Radio-activity survey data in Japan. No. 40. November 1975.
	United States of America
1542	Environmental quarterly, 1 October 1976, HASL-308.
1542/Add.1	Appendix to HASL-308.
	Germany, Federal Republic of
1543	Environmental radio-activity and radiation levels in 1974.
1544	Environmental radio-activity and radiation levels, annual report 1974.
	New Zealand
1545	Environmental radio-activity: annual report 1975. (NRL-F/55).

Document No.	Country and title
	Switzerland
1546	Nineteenth report to the Federal Council by the Federal Commission on Radioactivity, for 1975.
	Czechoslovakia
1547	The values of the ratio ^{90}Sr in vertebrae/^{90}Sr in diaphysis in different age groups.
	United States of America
1548	Environmental quarterly, 1 January 1977, HASL-315.
1548/Add.1	Appendix to HASL-315.
	United Kingdom of Great Britain and Northern Ireland
1549	The data submitted by the United Kingdom to UNSCEAR for the 1977 report to the General Assembly.
	Union of Soviet Socialist Republics
1550	The kinetics of disease and recovery processes occurring in fresh-water fish embryos incubated in a radio-active environment.
1551	Some properties of strontium-90 migration in food chains in the conditions of the far north.
1552	Radio-activity of the external environment and food-stuffs in the Ukrainian SSR in 1970-1974.
1553	Effect of pesticide (DDT) poisoning on sodium and metabolism kinetics in rats.
1554	Tritium content of liquid media and air in working areas of USSR atomic power stations.
1555	Caesium-137 and strontium-90 in the lichen-reindeer-human chain in the far northern USSR.
1556	Strontium-90 from global fall-out in the bone tissue of the Soviet population, 1970-1973.
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ANNEX A

Concepts and quantities in the assessment of human exposures

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Introduction

1. The purpose of this Annex is to define the concepts and quantities that are used by the Committee in collating and reporting data on human radiation exposures and to qualify their use. These concepts and quantities can be unequivocally defined, but a number of basic biological assumptions have to be made to justify their use for particular purposes. While some of these assumptions are presented in this Annex, a more extensive discussion, which a fuller understanding of the qualifications requires, can be found in Annexes G, H, I and J, which deal with the biological effects of radiation.

2. The concepts and quantities discussed in this Annex are designed for the purpose of dealing with low doses of radiation, as usually encountered in occupational and population exposures.

I. BASIC CONCEPTS

3. The mean absorbed dose in various human organs or tissues is the physical quantity usually taken as a basis for radiation risk estimates, and it is derived by averaging the absorbed dose over the mass of the organ or tissue under consideration. The absorbed dose[1] is defined as the mean energy imparted per unit mass at the point of interest (3). In this report, the word "dose", unless specifically qualified, refers to the mean absorbed dose over an organ or tissue.

4. The use of absorbed dose in tissues as a basis for risk assessments makes it necessary to present separately

[1] The SI unit of absorbed dose is the joule per kilogram, the special name for the unit being the gray (1 Gy = 1 J/kg). In the present document use is made of the previous special unit for absorbed dose, the rad (1 rad = 0.01 Gy).

those components of the absorbed dose which are due to high-LET[2] radiation, with specification of radiation type. For low-LET contributions to the absorbed dose, which comprise the most common types of human exposures, it is assumed that the influence of radiation quality and dose rate is negligible.

5. The relations between doses in tissues and risks of deleterious effects are complex; they are presented in detail and discussed in Annexes G, H, I and J. If the effects in laboratory experiments under controlled conditions, as reported in Annexes H, I and J, are plotted against doses, many different types of curves are obtained, some linear and some curvilinear. A significant consideration is that in heterogeneous human populations of all ages and states of health and subject to a number of insults acting with radiation, there may be especially sensitive individuals, in which case a threshold may be less probable. In research it is appropriate to analyse dose-effect curves and factors relating to them in detail in order to gain an insight into the mechanisms involved. For purposes of making risk estimates in humans, however, a different approach has been employed. As described in Annex G, most of the effects of radiation in human beings have been observed at doses (some tens or hundreds of rads) that are considerably higher than those near natural background levels. To estimate risks at low doses the incidence of effects at high dose levels is divided by the dose to give an incidence rate per unit dose, which presupposes that there is proportionality between dose and effect down to the lowest doses. This assumption will be made for present purposes, recognizing that it is also possible that there could be a much lower effect, and perhaps none, at low doses. These considerations indicate that the rates of incidence calculated in these Annexes from observations at high doses may overestimate the effects of low doses in the millirad range.

6. In the present state of knowledge, the possibility that the dose-effect curve has a zero slope at these low doses cannot be ruled out. However, at doses around natural background it is assumed that an approximate proportionality exists between dose increments and corresponding increments of risk, provided that the increments are small. The additional assumption is made that the severity of each type of effect is independent of dose at low doses.

7. In the case of inhomogeneous dose distributions within an organ or tissue, the linear assumption implies that the inhomogeneity does not affect the relationship between risk and absorbed dose, provided that local doses are in the range in which proportionality applies and are small enough not to cause significant cell sterilization. If the latter condition is not met, cell sterilization could reduce the risk per unit dose, and assessments based on the mean absorbed dose over the entire organ or tissue might tend to overestimate the risk.

[2] LET (linear energy transfer) is used in the unrestricted sense as equivalent to the linear collision stopping power (3). Low-LET radiation, in this report, means radiation for which the linear collision stopping power in water is less than 3.5 keV/μm.

II. EXPOSURE OF POPULATIONS

8. When population groups are exposed to radiation from several sources, it is often interesting to compare the exposures and, under some assumptions, to assess the relative importance of the potential hazards due to each source. If the population groups were homogeneously and simultaneously exposed to radiation from these sources, the dose due to each source would give useful information about the relative importance of the source. In the more general case, however, the size of the exposed population and the distribution of doses over this population vary for different sources. Furthermore, the distribution of the doses in time is an important factor to be considered since it may also vary for different sources.

A. THE COLLECTIVE DOSE AND DOSE COMMITMENT

9. Practices involving radiation sources can give rise to a distribution of dose rates in the exposed population. No single quantity can represent adequately the distribution in all possible situations. In some cases, however, a useful quantity for this purpose is the collective dose rate. The collective dose rate $\dot{S}$ in a population from a practice or source is defined by the expression

$$\dot{S} = \int_0^\infty \dot{D}\, N_{\dot{D}}(\dot{D})\, d\dot{D}$$

where $N_{\dot{D}}(\dot{D})$ is the population spectrum in dose rate, $N_{\dot{D}}(\dot{D})\, d\dot{D}$ being the number of individuals receiving a dose rate in a specified organ or tissue, due to a source, in the range $\dot{D}$ to $\dot{D} + d\dot{D}$. Integrals of this type are usually referred to as "weighted products", the collective dose rate from a source being therefore the weighted product of dose rate due to the source and number of individuals in the exposed population. The collective dose rate is thus not a dose rate in the sense of absorbed dose rate as defined in ICRU report 19 (3). The actual population exposed should be specified whenever possible.

10. The collective dose in a population over a specified period of time is defined as the time integral of the collective dose rate. The collective dose is an extensive quantity that can apply to one person, to a population group or to the whole world population. It is expressed in man rad. The period of integration depends upon the purpose of the assessment. If the period of integration is short, the population may be assumed to be composed of the same individuals during the whole period. Conceptually, however, the population for which the collective dose is assessed could comprise successive generations.

11. The collective dose in a defined group of individuals can also be assessed as the weighted product of individual dose and number of individuals:

$$S = \int_0^\infty D\, N_D(D)\, dD$$

where $N_D\,(D)\,dD$ is the number of individuals receiving a dose, in a specified organ or tissue, in the range D to $D + dD$. The defined group may comprise individuals who live at different times or individuals living in a given year, depending upon the purpose of the assessment.

12. The average dose to an individual in the defined exposed group due to a source, called the *per caput* dose $\bar{D}$ from that source, can be calculated as

$$\bar{D} = \int_0^\infty D\, N_D(D)\, dD \Big/ \int_0^\infty N_D(D)\, dD$$

and since $\int_0^\infty N_D\, dD = N$, the total number of individuals in the defined group, it follows that $S = \bar{D}N$.

13. The collective dose and the collective dose rate are particularly useful quantities in source-related assessments. The collective dose rate from a source k, $\dot{S}_k$, is obtained by including in the population under consideration all individuals simultaneously being exposed by the source k. As the value of $\dot{S}_k$ remains unchanged if the population is made arbitrarily larger than the actual exposed group by adding unexposed individuals, it is convenient for the purpose of assessing the collective dose rate from a source to define the population as the world population. This specification is not necessary when the exposed group is small and well defined in a way that every exposed person can be accounted for.

14. In some cases, the world population may be conveniently subdivided into several groups labelled by $j = 1, 2, 3, \ldots$, the collective dose rate then being calculated as

$$\dot{S} = \sum_j \int_0^\infty \dot{D}\, N_{j,\dot{D}}(\dot{D})\, d\dot{D} = \sum_j \dot{S}_j$$

where $N_{j\dot{D}}\,(\dot{D})$ is the population spectrum in dose rate of group j, and $\dot{S}_j$ is the contribution of group j to the collective dose rate. The collective dose rate from source k can be assessed as

$$\dot{S}_k = \sum_j \bar{\dot{D}}_{k,j}\, N_j$$

where $\bar{\dot{D}}_{kj}$ is the *per caput* dose rate contributed by source k in group j, and N_j is the number of individuals in group j. All these quantities are functions of time.

15. In order to have a measure of the total exposure of the population caused by a source, the collective dose commitment is used. The collective dose commitment S_k^c due to a given event, decision or finite practice k is defined as the infinite time-integral of the collective dose rate, $\dot{S}_k(t)$, caused by that event, decision or finite practice:

$$S_k^c = \int_0^\infty \dot{S}_k(t)\, dt$$

As discussed above, the collective dose rate $\dot{S}_k(t)$ at a given time can be assessed by integration or summation over the world population.

16. As in previous reports, the Committee has also found it convenient to define a *per caput* quantity for the purpose of assessing the total exposure resulting from a given event, decision or finite practice. This quantity is the dose commitment D_k^c, defined as the infinite time-integral of the *per caput* dose rate due to event, decision or finite practice k:

$$D_k^c = \int_0^\infty \bar{\dot{D}}_k(t)\, dt$$

where the *per caput* dose rate $\bar{\dot{D}}_k(t)$ is the quotient of the collective dose rate and the population size at time t, i.e., $\bar{\dot{D}}_k(t) = \dot{S}_k(t)/N(t)$. If the population size remains unchanged over the time period contributing to the integral, we have $S_k^c = D_k^c N$.

1. Use of the collective dose and collective dose commitment in detriment assessments

17. Under the assumptions given in paragraphs 5 and 6, the collective dose can be used in assessments of the relative detriments from several radiation sources. ICRP has introduced the concept of "detriment" as a quantitative measure of the expected harm in a group of people as a result of a given radiation exposure (4). The detriment is defined as the mathematical expectation of harm, taking into account the probability of occurrence of each type of deleterious effect and the severity of the effect. If the group is composed of N persons and if p_i is the probability of incurring the effect i, the severity of which is expressed by a factor g_i, the detriment G is

$$G = N \sum_i p_i g_i$$

18. Considering only individual exposures to the same type of radiation, and making the assumption that the probability of each effect i attributable to the source under consideration is directly proportional to the dose from that source ($p_i = r_i D$, where r_i is the risk factor) and the further assumption that the severity of the effects is independent of their frequency in the dose range of interest, the health detriment in a homogeneously exposed group becomes $G = ND\Sigma_i r_i g_i$. In the general case where there is a distribution of doses over the world population, the detriment to health due to source k is given by

$$G_k = \int_0^\infty \sum_i (D_k r_i g_i)\, N_{D_k}(D_k)\, dD_k = S_k \sum_i r_i g_i$$

since the sum $\Sigma_i r_i g_i$ is independent of the dose distribution under the assumptions made.

19. The validity of this expression depends therefore on the assumed linearity, with no threshold, between dose and risk, as has been discussed in paragraph 5. The Committee has stressed that this is a cautious assumption, the validity of which has not yet been established. The risk factors r_i may vary both with the previously accumulated dose to which the dose D from the source under consideration is added and also with the dose rate and radiation quality. It cannot be assumed that the values of r_i which can be derived from observations at high doses and dose rates also apply to small dose increments at low dose rates.

20. However, for practices resulting in small dose increments to doses of similar order of magnitude, e.g.,

small dose increments above the natural background, as well as for the background doses as such, and provided there is no large dose-rate dependence, it may be assumed that, in the first approximation, one and the same value of $\Sigma_i r_i g_i$ would apply. In these conditions it would be possible to assess the *relative* detriment from two practices as the ratio of their collective doses: $G_1/G_2 \simeq S_1/S_2$.

21. The use of the collective dose for relative detriment assessments would also be valid in cases where the practices under comparison generate similar dose distributions over the population. Furthermore, if the real dose-risk relationships have an approximate proportional region, the comparison of collective doses would be valid in cases in which all the individual doses fall in the region of proportionality.

22. The evaluation of the relative health detriment resulting from practices which deliver the doses over quite different times can be done, provided that the assumptions of paragraphs 20 or 21 apply, by comparing the collective dose commitments from these practices.

2. Use of the dose commitment in predictions relating to continued practices

23. Both the dose commitment and the collective dose commitment are usually proportional to the size of the originating event. For example, if the event under consideration is the release of a quantity of a radionuclide to the environment, the dose commitment and the collective dose commitment are proportional to the activity released, provided all other influencing factors remain constant.

24. In these conditions, the values of the *per caput* dose rate at given times after the originating event are also proportional to the size of that event. It is therefore possible to define for a type of practice a function $\bar{D}_1(t)$, giving the *per caput* dose rate per unit of originating event (e.g., per unit of activity released) as a function of time elapsed since the event. It is consequently possible to define the dose commitment per unit originating event D_1^c, and the collective dose commitment per unit originating event S_1^c, as

$$D_1^c = \int_0^\infty \bar{D}_1(t)\,dt$$

and

$$S_1^c = \int_0^\infty \bar{D}_1(t)\,N(t)\,dt$$

where $N(t)$ is the population size. If the population size remains constant over the period contributing to the integral, we have $S_1^c = ND_1^c$. In the more general case, the calculation of collective dose commitments often requires the use of a population growth model. For short projections into the future an approximate exponential growth has been assumed in this report. On the other hand, for exposures delivered over very long periods of time, the assessments are based on an assumed upper limit for the world population of 10^{10} individuals.

25. A continued practice causing radiation exposures can be considered as a sequence of originating events discussed in the previous paragraph. The dose commitment per unit practice can be used for predictions of the *per caput* dose rate in the future for the case of a repeated practice at a known and constant rate R. The *per caput* dose rate will increase and for short-lived radionuclides eventually reach a steady value $\bar{D}_\infty$, which can be calculated by integrating the dose rate contributions at an arbitrary time T, when a steady state has been reached:

$$\bar{D}_\infty = \int_{-\infty}^{T} R\,\bar{D}_1(T-t)\,dt = R\int_0^\infty \bar{D}_1(t)\,dt = RD_1^c$$

In the simplified case of a constant population size, we have $S_1^c = ND_1^c$, and therefore $\bar{D}_\infty = (R/N)S_1^c$. In many cases it is possible to make rough projections of the practice rate *per caput* R/N. It is then possible to predict the maximum *per caput* dose rate that will be experienced in the future due to the expanded and continuing practice.

26. For doses delivered over a very long time after a single originating event, it would not be realistic to postulate a continued practice for the long times required for the *per caput* dose rate to approach the steady state value. Again, it is interesting to assess the maximum *per caput* dose rate, $\bar{D}_{max}$, caused in the future by the practice. If the practice continues to a time τ at rate R and then is discontinued, the *per caput* dose rate at any time $T > \tau$ is given by

$$\bar{D}(T) = \int_0^\tau R\,\dot{D}_1(T-t)\,dt = R\int_{T-\tau}^{T} \dot{D}_1(t)\,dt$$

It can be shown that if the function $\bar{D}_1(t)$ has a single maximum at time θ and then declines monotonically, the maximum *per caput* dose rate occurs at a time T_m such that $\tau < T_m < \tau + \theta$. Since in most practical cases $\tau >> \theta$ (and therefore $T_m \simeq \tau$), the maximum *per caput* dose rate is approximately given by

$$\bar{D}_{max} \simeq R\int_0^\tau \bar{D}_1(t)\,dt$$

27. The integral $\int_0^\tau \bar{D}_1(t)dt = D_1^\tau$ does not relate to the total detriment per unit practice, but it is useful in assessing the maximum *per caput* dose rate that will result from a continuing but finite practice. If the population size remains constant during the time contributing to the integration, it is convenient to express the maximum *per caput* dose rate as a function of the practice rate *per caput* R/N as

$$\bar{D}_{max} = (R/N)\,S_1^\tau$$

where $S_1^\tau = ND_1^\tau$ will be referred to in this report as the incomplete collective dose commitment per unit practice.

B. ENVIRONMENTAL MODELS USED IN THE ASSESSMENT OF DOSE COMMITMENTS

28. The chain of events leading from the primary release of radioactive substances to the irradiation of human tissues can be schematically represented by compartment models, in which the rates of transfer of

radioactivity between compartments are specified by constants or by time functions. The use of compartment models, even when very complex, implies considerable simplification of the real transfer processes.

29. Since the dose commitment from a given source is the integral over infinite time of the *per caput* dose rate resulting from the input, steps in the sequence from input to the final dose commitment can be conveniently described in terms of the quotient of the infinite time-integral of the appropriate quantity in step *j* of the sequence to the infinite time-integral of the appropriate quantity in the preceding step *i*. These quotients define the *transfer factors* P_{ij} in the pathway from input of radionuclides into the environment to the subsequent radiation dose in man:

$$P_{ij} = \int_{-\infty}^{\infty} M_j(t)\,dt \Big/ \int_{-\infty}^{\infty} M_i(t)\,dt$$

where P_{ij} is the factor relating compartment j and the preceding compartment i, and $M_i(t)$ and $M_j(t)$ are the appropriate quantities (e.g. activity concentrations) in the respective compartments at time t. The factors P_{ij} must be expressed in terms of the dimensions of the two quantities they link.

30. The network of pathways linking the release of radioactive material (input) to the dose commitment consists of pathways in series and in parallel. The total transfer factor of a branch (pathway in series) is the product of the transfer factors involved; the total transfer factor of several branches in parallel is the sum of the transfer factors of the branches. The dose commitment, therefore, can be assessed from the input Y by the relation

$$D^c = Y \sum_{\text{parallel}} \prod_{\text{series}} P$$

Transfer factors, their estimation for a number of nuclides, and the uncertainties involved in this estimation because of the variability of the transfer processes were discussed extensively in the 1969 and 1972 reports of the Committee (10, 11). The essential information from those reports is summarized in the relevant annexes of this report.

III. QUANTITIES USED IN THE ASSESSMENT OF ORGAN DOSES

31. In assembling information on radiation levels, the Committee, as in its previous reports, has selected primary data which can be used for the derivation of absorbed doses in human tissues, collective absorbed doses and absorbed dose commitments. Data which describe conditions of exposure to radiation in a useful way for the Committee's purposes are released activities[3] and activity concentrations, from which internal or external irradiation may be assessed, and quantities specifying ambient radiation levels, from which external irradiation may be assessed.

[3] The SI unit of activity is the second to the power minus one, the special name of the unit being the becquerel (1Bq = 1 s^{-1}). In the present document use is made of the previous special unit for activity, the curie (1 Ci = 3.7 10^{10} Bq).

A. INTERNAL IRRADIATION

32. In the case of internal irradiation, the doses in the organs of interest of a given individual may be estimated from one or more of the following basic determinations:

(a) Measurements of activity concentrations in the environment and in diet components, leading to estimates of the intake and, by the use of appropriate metabolic models, to estimates of the residence of the activity in the tissues of interest;

(b) Assessments of the activity in the body or in the relevant tissues, made on the basis of measurements of radiation emitted from the body or of measurements of activity in tissue samples;

(c) Measurements of the activity of excreta or exhaled air leading, by the use of appropriate metabolic models, to estimates of the activity in the body.

33. The use of these three types of information for the purpose of dose assessments requires the postulation of models to describe the body and tissue radioactive contents as a function of time. For example, for contamination through the diet, the activity in the body or a tissue, as a function of time, is given by

$$Q(t) = \int_0^t I\,C(\tau)\,A\,r(t-\tau)\,d\tau$$

where $Q(t)$ is the activity in the body or tissue of interest at time t,
I is the diet consumption per unit time,
$C(\tau)$ is the activity concentration in the diet at time τ,
A is the fractional absorption into blood of the ingested activity, and
$r(t)$ is the fraction of the activity absorbed into blood that is retained in the body or the tissue under consideration at a time t after a single uptake.

The basic data for this equation are the diet concentrations as a function of time. Similar formulations can be derived to make use of basic information of types *(b)* and *(c)* referred to in paragraph 32.

34. For the purpose of assessing dose commitments, the population weighted average of $Q(t)$ is needed. The parameters of the expression given in paragraph 33, as well as the function $r(t)$, are usually functions of age, and this must be taken into account in the derivation of the *per caput* value $\bar{Q}(t)$.

35. The dose commitment is calculated as

$$D^c = K \int_0^{\infty} \bar{Q}(t)\,dt$$

where K is a conversion factor appropriate to the population group. The conversion factors involved in the calculation of absorbed dose from $\int_0^{\infty} Q(t)dt$ do not necessarily relate to the same tissue or organ for which $Q(t)$ is given. For example, the dose in the red bone marrow and the endosteal cells may be caused by irradiation from radionuclides in bone. Also, different

parts of one and the same organ or tissue may receive different doses, but as already mentioned, it is the *mean* dose in the specified organs and tissues which is of interest to the Committee.

B. EXTERNAL IRRADIATION

36. The assessment of organ doses from external irradiation requires, in principle, the knowledge of the energy and angular differential distribution of the fluence rate of each component of the radiation field. These differential distributions can be obtained by spectrometric measurements, but in general only calculated values, for cases where the source distributions are known, are available.

37. Most reported field measurements provide values of integral quantities, usually describing the field in the absence of an exposed person—in "receptor-free" conditions. These quantities, if specified unambiguously, can be used for the assessment of organ doses of a person introduced in the radiation field, provided some information is available on the characteristics of the field. The present report uses two quantities to describe receptor-free irradiation situations: the absorbed dose rate in air $\dot{D}_a$ and the absorbed dose index rate $\dot{D}_I$.

38. The absorbed dose rate in air $\dot{D}_a$ is used in this report to describe environmental exposure situations resulting from gamma-emitting nuclides, and it is unambiguously specified when it may be assumed that full secondary electron equilibrium exists in air. In this condition, the absorbed dose rate in air can be derived from the exposure rate $\dot{X}$ as $\dot{D}_a = a\dot{X}$, where the value of the conversion factor a is 0.869 rad/R. The absorbed dose rate in air will usually be expressed in microrad per hour.

39. For describing receptor-free irradiation situations due to cosmic radiation it is convenient to select a quantity which, for the purpose of comparison, could equally be used at any altitude and in space. The absorbed dose rate can be used for this purpose but its magnitude depends upon the geometry of the material in which it is determined. Selection of a specified geometry for such a determination provides an unambiguous value for the absorbed dose rate. Such a specified geometry is contained in the definition of the absorbed dose index rate $\dot{D}_I$ which is used in this report to describe receptor-free environmental radiation levels due to cosmic rays. The absorbed dose index rate is defined as the maximum absorbed dose rate that would occur in a 30-cm diameter tissue-equivalent sphere if the sphere were located with its centre at the point of interest (3). The $\dot{D}_I$ also will usually be expressed in microrad per hour.

40. From the environmental quantities, the absorbed doses in a number of human organs of interest will be assessed, usually as annual doses or as dose commitments per unit practice. These assessments necessitate a number of assumptions, both about factors which influence the depth dose calculations and on the periods of time during which persons are exposed to the various radiation fields.

41. When the receptor is located in the region of interest, the procedure of assessing organ dose rates from absorbed dose rates in air involves the following considerations: Absorbed dose rates in air are multiplied by the *s*-factor[4] to transform them to tissue dose rate. The change from receptor-free conditions to the situation where a person is present in the radiation field will influence the field at the surface of the body. Back-scattered radiation may increase the dose rate at the surface, but the body will also act as a shield and reduce the dose rate. The influence of body shielding will depend upon the location of the organ of interest, and the energy and angular distribution of the radiation.

42. Except for the rare case where the radiation field is monodirectional and the irradiated person is not moving, the "depth" of an organ would be the weighted average of the distance in the body that would have to be penetrated by rays entering from different directions. The difference in absorbed dose rate at the surface of the body when the radiation is monodirectional and exposing the surface under consideration, and when the field is isotropic, may be substantial. The ratio of the "monodirectional dose rate" to the "isotropic dose rate" at any depth, when the fields produce one and the same absorbed dose rate in air under receptor-free conditions, may be referred to as the isotropy factor k at that depth. The isotropy factor cannot exceed 2 for points near the surface of the body, and it approaches 1 near the centre of the body and at all locations if the absorbed dose rate is constant throughout the body.

43. The assessment of organ doses requires therefore that the absorbed dose in air (after having been transformed to tissue dose by multiplication by the *s*-factor) be then multiplied by the depth transmission factor d, the backscatter factor b and a shielding factor, which would be the inverse of the isotropy factor $1/k$. The absorbed dose rate in an organ would be

$$\dot{D}_{org} = sbdk^{-1}\dot{D}_a = sg\dot{D}_a$$

where the product of the factors b, d and k^{-1} could be called the geometry factor g.

44. In the 1972 report, the Committee referred to gonad dose calculations by Bennett (2), indicating that $sg = 0.82$ for external outdoor exposure (2π geometry), and to gonad dose measurements by Spiers and Overton (9), indicating that $g = 0.63$ ($sg = 0.69$) for exposure indoors. By transport calculations, O'Brien and Sanna (6) have assessed absorbed doses in several organs (in the MIRD phantom (8)) per unit exposure, as a function of the energy of gamma rays. Combining these calculations with the environmental gamma-ray exposure spectrum in energy (1), they have calculated organ absorbed doses per unit exposure for environmental conditions. From these calculations sg for gonads can be estimated to be about 0.8 in males and about 0.55 in females. As the mathematical phantom, however, uses the Reference Man mass (5) in all calculations, the factor for female gonads is somewhat underestimated. O'Brien (7) has

[4] The *s*-factor is the ratio of the mass energy absorption coefficients for tissue and air. A value of $s = 1.10$ is correct within ± 1 per cent for photon energies between 0.1 and 4 MeV for soft tissues.

recently calculated the organ doses for a female phantom. From these calculations the value of *sg* for female gonads is estimated to be about 0.6.

45. If the occupancy factor (i.e., the fraction of the year during which a person is actually exposed to a given source) is q, the annual gonad dose, assuming constant environmental irradiation levels, can be derived from the absorbed dose rate in air as

$$D = c_\gamma q \dot{D}_a$$

where c_γ = 7.2 mrad μrad^{-1} h for outdoor exposures and 6.0 mrad μrad^{-1} h for indoor exposure, using the values of *sg* given in the 1972 report. The calculations of O'Brien and Sanna (6) give a value of *sg* equal to about 0.7 for the ratio between the average absorbed dose in the body and the absorbed dose in air, and show that the doses in other organs of interest to the Committee are very nearly equal to the gonad dose. It will be assumed that the equation given above applies also to organs such as the breast, the lung and the red bone marrow.

46. In the case of exposures to cosmic radiation, it will be assumed that the absorbed dose index rate represents sufficiently well the relevant organ dose rates in an individual introduced at the location of consideration. If the occupancy factor for that location is q, the annual organ dose can be derived from the absorbed dose index rate, assuming constant environmental levels, as

$$D = c_c q \dot{D}_I$$

where D is the annual organ dose, and c_c is 8.76 mrad μrad^{-1} h.

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ANNEX B

Natural sources of radiation

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Introduction

1. Man has always been exposed to ionizing radiation from various natural sources. A distinguishing characteristic of this natural irradiation is that it involves the entire population of the world and that it has been experienced at a relatively constant rate over a very long period of time. On the other hand, the exposure to natural radiation sources varies substantially from place to place and even locally, for example within one building.

2. The assessment of the radiation doses in man from the natural sources is of particular importance because natural irradiation is the largest contributor to the collective dose of the world population. Furthermore, the study of the extent of the variation of natural radiation with location is of practical interest, since it may influence attitudes towards any additional exposure caused by man-made sources.

3. The various natural radiation sources include:

(a) External sources of extraterrestrial origin (cosmic rays) and external sources of terrestrial origin, i.e., the radioactive nuclides present in the crust of the earth, in building materials and in the air;

(b) Internal sources, comprising the naturally occurring radionuclides which are taken into the human body. The concentration of a few radionuclides in the body, such as naturally occurring ^{14}C and ^{40}K, are relatively constant and independent of their concentration in diet or in air, because they are isotopes of elements with practically constant specific activity, which are homeostatically controlled in the human body. For the majority of the natural radionuclides, on the other hand, these two conditions do not apply and their concentrations in the body vary according to the concentrations in the environment.

4. As explained in Annex A, the primary data selected for this document are those that can be used in assessments of absorbed doses in various organs and tissues of the human body. In some instances the data can be used directly in the calculations of dose; in other cases their use is indirect, constituting the basis for the assumptions used for the calculations.

5. In addition to the exposures to natural radiation sources experienced both outdoors and indoors, this Annex, in chapter IV, discusses situations in which the exposure to natural sources is enhanced as a result of technological developments. It is sometimes difficult to separate normal and technologically enhanced radiation exposure, since this separation depends on what is considered to be a normal exposure. However, because of current interest, chapter IV considers several examples of what might reasonably be deemed technologically enhanced exposures, including those resulting from irradiation by cosmic rays in aeroplanes, the irradiation resulting from the phosphate industry, and the irradiation due to the release of naturally occurring radionuclides from coal-fired power plants.

6. The exposures from widely used consumer products are dealt with in an appendix. While they cannot be described as cases of technologically enhanced exposures to natural sources, they present several similarities to these exposures, and in many cases the radionuclides involved are naturally occurring.

I. EXTERNAL IRRADIATION

A. COSMIC RAYS

7. The high-energy radiations that enter the earth's atmosphere from outer space are known as primary cosmic rays. When they interact with atomic nuclei in the atmosphere, secondary particles and electromagnetic radiation are produced, and these are called secondary cosmic rays.

1. Primary cosmic rays

8. The origin of the primary cosmic rays is still not completely determined. However, it is known that most of the observed radiation originates in our galaxy. In addition to the galactic cosmic rays, the sun produces solar cosmic rays related to solar flares.

(a) *Primary galactic cosmic rays*

9. Primary galactic cosmic rays largely consist of high-energy protons which enter the solar system from interstellar space, together with ^{4}He ions in the proportion of about 10 per cent. Much smaller

proportions of heavier particles are also present, together with electrons, photons and neutrinos. The energy spectrum of the primary cosmic-ray protons has been measured both in and above the earth's atmosphere by means of instruments carried on balloons and spacecraft. The energy spectrum is peaked around 300 MeV per particle and is very broad, extending from about 1 to 10^{14} MeV. Above about 1000 MeV, the proton flux density decreases markedly with increasing energy. Primary cosmic-ray protons with energies above 100 MeV are believed to be essentially of galactic origin, while those with energies below 20 MeV are of solar origin (187).

10. Although all cosmic rays with energies below 10^{12} MeV have their origin within the galaxy (59), the details of their origin are not yet known. From the elemental distribution present, it is thought that cosmic-ray nuclei are synthesized in supernova events, and are subsequently accelerated by undetermined processes, for which several theories have been postulated. From the abundance in primary cosmic rays of Fe, Co and Ni nuclei, some of which have undergone decay by electron capture, it is inferred that there is a time lapse of more than one year between nucleosynthesis and acceleration to high energy (59). The average "age" of galactic cosmic rays reaching the solar system, which alternatively may be called the escape lifetime from the galaxy, can be estimated from the abundance of ^{10}Be and ^{36}Cl. The most recent measurements indicate a lifetime between 2.5 10^6 and 33 10^6 y (235).

11. From measurements of the products of the reaction of high-energy cosmic rays with nuclei (spallation products) in meteorites, estimates have been made of the changes in cosmic-ray flux density with time. Within a factor of two, the galactic cosmic-ray flux density has remained constant over the past 10^9 y (304). The flux density averaged over the past 400 y is within 10 per cent of that averaged over the past 4 10^5 y, which in turn is some 50 per cent higher than that averaged over the past 10^9 y. This latter variation may be due to a cosmic-ray gradient perpendicular to the galactic plane.

12. Within the solar system, the galactic cosmic-ray flux density increases with increasing distance from the sun. The radial gradient of the flux density has been determined from spallation products in meteorites (304) and more recently by direct measurement on board the Pioneer 10 and 11 spacecraft (225, 227). For cosmic-ray particles with energies above 30 MeV per nucleon, the gradient is about +5 per cent per AU (1 AU = 149.6 10^6km).

13. Below 10^4 MeV, the primary flux density is modified by two processes. In the first, it is affected by the earth's magnetic field, which deflects lower-energy charged particles back into space. This effect is dependent on the geomagnetic latitude, so that the flux density of low-energy protons at the top of the atmosphere is greater at the poles than in equatorial regions. Thus, the ionization produced at a given altitude in the atmosphere, which is a function of the "atmospheric depth", the mass of air above a unit of area at that altitude, is also latitude dependent (fig. I).

14. In the second process, the flux density of the galactic low-energy protons in the upper atmosphere varies with the 11-year solar cycle, the flux density being at a minimum during times of maximum solar activity and passing through a maximum during the period of low solar activity. The phenomenon is known as modulation (89, 313). The modulation of galactic cosmic rays with the solar cycle has been observed for many years. It has been proposed that it is due to changes in the flux of magnetic bubbles (large volumes of ionized gas) of solar origin (256). Solar flares blast open the overlying solar magnetic field, thus enabling corona particles access to the interplanetary medium, the large bubbles so formed moving away from the sun with velocities of 200-1000 km s^{-1}.

15. During the 11-year solar cycle the density of these magnetic bubbles in interplanetary space undergoes a cyclical change, reaching a maximum during increased solar activity and a minimum during the period of the quiet sun. Because galactic cosmic-ray particles with energies less than 10^4 MeV are deflected away from the inner solar system by these magnetic irregularities, an 11-year modulation of the galactic cosmic-ray flux density is produced at the earth.

(b) *Primary solar cosmic rays*

16. Solar flares are observed as bright flame-like protuberances on the sun's surface which reach maximum brightness in about 10 min and then slowly subside (74). They tend to occur more frequently during periods of sun-spot maximum. Large amounts of energy in the form of visible, ultraviolet and x-radiation are emitted, and in the largest flares large quantities of charged particles, mainly protons and alpha particles, are also released. Measurements indicate that most of the protons have energies in the range 1-40 MeV.

17. Because the solar cosmic rays from solar flares have relatively low energy, they do not usually cause significant increases in radiation doses at the earth's surface. In fact, between 1942 and 1962 only 13 flares produced observable effects in the lower atmosphere (150). However, large flares can increase the absorbed dose index rate in the upper atmosphere by a factor of about 100 for short periods of time.

(c) *Radiation belts*

18. There are two radiation belts, often called the Van Allen belts, situated between 1.2 and 8 earth radii above the equator. The lower belt extends to latitudes between 30° and 60° north and south (3, 129). The outer belt is confined more to low-latitude regions. The energetic particles, mainly protons and electrons, with some alpha particles in the outer belt, are trapped in these belts by the earth's magnetic field. They spiral along the lines of magnetic force, being reflected back and forth owing to the increased convergence of the magnetic field towards the polar regions.

19. The inner radiation belt consists mainly of protons with energies from several to several hundred mega-electronvolts, the peak flux density being at about

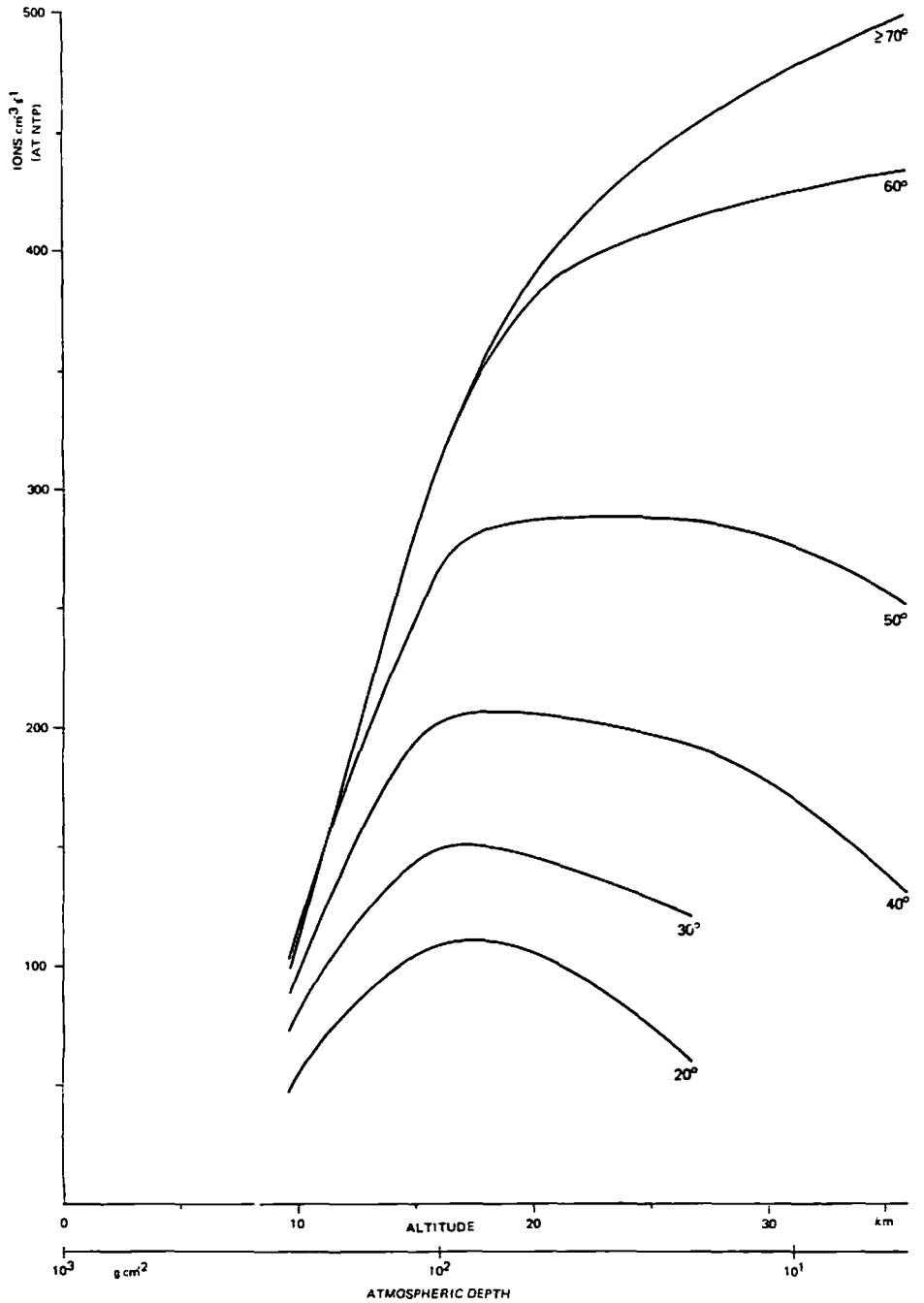

Figure I. Variation of ionization with altitude and atmospheric depth at different geomagnetic latitudes. Based upon the results of Neher (253)

50 MeV, and electrons with a flux density that is fairly flat over the energy range 100-400 keV. The maximum proton flux density is about 4 10^4 particles cm^{-2} s^{-1}, and this occurs at a height of about 1.5 earth radii over the equator (3). In the outer belt, the proton energies are mainly in the range 0.1-5 MeV, most of the particles being in the low-energy region. The outer belt also contains electrons and to a lesser extent alpha particles (3, 129). The flux density in the radiation belts is fairly constant in time, but does change with the flux density of primary cosmic rays during the 11-year solar cycle (129).

20. It is believed that the origin of most of the more energetic particles in the inner radiation belt is the decay of cosmic-ray albedo neutrons (233). The high-energy primary cosmic-ray protons collide with atoms in the air to produce neutrons by knock-on (direct) reactions, with energies between 1 and 1000 MeV, or by compound nuclear reactions that produce evaporation neutrons with energies of about 8 MeV. Many of these neutrons escape from the atmosphere either directly, if their energy is high, or by diffusion, if it is low. These escaping neutrons are called albedo neutrons; they decay to protons and electrons in an average time of 1000 s, and since these particles are charged, they will spiral along the flux lines of the earth's magnetic field. They are reflected back along the magnetic lines of force in high-latitude regions where the magnetic flux lines converge. If the height where the reflection takes place, termed the image height, is above the atmosphere, the particles will remain trapped in the earth's magnetic field

(129). The origin of the particles in the outer belt is less certain. Since there is an alpha-particle component, it is thought that some of the particles are of solar origin.

2. Secondary cosmic rays

21. When primary cosmic-ray particles enter the atmosphere, those with higher energy undergo nuclear reactions with nuclei of atoms present in the air, producing neutrons, protons, pions and kaons. Those with lower energy lose energy by causing ionization. Many of the secondary particles have sufficient energy to initiate whole sequences of further nuclear reactions with nitrogen and oxygen nuclei. The initial high-energy reactions are called spallation reactions and quite a variety of reaction products (cosmogenic nuclides) are formed, such as ^{3}H, ^{7}Be, ^{10}Be, ^{22}Na and ^{24}Na.

22. The important initial secondary cosmic-ray particles are high-energy protons, neutrons and pions, many of which react further with nuclei in the air to form more secondary particles (100, 277). As this process continues, the number of secondary particles builds up; such a process is called a cascade. The pions decay into muons or photons, initiating other cascades.

23. The protons and neutrons contribute significantly to the absorbed dose index rate in the upper atmosphere. The neutrons lose energy by elastic collisions, and when thermalized they are captured by ^{14}N to form ^{14}C. Because nucleons rapidly lose energy by ionization and nuclear collisions, the nucleonic flux density is considerably attenuated in the lower part of the atmosphere and at sea level accounts for only a few per cent of the absorbed dose index rate.

24. At lower altitudes in the atmosphere, the major contribution to the absorbed dose index rate is provided by the muons produced by the decay of charged pions at higher altitudes and by the associated collision electrons. Since muons have only a small cross-section for interaction with atomic nuclei, have a mean life at rest of 2.2 μs before decay into electrons, and move largely at relativistic velocities, they penetrate quite effectively into the lower layers of the atmosphere and through structural building materials (301). Electrons are also produced by muon decay, by ionization due to other charged particles and in electromagnetic cascade processes. Except in the lower layers of the atmosphere, electrons are the main contributor to the absorbed dose index rate.

25. The flux densities of all cosmic-ray particles undergo variations in time due to modulation over the solar cycle, the effects of solar flares and changes in atmospheric pressure or temperature. The approximate amplitude variations expected from these various effects are shown in table 1. It should be noted that the flux densities of various secondary cosmic rays at a given altitude depend primarily on the atmospheric depth (see paragraph 13). However, for the purposes of radiation-dose estimates, atmospheric depth is converted into altitude (in kilometres) in this report, assuming a standard atmosphere.

TABLE 1. AMPLITUDE AND PERIOD OF THE TIME VARIATION OF COSMIC-RAY FLUX DENSITY

Source of variation	*Cosmic-ray component*	*Altitude above sea level (km)*	*Latitude (N and S)*	*Relative amplitude (100 Δ N/N$_0$)*[a]	*Period*	*Reference*
Solar modulation	Charged particles	9	> 50°	22		253
	Charged particles	5.5	> 50°	16		253
	Muons	0	> 50°	5	11 y	89
	Neutrons	3.5	> 50°	25		313
	Neutrons	0	> 50°	20		313
Solar flares	Muons	0	> 50°	0-400	Hours	74,301
	Neutrons	0	0°-90°	0-10 000	Hours	301
Atmospheric pressure variations	Charged particles	0	0°-90°	< 10	Days	
	Neutrons	0	0°-90°	< 15	Days	
Atmospheric temperature variations	Muons	0	0°-90°	< 5	1 y	54

Source: Reference 249.

[a] Total amplitude of variation relative to "normal" or average flux density N_0.

3. Ionization in the atmosphere

26. Many measurements of cosmic-ray ionization at various altitudes have been reported. The ionization rate per unit volume in free air is a measure of the flux density of the total charged-particle component of the cosmic-ray field and is usually expressed as the number of ion pairs formed per second in each cubic centimetre of air at normal temperature and pressure (NTP) (9, 95, 96, 210, 291, 312). As figure I shows, ionization in the atmosphere becomes increasingly latitude-dependent with increasing altitude. The ionization also varies over the solar cycle, being greatest during solar minimum and smallest during solar maximum (213, 254).

27. For estimating the absorbed dose index rate at altitudes above sea level, use was made of the measurements of Neher (254) over Thule, Greenland, between 1954 and 1959, of Raft *et al.* (291) made at latitude 54°N in 1969, and of George (95), who made measurements at altitudes of 400 and 1500 km in 1969. Lowder and Beck (210) also reported ionization

measurements in the lower atmosphere up to an altitude of about 3 km. In its 1972 report, the Committee discussed inconsistencies in some of the earlier measurements, particularly the differences between the measurements of George (96) and those of Lowder and Beck (210) and Shamos and Liboff (312). A value for the ion-pair production rate of 2.14 cm^{-3} s^{-1} was used as the average ionization at sea level. Lowder and O'Brien (213) adopted a value of 2.0-2.2 cm^{-3} s^{-1}. For the purposes of computing the absorbed dose index rate, a value of 2.1 cm^{-3} s^{-1} will be assumed in this report.

4. Cosmic-ray neutrons in the atmosphere

28. Most of the dose delivered by low-energy neutrons arise from capture reactions such as (n, γ) and (n, p), while for high-energy neutrons it comes from knock-on protons. Since the significant part of the cosmic-ray neutron energy spectrum extends from 10^{-1} to some 10^{9} electronvolts, some knowledge of its shape is necessary to compute the dose from neutrons.

29. As discussed in the 1972 report, a number of calculations have been made of the neutron differential energy spectrum at different altitudes. In general, these agree with measurements made of neutrons in the range 1-10 MeV at various altitudes. Merker *et al.* (234) have recently reported balloon and aircraft measurements of neutrons in that energy range during the period 1964-1971. These results agree well with the data that was used to compute neutron doses at higher altitudes in the 1972 report. Light *et al.* (201) have carried out Monte Carlo calculations of the neutron energy spectrum and normalized their results using the experimental data of Merker *et al.* (234). These authors assessed the neutron production rate averaged over a solar cycle to be 4.0 cm^{2} s^{-1}.

5. Tissue absorbed doses from cosmic rays

30. Traditionally, two quantities that are useful for estimating dose rates from cosmic rays have been measured, the ionization in air and the neutron flux density. Since the radiation quality of these two components is different, the absorbed dose index rates from the ionizing and neutron components will be treated separately. The absorbed dose index rate can be assessed from measured ionization in and above the atmosphere, and from measurements of particle flux density and energy spectrum. The contribution from the neutron component can be calculated from data on the neutron flux density.

(a) *Ionizing component*

31. The estimation of the absorbed dose rate in air from the ionizing component of cosmic rays is straightforward. Assuming each ion pair requires 33.7 eV to be produced, the absorbed dose rate for an ionization rate of 1 cm^{-3} s^{-1} is 1.50 μrad h^{-1}. Using the value for the ionization rate at sea level of 2.1 cm^{-3} s^{-1} (para. 27), the absorbed dose rate in air is 3.2 μrad h^{-1}. This value is quantitatively equal to the absorbed dose index rate at ground level. Using reported values of ionization in the upper atmosphere, absorbed dose index rates have been computed there in a similar manner and are shown in figure II (347). Kolb and Lauterbach (191) have recently reported measurements in the lower atmosphere with both an ionization chamber and a scintillation spectrometer. The ionization chamber results agreed with those reported by Lowder and Beck (210), but the measurements with the scintillator were consistently higher.

32. At sea level about 75 per cent of the ionization is from muon collision electrons, 15 per cent from muon decay electrons and 10 per cent from other electron, proton and neutron processes (249). As the absorbed dose index rate is reduced by about 30 per cent by 50 g cm^{-2} of material, mostly due to attenuation of the incident electrons, a building may provide substantial structural shielding.

33. If this structural shielding effect is not taken into account, the annual absorbed dose in human tissues D is given by

$$D = c_c q \dot{D}_I$$

(see Annex A), where c_c = 8.76 mrad μrad^{-1} h; q = 1; and $\dot{D}_I$ is the outdoor absorbed dose index rate. With a value of $\dot{D}_I$ of 3.2 μrad h^{-1} (para. 31), the annual absorbed dose in human tissues from the ionizing component of cosmic rays at sea level is approximately 28 mrad.

(b) *Neutron component*

34. The dose rate from the neutron component was derived in the 1972 report from computed absorbed dose rates in 30-cm tissue slabs. As indicated in Annex A, the absorbed-dose index rate is used in this report to describe cosmic-ray irradiation conditions. Hajnal *et al.* (112) found that the variation of dose rate with depth, 0-15 cm, for the bilateral incidence of cosmic-ray neutrons on a 30-cm slab was not very great. The maximum dose rate (at 1 cm) was only 6 per cent greater than the average for 0-15 cm. For a 30-cm sphere, the dose rate would be expected to be even more uniform, and so for cosmic-ray neutrons it can be assumed that the absorbed dose index rate is the same as the average absorbed dose rate computed from the 30-cm slab. The factor to convert neutron flux density to absorbed dose index rate is 4.93 μrad h^{-1} cm^{2} s (112).

35. A number of data on the cosmic-ray neutron flux density at sea level were reported in the 1972 report, varying from 0.0065 to 0.018 cm^{-2} s^{-1}. A neutron flux density of 0.008 cm^{-2} s^{-1} was adopted for the purpose of estimating doses at high latitudes. Using the conversion factor from the previous paragraph, the absorbed-dose index rate is 0.04 μrad h^{-1}. This value is in good agreement with tissue absorbed dose rates calculated by O'Brien and McLaughlin (263).

36. The annual absorbed dose in human tissues at sea level and at latitudes above 40°, calculated by the

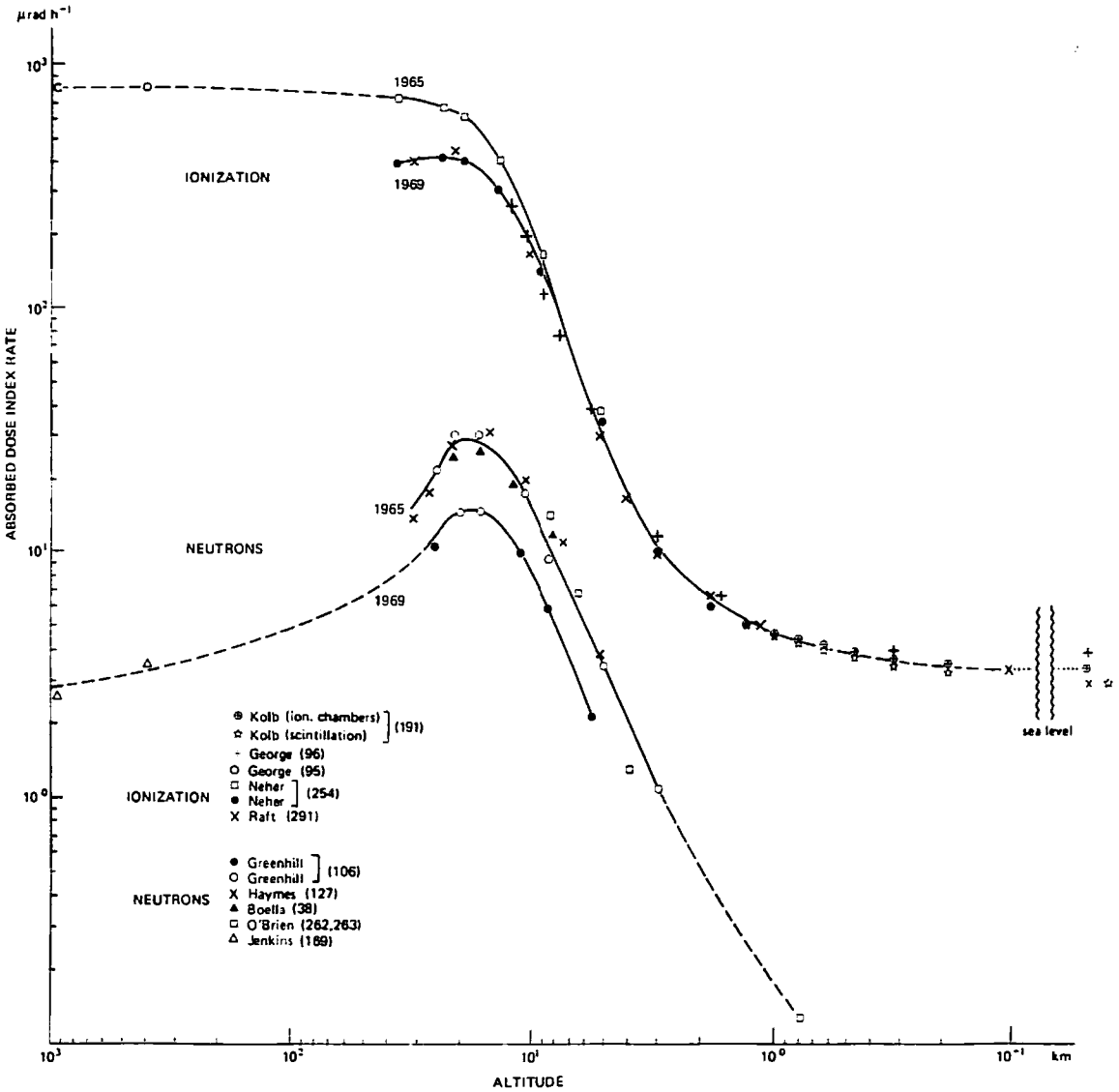

Figure II. Absorbed dose index rates at high geomagnetic latitudes (~50°) from the ionizing and neutron components of cosmic rays at different altitudes for 1969 (solar maximum) and 1965 (solar minimum) (347). The ionization component of the absorbed dose rate at 10^{-1} km is inferred from that at ground level

expression given in paragraph 33, is therefore 0.35 mrad. In equatorial regions, the annual absorbed dose in human tissues is about 0.2 mrad (347).

37. Although at sea level the neutron absorbed dose index rate is quite small, it increases rapidly with altitude, reaching a maximum at altitudes between 10 and 20 km. Measured neutron flux densities at various altitudes reported in the literature differ in the energy range they cover, latitude and time in the solar cycle. These reported values were normalized for these factors, using a published energy spectrum (112) to assess the total flux density from the reported values. The absorbed dose index rates were computed using a factor of 4.93 μrad h^{-1} cm^2 s to convert the neutron flux density to the absorbed dose index rate, and are shown plotted in figure II *versus* altitude.

38. Foelsche *et al.* (88) have recently computed the dose-equivalent rate from cosmic-ray neutrons at high altitude using a new energy spectrum that does not drop off so quickly in the high-energy region as that used in the 1972 report. The use of this new spectrum results in a higher absorbed dose index rate with a much higher contribution from neutrons in the high-energy region above 10 MeV. However, there is some question as to the validity of this spectrum in the high-energy region (88).

B. EXTERNAL RADIATION FROM NATURALLY OCCURRING RADIONUCLIDES (TERRESTRIAL RADIATION)

1. Source radionuclides

39. Radioactive nuclides have always been present in the natural environment. The decay of natural radionuclides produces alpha particles, electrons and electromagnetic radiation. Because the human organs and tissues in which the doses are calculated for the purposes of this document are shielded by at least a few millimetres of tissue, which absorbs practically all of the energy of the alpha particles and electrons given off by the natural radionuclides, only the gamma contribution will be considered here. It is worth noting, however, that

the skin and, to a lesser extent, the lens of the eye, being at or near the surface of the body, receive higher doses than the tissues and organs of primary interest to the Committee.

40. The natural radionuclides in the environment are of two general classes, the primordial and the cosmogenic. The cosmogenic radionuclides are mainly produced through interaction of the cosmic rays with target atoms in the atmosphere and, to a much lesser extent, in the earth. The three main cosmogenic contributors to external exposure at ground level are ^{7}Be, ^{22}Na and ^{24}Na.

41. Among the primordial radionuclides, the main contributors to external exposure are ^{40}K and the radioactive series headed by ^{238}U and ^{232}Th, which are presented in tables 2 and 3. Potassium-40, ^{238}U and ^{232}Th are long-lived radionuclides that have existed in the earth's crust throughout its history.

TABLE 2. RADIOACTIVE DECAY PROPERTIES OF THE ^{238}U SERIES

Nuclide	Historical name	Half-life	Major radiation energies (MeV) and intensities		
			α	β	γ
$^{238}_{92}U$	Uranium I	4.51 10^9 y	4.15 (25%) 4.20 (75%)	–	–
$^{234}_{90}Th$	Uranium X_1	24.1 d	–	0.103 (21%) 0.193 (79%)	0.063 (3.5%) 0.093 (4%)
$^{234m}_{91}Pa$	Uranium X_2	1.17 min	–	2.29 (98%)	0.765 (0.30%) 1.001 (0.60%)
99.87% | 0.13%					
$^{234}_{91}Pa$	Uranium Z	6.75 h	–	0.53 (66%) 1.13 (13%)	0.100 (50%) 0.70 (24%) 0.90 (70%)
$^{234}_{92}U$	Uranium II	2.47 10^5 y	4.72 (28%) 4.77 (72%)	–	0.053 (0.2%)
$^{230}_{90}Th$	Ionium	8.0 10^4 y	4.62 (24%) 4.68 (76%)	–	0.068 (0.6%) 0.142 (0.07%)
$^{226}_{88}Ra$	Radium	1602 y	4.60 (6%) 4.78 (95%)	–	0.186 (4%)
$^{222}_{86}Rn$	Emanation Radon (Rn)	3.823 d	5.49 (100%)	–	0.510 (0.07%)
$^{218}_{84}Po$	Radium A	3.05 min	6.00 (~100%)	0.33 (~0.019%)	–
99.98% | 0.02%					
$^{214}_{82}Pb$	Radium B	26.8 min	–	0.65 (50%) 0.71 (40%) 0.98 (6%)	0.295 (19%) 0.352 (36%)
$^{218}_{85}At$	Astatine	~2 s	6.65 (6%) 6.70 (94%)	? (~0.1%)	–
$^{214}_{83}Bi$	Radium C	19.7 min	5.45 (0.012%) 5.51 (0.008%)	1.0 (23%) 1.51 (40%) 3.26 (19%)	0.609 (47%) 1.120 (17%) 1.764 (17%)
99.98% | 0.02%					
$^{214}_{84}Po$	Radium C'	164 μs	7.69 (100%)	–	0.799 (0.014%)
$^{210}_{81}Tl$	Radium C''	1.3 min	–	1.3 (25%) 1.9 (56%) 2.3 (19%)	0.296 (80%) 0.795 (100%) 1.31 (21%)
$^{210}_{82}Pb$	Radium D	21 y	3.72 (.000002%)	0.016 (85%) 0.061 (15%)	0.047 (4%)
$^{210}_{83}Bi$	Radium E	5.01 d	4.65 (.00007%) 4.69 (.00005%)	1.161 (~100%)	–
~100% | .00013%					
$^{210}_{84}Po$	Radium F	138.4 d	5.305 (100%)	–	0.803 (0.0011%)
$^{206}_{81}Tl$	Radium E''	4.19 min	–	1.571 (100%)	–
$^{206}_{82}Pb$	Radium G	Stable	–	–	–

Source: Reference 288.

TABLE 3. RADIOACTIVE DECAY PROPERTIES OF THE ^{40}K AND THE ^{232}Th SERIES

Nuclide	Historical name	Half-life	Major radiation energies (MeV) and intensities		
			α	β	γ
^{40}K		$1.26\ 10^{9}$ y	–	1.32 (89%)	1.46 (11%)
10.7% | 89.3%					
^{40}Ar — ^{40}Ca		Stable	–		
$^{232}_{90}Th$	Thorium	$1.41\ 10^{10}$ y	3.95 (24%) 4.01 (76%)	–	–
$^{228}_{88}Ra$	Mesothorium I	5.8 y	–	0.055 (100%)	–
$^{228}_{89}Ac$	Mesothorium II	6.13 h	–	1.18 (35%) 1.75 (12%) 2.09 (12%)	0.34 (15%) 0.908 (25%) 0.96 (20%)
$^{228}_{90}Th$	Radiothorium	1.910 y	5.34 (28%) 5.43 (71%)	–	0.084 (1.6%) 0.214 (0.3%)
$^{224}_{88}Ra$	Thorium X	3.64 d	5.45 (6%) 5.68 (94%)	–	0.241 (3.7%)
$^{220}_{86}Rn$	Emanation Thoron (Tn)	55 s	6.29 (100%)	–	0.55 (0.07%)
$^{216}_{84}Po$	Thorium A	0.15 s	6.78 (100%)	–	–
$^{212}_{82}Pb$	Thorium B	10.64 h	–	0.346 (81%) 0.586 (14%)	0.239 (47%) 0.300 (3.2%)
$^{212}_{83}Bi$	Thorium C	60.6 min	6.05 (25%) 6.09 (10%)	1.55 (5%) 2.26 (55%)	0.040 (2%) 0.727 (7%) 1.620 (1.8%)
64.0% | 36.0%					
$^{212}_{84}Po$	Thorium C′	304 ns	8.78 (100%)	–	–
$^{208}_{81}Tl$	Thorium C″	3.10 min	–	1.28 (25%) 1.52 (21%) 1.80 (50%)	0.511 (23%) 0.583 (86%) 0.860 (12%) 2.614 (100%)
$^{208}_{82}Pb$	Thorium D	Stable	–	–	–

Source: Reference 288.

42. The concentration of the primordial radionuclides in soil is determined by the radioactivity of the source rock and by the nature of the processes which had been involved in the formation of the soil. Table 4 shows typical natural concentrations in common rocks (249). In igneous rocks, the concentration of radioactive nuclides is related to the quantity of silicates, being highest in acidic rocks and lowest in the ultrabasic rocks. Igneous rocks generally exhibit higher radioactivity than sedimentary rocks, while metamorphic rocks have concentrations typical of the rocks from which they were derived. However, certain sedimentary rocks, notably some shales and phosphate rocks, are highly radioactive (249).

TABLE 4. TYPICAL ACTIVITY CONCENTRATION OF ^{40}K, ^{238}U AND ^{232}Th IN COMMON ROCKS AND ESTIMATED ABSORBED DOSE RATE IN AIR 1 m ABOVE THE SURFACE

Type of rock	Typical activity concentration (pCi g^{-1})			Absorbed dose rate in air (μrad h^{-1})
	^{40}K	^{238}U	^{232}Th	
Igneous				
Acidic (e.g. granite)	27	1.6	2.2	12
Intermediate (e.g. diorite)	19	0.62	0.88	6.2
Mafic (e.g. basalt)	6.5	0.31	0.30	2.3
Ultrabasic (e.g. durite)	4.0	0.01	0.66	2.3
Sedimentary				
Limestone	2.4	0.75	0.19	2.0
Carbonate	–	0.72	0.21	1.7
Sandstone	10	0.5	0.3	3.2
Shale	19	1.2	1.2	7.9

Sources: References 1, 353.

43. The concentration of radionuclides in soil, which is directly relevant to the outdoor exposure, is that of the rock from which it is derived, diminished by the leaching action of moving water, diluted by increased porosity and by added water and organic matter, and augmented by sorption and precipitation of radionuclides from incoming water (250). An extensive study of the mean concentration of the natural radionuclides in soils of various types in the Soviet Union (188) shows that there is a regular trend for all the natural radionuclides which partly reflects the extent of bio-geochemical reworking of the original soil-forming rocks (table 5). It should be noted, however, that the main factor influencing the concentration of the natural radionuclides in soil is not the soil-forming process but the corresponding concentration in the soil-forming rocks. Table 5 also includes an estimate of the average soil concentration on a world-wide basis (249), as well as typical ranges of values reported in the literature (18, 107, 353).

TABLE 5. AVERAGE ACTIVITY CONCENTRATION OF ^{40}K, ^{238}U AND ^{232}Th IN VARIOUS TYPES OF SOIL AND ABSORBED DOSE RATE IN AIR 1 m ABOVE THE SURFACE

Type of soil	*Average activity concentration (pCi g^{-1})*			*Absorbed dose rate in air (μrad h^{-1})*
	^{40}K	^{238}U	^{232}Th	
Serozem	18	0.85	1.3	7.4
Gray-brown	19	0.75	1.1	6.9
Chestnut	15	0.72	1.0	6.0
Chernozem	11	0.58	0.97	5.1
Gray forest	10	0.48	0.72	4.1
Sodpodzolic	8.1	0.41	0.60	3.4
Podzolic	4.0	0.24	0.33	1.8
Boggy	2.4	0.17	0.17	1.1
World average	10	0.7	0.7	4.6
Typical range[a]	3-20	0.3-1.4	0.2-1.3	1.4-9

Sources: References 18, 107, 188, 249, 353.

[a] Values based on data contained in references 18, 107 and 353.

2. Exposure outdoors

(a) *Source-exposure relationships*

44. Methods of calculation of the absorbed dose rate in air[1] from the radionuclides present in the atmosphere and in the soil are discussed in references 26, 86, 142 and 237. Table 6 presents the absorbed dose rates in air 1 m above ground for a representative soil containing unit activity concentrations of the natural radionuclides, assumed to be uniformly distributed with depth. The representative soil is described by its density, 1.6 g cm^{-3}, and its constituent concentrations (weight per cent): SiO_2, 67.5; Al_2O_3, 13.5; Fe_2O_3, 4.5; CO_2, 4.5; H_2O, 10.0. The absorbed dose rates in air have been calculated using the assumption that all the decay products of ^{238}U and ^{232}Th are in radioactive equilibrium with their precursors. This assumption, which is reasonable for rocks, is not strictly valid for soils, since (a) differentiation may result from the soil-forming process and biological reworking and (b) a fraction of the radon produced in the soil escapes into the soil air and diffuses into the atmosphere from the upper soil layers.

TABLE 6. ABSORBED DOSE RATE IN AIR 1 m ABOVE GROUND FOR A REPRESENTIVE SOIL CONTAINING UNIT ACTIVITY CONCENTRATIONS OF ^{40}K, ^{238}U AND ^{232}Th

Radionuclide[a]	*Dose rate (μrad h^{-1} per pCi g^{-1})*
^{40}K	0.16
^{238}U	1.58
^{232}Th	2.45

Source: Reference 24.

[a] All the decay products of ^{238}U and ^{232}Th are assumed to be in radioactive equilibrium with their precursor.

45. The conversion factors of table 6 were used to calculate the absorbed dose rates in air above the rocks and soils for which typical concentrations were given in tables 4 and 5 (last column). The main contributors to the absorbed dose rate in air are ^{208}Tl and ^{228}Ac in the ^{232}Th series, while for the ^{238}U series, about 99 per cent of the dose rate is due to ^{214}Pb and ^{214}Bi, which are short-lived decay products of ^{222}Rn. The gamma rays that these nuclides emit range in energy up to 2.6 MeV and are partly absorbed in the soil. For a typical natural radiation field, the layer of soil which makes the predominant contribution to external irradiation above the ground is about 30 cm thick (fig. III).

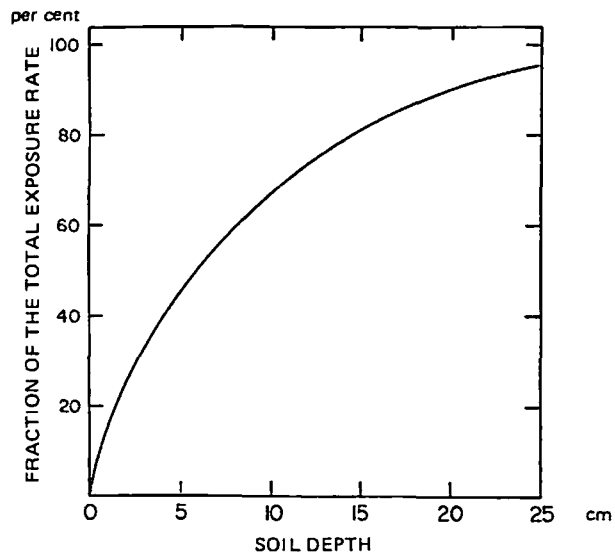

Figure III. Calculated relative contribution of naturally occurring radionuclides to the total exposure rate 1 m above the ground, as a function of soil thickness (24)

(b) *Environmental exposure levels*

46. In recent years, several surveys have been performed over whole countries and areas for the purpose of estimating the exposure of the populations of those countries and areas to natural radiation (table 7).

[1] As indicated in Annex A, the absorbed dose rate in air is used in this report to describe environmental exposure situations resulting from gamma-emitting radionuclides and is unambiguously specified, assuming full equilibrium in air.

TABLE 7. ESTIMATES OF THE AVERAGE ABSORBED DOSE RATE IN AIR 1 m ABOVE GROUND LEVEL FROM TERRESTRIAL RADIATION

Based on country- and area-wide surveys

Country or area	*Estimated population[a] in 1975 (10^6)*	*Area (10^3 km^2)*	*Average absorbed dose rate in air (μrad h^{-1})*	*Number of measurements*	*Type of survey and instrumentation used*	*Reference*
Austria	10	84	5.0	> 1 000	Ground survey with a Geiger-Müller counter	343
German Dem. Rep.	17	108	9.1	1 005	Ground survey with an ionization chamber and scintillation dosimeters	264
Germany, Fed. Rep. of	62	246	5.9	> 20 000	Ground survey with scintillation dosimeters	189
India	633	3 282	3.6[b]	35 stations sampled	Analysis of soil samples by gamma spectrometry	239
Italy	56	301	7.2	1 365	Ground survey with an ionization chamber	53
Japan	110	370	4.1[b]		Analysis of soil samples by gamma spectrometry	374
Poland	35	312	5.8	16 stations sampled	Ground survey with gamma spectrometers	269
Switzerland	7	41	7.4	Not indicated	Ground survey with an ionization chamber	128
United States	219	7 985	4.5	25 areas covered[c]	Aerial survey with gamma spectrometers	261
Island of Taiwan	12	36	6.0	26	Analysis of soil samples by gamma spectrometry	362

[a] With the exception of the island of Taiwan, the population estimates are taken from table A.6.1 of *United Nations Population Studies No. 53* (348).

[b] Calculated from the average concentration of ^{40}K, ^{238}U (or ^{226}Ra) and ^{232}Th in soil using the conversion factors given in table 6.

[c] Including approximately 30 per cent of the population.

The results are not altogether coherent as regards the quantity measured, which in practice is the quantity for which the measuring device was calibrated. Some authors report exposure rates, others, absorbed dose rates in air, and still others, "tissue doses in free air". Unless the measuring conditions are well specified, the quantities are often ambiguous, and intercomparisons between different investigations may be difficult.

47. The surveys were conducted using various methods and types of instrumentation. In the United States of America, aerial surveys were made in which an array of large NaI(Tl) crystals was flown in an aircraft at altitudes of 100-150 m above the terrain (50). This method was also used in other large countries, such as Canada (349) and the Union of Soviet Socialist Republics (188), but in these cases the results have not so far been used to estimate the average dose to the country's population.

48. Ground surveys were conducted in the other countries listed in table 7. Direct (or *in situ*) measurements were made in Austria, German Democratic Republic, Germany, Federal Republic of, Italy, Poland and Switzerland, the detectors being Geiger-Müller counters in Austria, ionization chambers in the German Democratic Republic, Italy and Switzerland, gamma spectrometers in Poland, and scintillation dosimeters especially developed for the purpose in the Federal Republic of Germany. In India and Japan and on the island of Taiwan, soil samples were taken over wide areas and then analysed by gamma spectrometry in a laboratory.

(c) *Variation of the absorbed dose rate in air with time*

49. One common aspect of the surveys is that the variation with time of the absorbed dose rate in air was not taken into account. The most significant changes with time are associated with variations in the amount of snow cover and soil moisture and in the atmospheric concentration of ^{222}Rn decay products.

50. Snow cover introduces an effective shielding of gamma radiation from ground sources; a 20-cm blanket of typical snow brings about a reduction of about 50 per cent in the exposure rate (250). As a result, a strong seasonal pattern in outdoor exposure rates is observed in regions with significant snowfall (218, 270), as shown in figure IV. It may be noted that, for a given thickness of snow, the value of the absorbed dose rate in air depends on whether the snow is accumulating or melting. The reason is that the soil moisture content is higher during thawing than during the period of snow accumulation (273). The influence of soil moisture content is discussed in paragraph 51.

51. Changes in soil moisture content affect soil bulk density, so that the absorbed dose rate in air above the ground decreases with increasing soil moisture content. For the ^{238}U series, however, this effect is superimposed on a change of ^{222}Rn emanation, which generally decreases with increasing soil moisture content. The absorbed dose rate in air from this decay chain is therefore essentially independent of soil moisture, as the shielding effect and the increased source effect roughly compensate (250). For ^{40}K and the ^{232}Th series, the absorbed dose rate in air is significantly reduced by soil moisture. Data reported by Beck *et al.* (26) show that the total external terrestrial annual doses in air in a given area during dry years generally average about 20 per cent more than those for wet years.

52. As a result of variations in the stability conditions of the lower atmosphere, the night-time concentrations of ^{222}Rn decay products in the air near the ground are usually a few times higher than those existing during the day (250). Beck (25) has calculated the gamma absorbed dose rate in air from atmospheric ^{222}Rn decay products

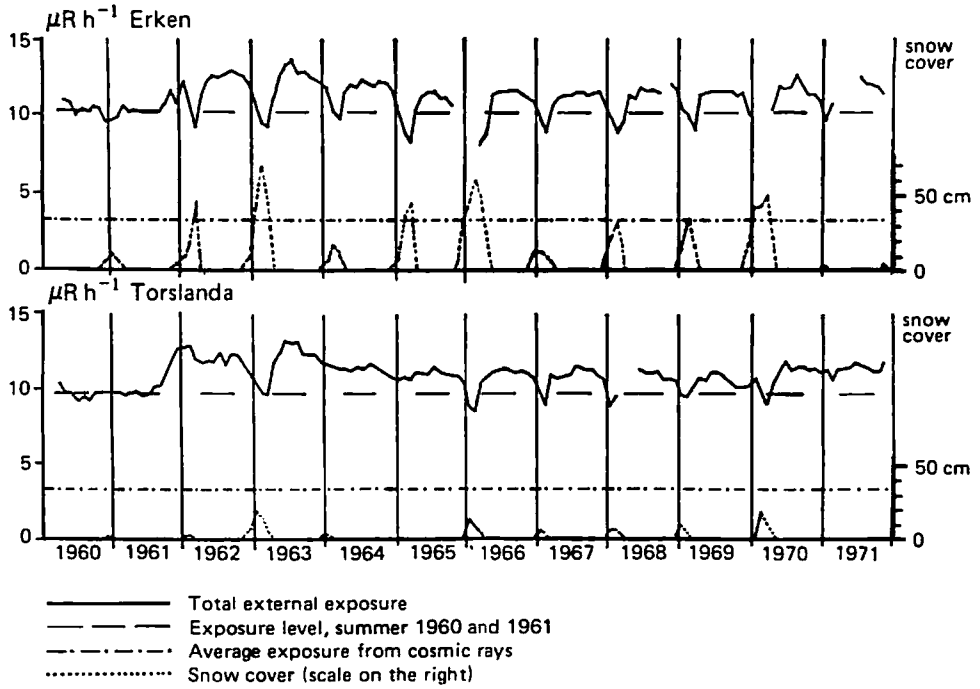

Figure IV. Exposure rates 2.5 m above ground and monthly averages of snow cover in Sweden, 1960-1971 (218, 336)

at 1 m above the ground for four different conditions of atmospheric stability. The values are 0.05, 0.1, 0.3 and 1 μrad h^{-1} for strong mixing, normal turbulence, weak mixing, and strong inversion conditions, respectively. It is believed that usually the absorbed dose rate in air from atmospheric ^{222}Rn decay products is approximately 0.1-0.2 μrad h^{-1}.

(d) *Estimate of the average exposure level*

53. The average absorbed dose rates in air at 1 m above the ground given in table 7 are, in the case of Federal Republic of Germany, German Democratic Republic, Italy, Japan and Switzerland, population-weighted, i.e., the values obtained in the subdivisions of the country have been weighted according to their population. In the case of India and Poland, the figures are the reported or arithmetic averages, while for the island of Taiwan, the average absorbed dose rate in air has been calculated from the average concentration of ^{40}K, ^{238}U and ^{232}Th in surface soil. Although the surveys did not take into account the variation of absorbed dose rate in air with time, and differed widely in the type of instrumentation used and in the number and type of measurements, the average absorbed dose rates in air obtained fall within the relatively narrow range of 3.6-9.1 μrad h^{-1}.

54. The population-weighted average absorbed dose rate in air for the surveys listed in table 7 is 4.3 μrad h^{-1}. The population involved is about 30 per cent of that of the world, and the value could be considered to be roughly representative of the world population exposure. The areas covered by the surveys, however, represent only 2 per cent of the total land area of the world and all are located in three separate regions of the northern hemisphere. It is conceivable that the rest of the world population might live in areas where the absorbed dose rate in air is very different from 4.3 μrad h^{-1}. However, the result based on the estimate of the world-wide average concentration of primordial radionuclides in soil is 4.6 μrad h^{-1} (table 6) and thus, in the absence of contradictory evidence, the Committee believes that a value of 4.5 μrad h^{-1} is a reasonable estimate, on a global basis, of the outdoor average absorbed dose rate in air, 1 m above ground, from terrestrial radiation.

55. As to the cosmogenic nuclide contribution to external irradiation, if the concentration of ^{7}Be, ^{22}Na and ^{24}Na are taken as $7\,10^{-2}$, 10^{-5} and $2\,10^{-5}$ pCi m^{-3}, respectively (168, 378), the corresponding absorbed dose rates in air are about $3\,10^{-6}$, 10^{-8} and $6\,10^{-8}$ μrad h^{-1}. An estimate can also be made of the total dose rate from all the other radionuclides produced by cosmic rays. From the existing experimental determinations of the atmospheric production rate for ^{24}Na, the estimated production rates for some of the short-lived radionuclides, and the cross-sections for the very short-lived radionuclides of less than 10-s half-life, it can be calculated (250) that for every disintegration of ^{24}Na at ground level there are 10^{6} disintegrations of short-lived cosmogenic radionuclides. Assuming an average gamma energy of 1 MeV per disintegration, the absorbed dose in air from the short-lived cosmogenic radionuclides would be of the order of 0.02 μrad h^{-1}. The contribution of all the radionuclides produced by cosmic rays to the absorbed dose rate in air is therefore insignificant compared to the contribution from the primordial nuclides in the ground.

(e) *Variability of the exposure*

56. The variability of the exposure around the mean value can be roughly assessed from data from some of the surveys listed in table 7. The surveys in four of the

countries, each with a population of more than 50 million people, provided the average doses for the populations of their administrative subdivisions: the 11 Länder of the Federal Republic of Germany, the 20 regions of Italy, the 22 districts of Japan, and the 50 states and capital district of the United States. The populations of those subdivisions range from 0.1 to 20 million people.

57. The frequency distribution of the population over absorbed dose rate in air is presented in figure V for each of the four countries, and in figure VI for the four countries taken together. If the volcanic regions of Lazio and Campania of Italy are excluded, the combined data of figure VI are fitted rather well by a Gaussian distribution, as shown in figure VII. Thus, for the four countries considered, a large fraction of the population lives in areas where the population-weighted distribution of the outdoors absorbed dose rate in air is normally distributed, while another fraction, much smaller, lives in areas outside of the normal distribution. The average absorbed dose rate in air in the "normal" areas of the

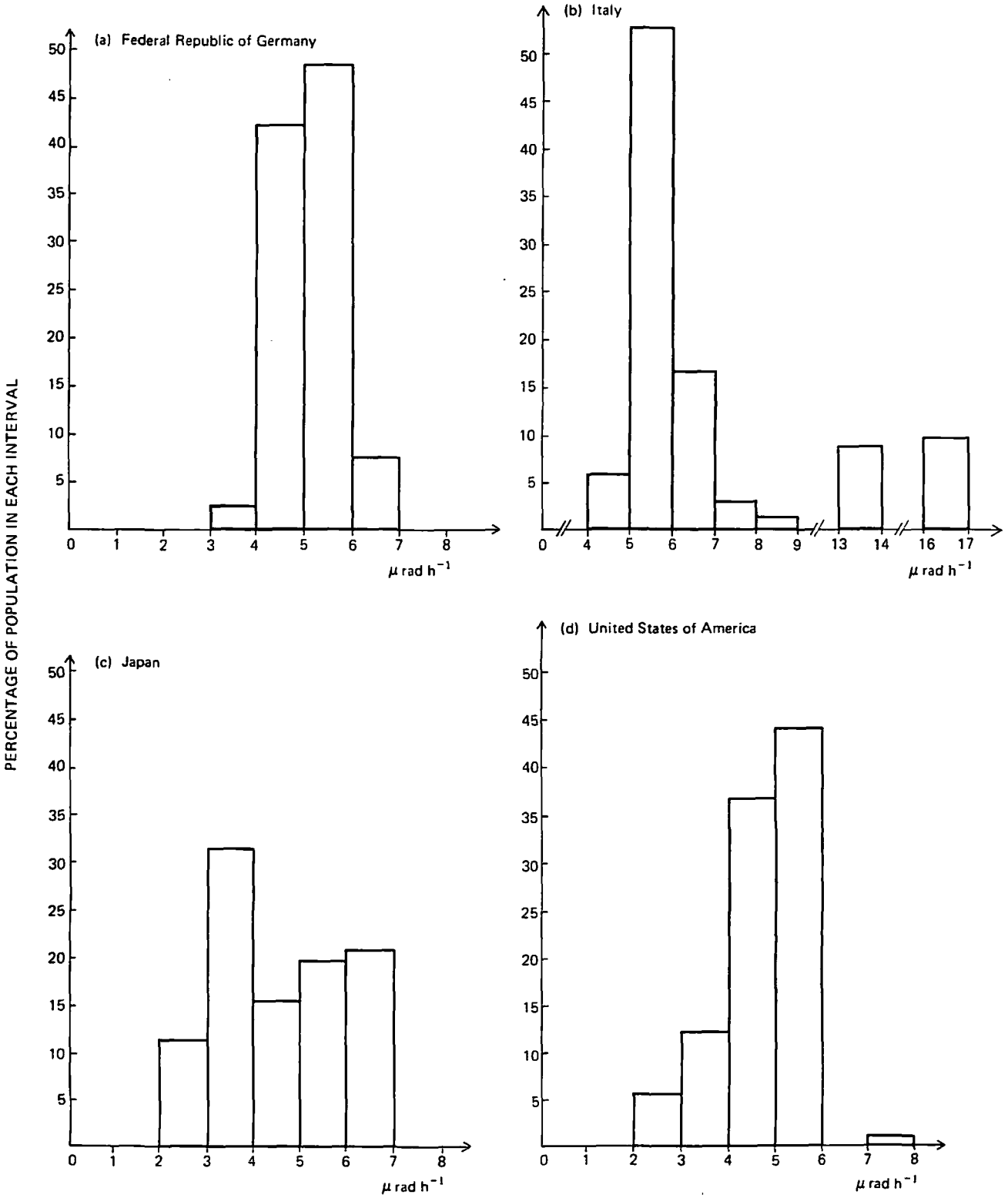

Figure V. Population-weighted distribution of absorbed dose rates in air from terrestrial radiation in four countries

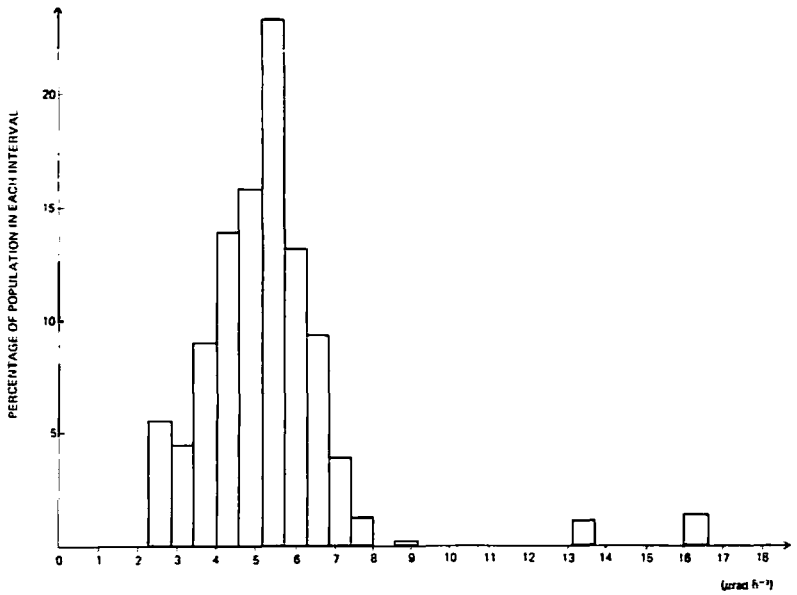

Figure VI. Frequency distribution of outdoor absorbed dose rate in air from terrestrial radiation. Combined data from the Federal Republic of Germany, Italy, Japan and the United States. (The isolated bars on the right represent data from the Italian regions of Lazio and Campania)

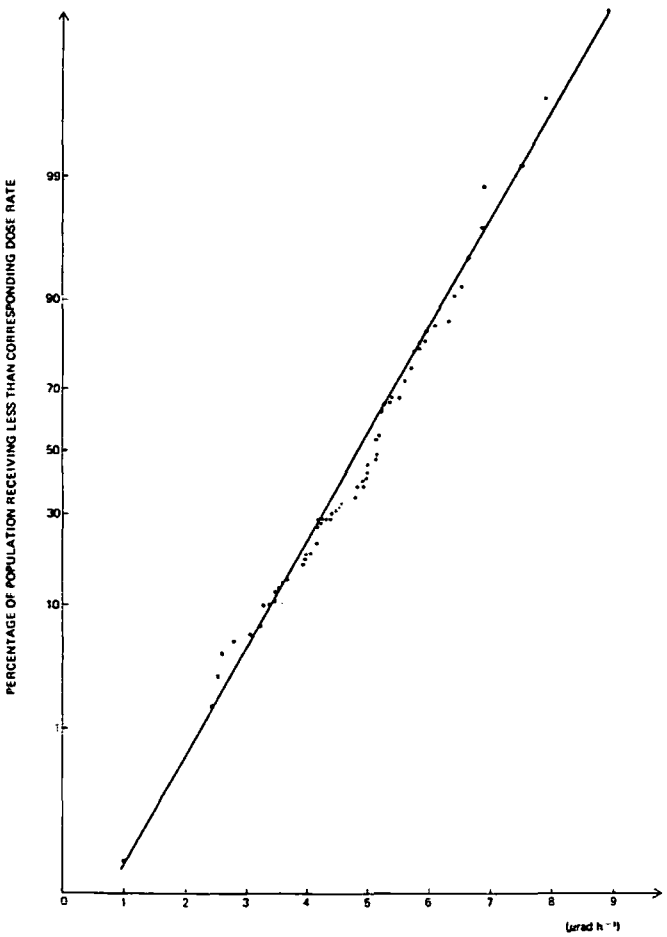

Figure VII. Cumulative frequency distribution of the outdoor absorbed dose rate in air from terrestrial radiation. Combined data from the Federal Republic of Germany, Italy, Japan and the United States. (The data from the Italian regions of Lazio and Campania have not been included)

four countries is 4.85 μrad h^{-1}, with a standard deviation of 1.1 μrad h^{-1}. Assuming that the distribution holds on a global basis, 95 per cent of the world population residing in areas of "normal" natural radiation would live where the outdoor absorbed dose rate in air from the primordial radionuclides falls between about 3 and 7 μrad h^{-1}. However, it should be borne in mind that these values are themselves averages, corresponding to population groups of at least 10^5 people.

(f) *Areas with high natural radiation levels*

58. As indicated above, there are regions in the world where the outdoor absorbed dose rate in air substantially exceeds the range mentioned in paragraph 57. In addition to the Italian provinces of Lazio and Campania, such regions are known to exist in Brazil, France, India, Iran, Madagascar and Nigeria (45). The best known from a dosimetric point of view are those located in Brazil and India.

59. Deposits of radioactive minerals occur in littoral formations along the coastal regions of India. Of particular interest is a stretch about 250 km long and about 0.5 km wide on the south-west coast in the states of Kerala and Tamil Nadu. These deposits are rich in monazite, which contains principally ^{232}Th and its decay products together with several rare earths; the monazite deposits are admixed with ilmenite, rutile, sillimanite and zircon. The most concentrated deposits along the Kerala coast are located on a 55-km strip populated by about 70 000 persons, where the thorium concentration in the monazite ranges from 8.0 to 10.5 per cent by weight, being the highest known in the world (103). Additional features of this area are that it has definable geographical landmarks, with the backwaters separating this strip from the mainland, and it supports a high density of human population. Further south, another coastal strip about 2.5 km long in the state of Tamil Nadu also has high concentrations of monazite.

60. In a radiometric survey carried out in the late 1950s, measurements of gamma exposure rates were

made at the main entrance of 200 houses selected at random in the 55-km strip of Kerala coast described above. Values varied widely between houses, demonstrating the rather patchy distribution of monazite along the coastal strip. On the basis of these measurements, it was estimated that the average absorbed dose rate in air from terrestrial radiation in the region was about 130 μrad h^{-1} (103).

61. Two types of high-background regions have been found in Brazil: the monazite sand region along the Atlantic coast of the states of Espirito Santo and Rio de Janeiro and the volcanic intrusive anomalies along a geological fracture that extends from the coast through the inland state of Minas Gerais (274). Weathering and decomposition of archeogneisses in the mountain range that parallels a long extension of the Brazilian Atlantic coast produced a natural separation of very insoluble and hard minerals, such as ilmenite, zirconite and monazite. Ground to fine particles and carried downstream by many rivers emptying into the ocean, these minerals underwent stratification and were deposited on fluvial and marine regions (274). The radiation levels in three towns (Guarapari, Meaipe and Cumuruxatiba) built over monazite sands along the Atlantic coast were surveyed in detail by Roser and Cullen (299). Guarapari is a town of 12 000 people which receives an influx of about 30 000 vacationers every summer. In that town, the absorbed dose rates in air were found to range from 100 to 200 μrad h^{-1} in the streets and up to 2000 μrad h^{-1} over selected spots on the beach (275, 299). Meaipe is a fishing village of about 300 people, situated 50 km to the south of Guarapari, where the radiation environment is similar: the average absorbed dose rate in air is about 100 μrad h^{-1} with levels up to 1000 μrad h^{-1} (274). In Cumuruxatiba, the average level is 50 μrad h^{-1} (299).

62. In the state of Minas Gerais, two volcanic regions have been intensively studied, Poços de Caldas and Araxá-Tapira. Near the city of Poços de Caldas stands a hill where absorbed dose rates in air of up to 2800 μrad h^{-1} have been reported. However, this hill is small and uninhabited. The radioactivity of the Araxá-Tapira region originated from an alkaline intrusive, the mineralization consisting mostly of apatite. The radioactive components occur almost exclusively in the form of pyrochlore, a mineral containing up to 60 per cent niobium oxide, 1.9 per cent thorium oxide and 1.3 per cent uranium oxide (274). In Araxá-Tapira, absorbed dose rates in air up to 400 μrad h^{-1} have been measured.

63. Information on the tissue absorbed doses in the populations living in areas of high external terrestrial radiation in Brazil and India are given in paragraphs 76 and 77.

64. Quantitative information on the outdoor absorbed dose rates in air in other areas of high natural radiation levels is very scarce. In the city of Ramsar, Iran, absorbed dose rates in air ranging from 200 to 5000 μrad h^{-1} have been measured within an area of a few square kilometres, characterized by the presence of ^{226}Ra-rich spring water (181). In France, absorbed dose rates in air of 200 μrad h^{-1} are not uncommon and a very localized value of 10 000 μrad h^{-1} has been discovered (71).

3. Exposure indoors

65. Knowledge of radiation levels in buildings is important in the assessment of population exposure, as most individuals spend a large proportion of their time indoors. However, large-scale surveys of indoor exposure are still relatively few compared to those conducted outdoors.

(a) *Activity of building materials*

66. Information on the radioactivity of building materials is still scarce. Table 8 presents the results of investigations which have been conducted in the Federal Republic of Germany, Sweden, the United Kingdom of Great Britain and Northern Ireland and the USSR. The range of concentrations found in a given type of commonly used building material is very wide, but the average values obtained in the four countries are reasonably close. Wood and materials used for thermal insulation, with the exception of the light-weight aggregate used in Sweden, are of low radioactive content; natural plaster and cement are also relatively low, while granites, bricks and concrete are in the upper part of the range.

(b) *Source-exposure relationship*

67. Estimates of indoor exposure could be derived from the activity concentration of the various building materials, their dimensions and distribution in the building, the geometrical conditions of irradiation and the radiation field outdoors, although it would be extremely difficult to take all those variables into proper account. Furthermore there is not yet sufficient information available on the activity concentrations of natural radionuclides in the various building materials. Therefore, the average absorbed dose rate in air indoors has been estimated from the outdoor values using conversion factors accounting for the type of basic building material used. These conversion factors are based mainly on the results of the few surveys that have involved at least about one hundred dwellings (table 9). The conversion factors take into account that building materials act both as sources of radiation and attenuators of outdoor radiation.

68. The importance of the shielding effect of building materials can be estimated from figure III. If the density of the soil is assumed to be 1.6 g cm^{-3}, a wall thickness of 50 g cm^{-2} absorbs practically all of the radiation from outdoors and a thickness of 10 g cm^{-2} is sufficient to absorb half of it. Therefore, the transmission of radiation through the walls will only play a significant role in light constructions such as wooden or prefabricated houses.

69. The shielding effect is clearly seen in wooden houses, for which the source effect is negligible. Surveys conducted in Australia (377) and in the United States (202, 211, 376) have shown that the indoor absorbed dose rate in air on the ground floor of wooden houses is about 75 per cent of that measured outdoors. One floor above ground level, the values are lower by a further 10-20 per cent (202, 376). In prefabricated houses made

TABLE 8. CONCENTRATION OF ^{40}K, ^{226}Ra AND ^{232}Th IN BUILDING MATERIALS AND ABSORBED DOSE RATE IN AIR

Type of building material	*Country*	*Number of samples*	*Average activity concentration (pCi g^{-1})*			*Absorbed dose rate in air (μrad h^{-1})*[a]	*Reference*
			^{40}K	^{226}Ra	^{232}Th		
Bricks	Germany, Fed. Rep. of	132	16	2.6	2.6	26	327
Bricks	Sweden	21	25	2.6	3.4	33	335
Red bricks	USSR	55	20	1.5	1.0	16	194
Clay bricks	United Kingdom	23	17	1.4	1.2	16	117
Concrete	Germany, Fed. Rep. of	69	15	1.8	1.7	19	327
Heavy concrete	Sweden	15	19	1.3	2.3	21	335
Aerated concrete without alum shale	Sweden	22	9	1.5	1.9	17	335
Heavy concrete	USSR	87	15	0.9	0.8	12	194
Light concrete	USSR	16	14	2.0	0.9	15	194
Concrete	United Kingdom	5	14	2.0	0.8	15	117
Cement	Germany, Fed. Rep. of	19	5.2	1.2	1.2	11	327
Cement	Sweden	8	6.3	1.5	1.5	13	204
Cement	USSR	7	6	1.2	1.2	8	194
Natural plaster	Germany, Fed. Rep. of	23	2	< 0.5	< 0.3	< 4	327
Natural plaster	Sweden	4	0.6	0.09	< 0.04	< 1	335
Plaster	USSR	1	10	0.25	0.17	5	194
Natural plaster	United Kingdom	69	4	0.6	0.2	4	117
Granite	Germany, Fed. Rep. of	34	33	2.6	2.2	30	327
Granite	USSR	2	40	3	4.5	46	194
Granite bricks	United Kingdom	7	28	2.4	2.3	28	117
Pumice stone	Germany, Fed. Rep. of	20	29	3.0	3.4	35	327
Tuff	USSR	13	18	2.6	2.0	24	194
Limestone and marble	Germany, Fed. Rep. of	20	1	< 0.5	< 0.5	< 5	327
Rock aggregate	Sweden	296	22	1.3	1.9	20	111
Rock aggregate	United Kingdom	3	22	1.4	0.1	12	117
Gravel and sand	Germany, Fed. Rep. of	50	7	< 0.4	< 0.5	< 6	327
Natural sand and sand rejects	USSR	32	7.1	0.63	0.5	7	194, 195
Wood	Sweden	1	–	–	–	< 0.4	142
Rock and silica wool	Sweden	2	6	0.4	0.4	5	335
Rock and silica wool	United Kingdom	2	negligible				117
Lightweight aggregate	Sweden	10	27	3.9	4.3	42	335

[a] Assuming 4π-geometry and infinite thickness, and using the conversion factors given in table 6. The values obtained are an index allowing the comparison between building materials and not an estimate of the doses that would be received in dwellings constructed with those building materials.

TABLE 9. RESULTS OF SURVEYS OF THE INDOOR ABSORBED DOSE RATE IN AIR DUE TO TERRESTRIAL RADIATION

Country	*Number of dwellings*	*Type of building*	*Indoor average absorbed dose rate in air (μrad h^{-1})*	*Population-weighted average absorbed dose rate in air (μrad h^{-1})*	*Indoors-to-outdoors ratio*	*Population-weighted indoors-to-outdoors ratio*	*Reference*
German Democratic Republic	480 in old buildings[a]	Brick (old)	7.2	7.4		0.78	264
		Brick (new)	6.5				
		Half-timbered (old)	7.6				
	187 in new buildings[a]	Store (old)	11.2				
		Mixed construction (new)	5.7				
		Prefabricated (new)	5.9				
Germany, Fed. Rep. of	> 20 000	Solid	6.8	6.8		1.3	192
		Frame	6.9				
		Prefabricated (concrete)	4.2				
		Wood	4.2				

Country	Number of dwellings	Type of building	Indoor average absorbed dose rate in air (μrad h^{-1})	Population-weighted average absorbed dose rate in air (μrad h^{-1})	Indoors-to-outdoors ratio	Population-weighted indoors-to-outdoors ratio	Reference
Norway	823	Wood	7.1				
	594	Concrete	10.5				329
	609	Brick	11.9				
Poland	37	Concrete	4.9		0.73		271
	49	Prefabricated (fly-ash and slag)	6.4		1.1		
	11	Brick	5.7				
Sweden[b]	259	Wood (old)	5.1				142
	126	Wood (new)	4.8				241
	365	Brick (old)	10.6				142
	93	Brick (new)	10.6				241
	43	Concrete (new)	12.5				241
United Kingdom	71	Solid: sedimentary rock (Dundee)	7.6		1.07		
	155	Solid: sedimentary rock (Edinburgh)	6.8		1.24		320
	103	Solid: granite (Aberdeen)	9.7		0.82		
	172	Solid: granite (Aberdeenshire)	9.4		1.17		
United States	110	Wood	3.9[c]		0.75		203
	160	Wood			0.70		211

[a] Old: built before 1945. New: built after 1945.

[b] Two surveys have been conducted in Sweden, one in 1956 and one in 1976. The buildings surveyed in 1956 are referred to as old. A large percentage of the buildings surveyed in 1976 are likely to have been built after 1956 and are referred to as new.

[c] Median value.

out of concrete and in wooden houses it has been determined in the study conducted in the Federal Republic of Germany that absorbed dose rates in air indoors are lower than outdoors, the average reduction being 3 per cent for the prefabricated houses and 6 per cent for the wooden houses (189).

70. In the other types of houses, outdoor radiation is almost completely shielded by the walls. This has been demonstrated in various studies (264, 376) in which it has been observed that the levels are about the same on various floors of a given masonry building. Therefore, in these dwellings, the indoor levels cannot be compared to those outdoors unless the building materials are of local origin. If the concentration of radioactive substances in the ground of a given locality is equal to that in building materials, the absorbed dose rate in air might be expected to be somewhat less than twice as large indoors as outdoors, as a result of the change of source geometry. However, correction coefficients should be applied allowing for the presence of windows and doors (195), which makes the ratio much smaller than 2. Direct determinations of these correction coefficients have not been reported.

71. An estimate of the average indoors-to-outdoors dose ratio in masonry buildings may be obtained from the extensive country-wide study from the Federal Republic of Germany, in which nearly 30 000 apartments were surveyed. Preliminary information indicates that the average ratio of the indoors-to-outdoors absorbed dose rate in air is about 1.3 (192). Assuming that, on the average, the radioactive content of the building materials is about the same as that of the soils, roads and pavements around the building, the conversion factor between the indoor and the outdoor absorbed dose rates in air for masonry buildings would then be about 1.3. This figure is in reasonable agreement with the results of the United Kingdom study (320) but is higher than those obtained in the German Democratic Republic (264) and Poland (271). However, each of these three surveys involved less than 1000 dwellings, and the conversion factors derived from their results might be less representative than that obtained from the country-wide study conducted in the Federal Republic of Germany, where all types of dwellings were included.

(c) *Estimate of the average indoor level of the absorbed dose rate in air*

72. Assuming that the proportion of wooden buildings (dwellings, offices, factories, shops, theatres etc.) is about 20 per cent of the total and taking the average ratio of the indoor to the outdoor absorbed dose rate in air to be 0.7 and 1.3 for wooden and masonry buildings, respectively, the average indoor absorbed dose rate in air would be 18 per cent higher than that outdoors. Therefore, the indoor absorbed dose rate in air, averaged over the world, is estimated to be about 5.3 μrad h^{-1}.

(d) *Variability of the absorbed dose rate in air*

73. Indications on the variability of the indoor dose rates in relation to the average may be derived from the survey conducted in the Federal Republic of Germany (189, 192). As in the case of the outdoor absorbed dose rate in air, the population-weighted distribution seems to be normal (fig. VIII). The mean value of the indoor absorbed dose rate in air is 6.7 μrad h^{-1}, and its standard deviation, 1.0 μrad h^{-1}, while the corresponding values outdoors are 4.9 and 0.5 μrad h^{-1}. The

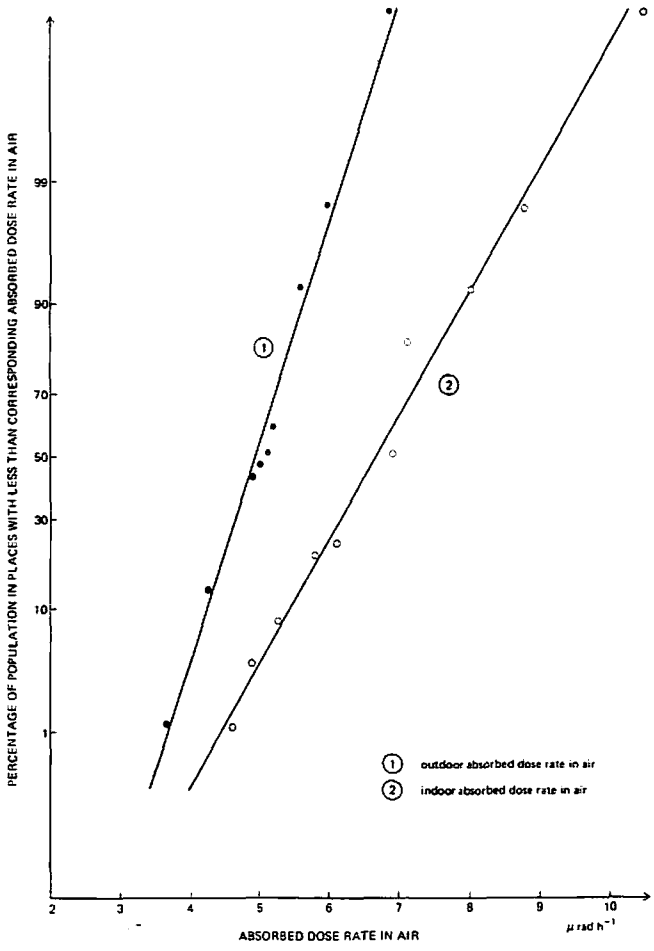

Figure VIII. Cumulative frequency distribution of the absorbed dose rate in air measured in the Federal Republic of Germany (189, 192)

outdoor coefficient of variation in the Federal Republic of Germany is about half of the value derived for global conditions (para. 5*i*). Assuming that the same relation applies to the indoor coefficient of variation, it is tentatively estimated that 95 per cent of the world population would be subject to indoor absorbed dose rates in air ranging from 2 to 9 μrad h^{-1}.

4. Tissue absorbed doses from terrestrial radiation

74. From the analysis contained in Annex A, the annual gonad absorbed dose D can be derived from the absorbed dose rate in air $\dot{D}_a$ as

$$D = (cq\dot{D}_a)_{\text{outdoors}} + (cq\dot{D}_a)_{\text{indoors}}$$

where c, the conversion factor from the absorbed dose rate in air to the gonad annual absorbed dose, is taken as 7.2 mrad μrad^{-1} h for outdoor exposure and 6.0 mrad μrad^{-1} h for indoor exposure, and q, the occupancy factor, is estimated in a later paragraph to be 0.8 indoors, and thus 0.2 outdoors.

75. From $\dot{D}_a = 4.5$ μrad h^{-1} outdoors and 5.3 μrad h^{-1} indoors, it can be estimated that the annual gonad absorbed dose from external terrestrial radiation is, on average, 32 mrad; 95 per cent of the world population would receive annual gonad doses in the range of 21 to 43 mrad. The doses in other organs of interest to the Committee are nearly equal to the gonad dose. The annual collective dose from terrestrial radiation, for the present size of the world population, is of the order of 10^8 man rad.

76. Populations living in areas of high external terrestrial radiation, such as those of Brazil and India, incur much greater tissue doses. Relevant information has been obtained in both countries by means of thermoluminescent dosimeters distributed to a fraction of the population. Gopal-Ayengar *et al.* (102, 103) carried out a dosimetric survey on the 55-km long coastal strip described in paragraphs 59 and 60, which was selected on the basis of high exposure rate, definable geographical boundaries and high population density. From results for a sample of 8513 individuals, the average annual tissue absorbed dose for the 70 000 people residing in the region was estimated at 380 mrad. It was estimated that about 24 per cent of the people experienced annual doses in excess of 0.5 rad, about 6 per cent exceeded 1 rad and about 0.7 per cent exceeded 2 rad.

77. On the Brazilian coast (see paragraph 61), Cullen (63) determined the average annual tissue dose from external terrestrial irradiation for a group of 317 inhabitants of Guarapari to be 0.55 rad, with a range of 0.09-2.8 rad.

II. INTERNAL IRRADIATION

78. Radioactive nuclides occurring in the biosphere enter the human body through ingestion and inhalation. In order to assess the doses from internal exposure in the organs and tissues of interest to the Committee (lung, gonads, red bone marrow, and endosteal cells), two types of information are necessary: (a) the concentration of radionuclides in the organs and tissues mentioned above and also in neighbouring tissues, such as bone and yellow marrow, and (b) the dosimetric factors linking the concentrations to the dose rates. The following paragraphs deal with the estimation of the relevant dosimetric factors and their application.

79. If a radionuclide emits only one type of monoenergetic particle per disintegration, the dose rate $\dot{D}_i$ in an organ or tissue i, can be assessed from the expression:

$$\dot{D}_i = \Sigma_j \varphi_E(i, j) C_j$$

where E is the energy of the particle, C_j the activity concentration of the radionuclide in organ or tissue j that may contribute to dose in tissue i, and φ_E (i,j) is the dosimetric factor, quantitatively equal to the dose-rate contribution in tissue i from a unit activity concentration in organ j. In the case of beta decay, the same expression is valid, provided that there is only one transition in the decay scheme. The energy E, in this case, would be the average energy of the beta particles emitted in the transition. In the most general case, several types of radiation with several energies are emitted. The dose rate in organ i becomes

$$\dot{D}_i = \Sigma_k \Sigma_E f_{k,E} \Sigma_j \varphi_{k,E}(i, j) C_j$$

where $f_{k,E}$ is the yield of particles including photons of type k of energy E per disintegration, and $\varphi_{k,E}(i, j)$ represents that contribution to the dose rate in organ or tissue i from a unit activity concentration in organ j which is due to particles of type k and energy E.

80. The dosimetric factors, symbolized as $\varphi(i,j)$–i and j being the target and the source organs, respectively–are given as a function of energy in figures IX, X, XI and XII, separately for the three types of radiation (alpha, beta, gamma) encountered in internal exposure from natural radionuclides. Four target organs have been considered, namely, the lung, the gonads, the red bone marrow, and the bone lining cells, which are defined as the cells lying on endosteal surfaces of bone (mainly trabecular), assumed to form a layer 10 μm thick. In the case of the alpha emitters, the dosimetric factors relating the activity concentration in bone to the dose rates in red bone marrow and in bone lining cells have been estimated for two types of distribution, (a) distribution throughout the bone matrix and (b) deposition on bone surfaces. For gamma emitters, two types of distribution in the human body have been considered; (a) uniform distribution over the whole body and (b) preferential distribution in the skeleton. In the latter case, which is that of the bone seekers, the dosimetric factors have been calculated using the assumption that the low activity present in the soft tissues is distributed over the whole body and is superimposed over the distribution in the skeleton. Although most of the dosimetric factors given here can be used for humans of any age and sex, they apply strictly to adult man. They have been derived from published models (147, 318, 319, 321).

A. COSMOGENIC RADIONUCLIDES

81. Very little of the dose from natural background is contributed by the cosmogenic radionuclides. Of the many nuclides produced by cosmic rays, only ^{3}H, ^{7}Be,

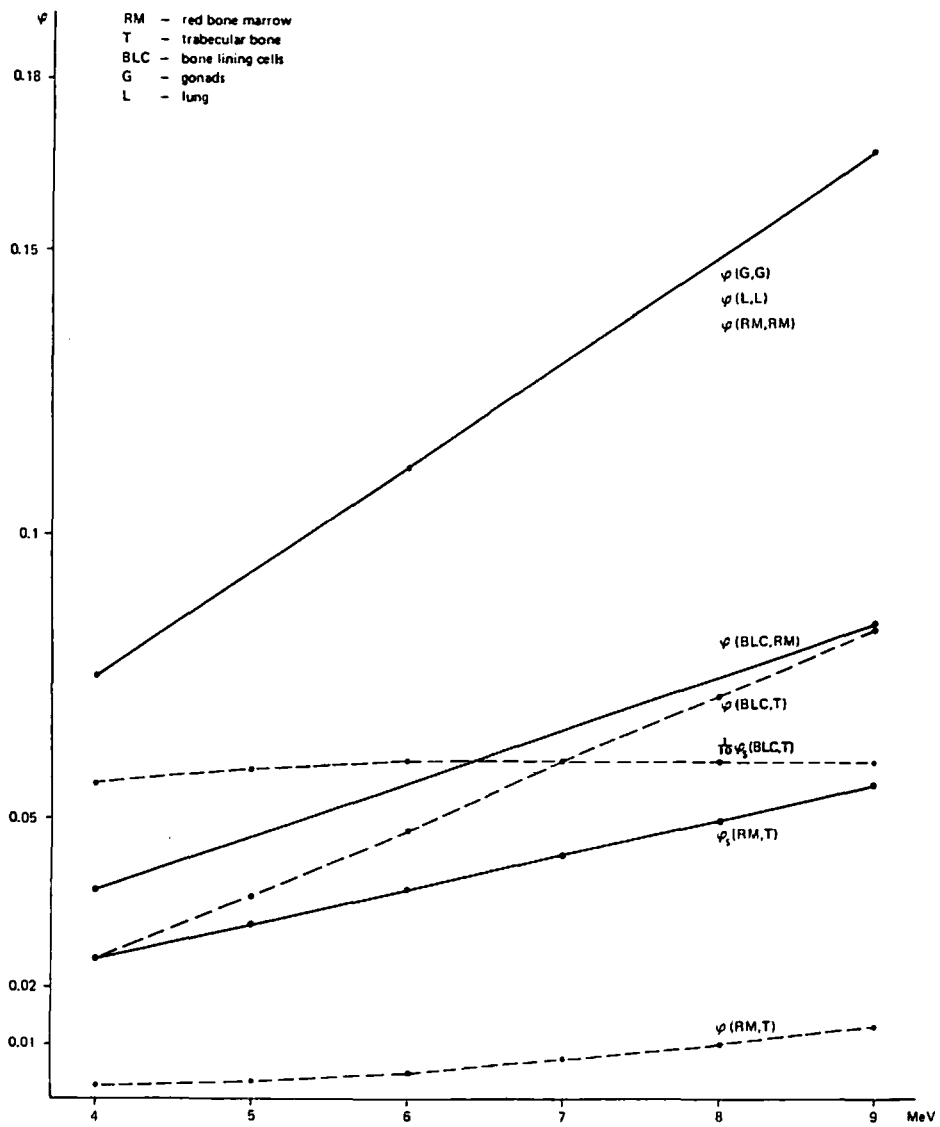

Figure IX. Dosimetric factors for alpha-emitting radionuclides (mrad y^{-1} per pCi kg^{-1})

The subscript s denotes that the alpha emitter is assumed to be distributed on the bone surfaces. The absence of subscript indicates that the alpha emitter is assumed to be uniformly distributed throughout the whole matrix

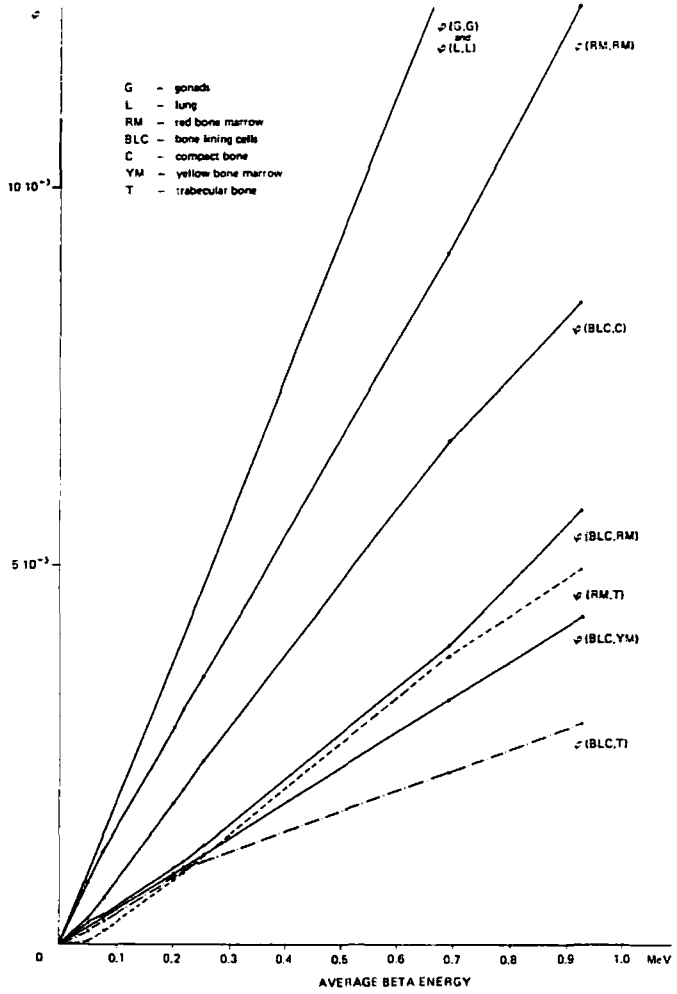

Figure X. Dosimetric factors for beta-emitting radionuclides (mrad y^{-1} per pCi kg^{-1})

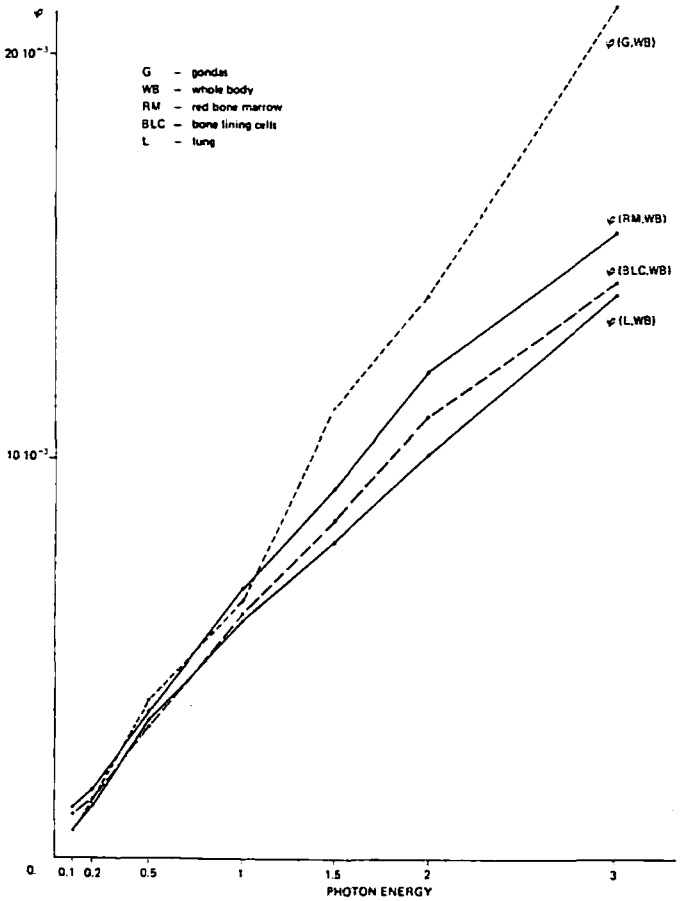

Figure XI. Dosimetric factors for gamma-emitting radionuclides distributed uniformly over the whole body (mrad y^{-1} per pCi kg^{-1})

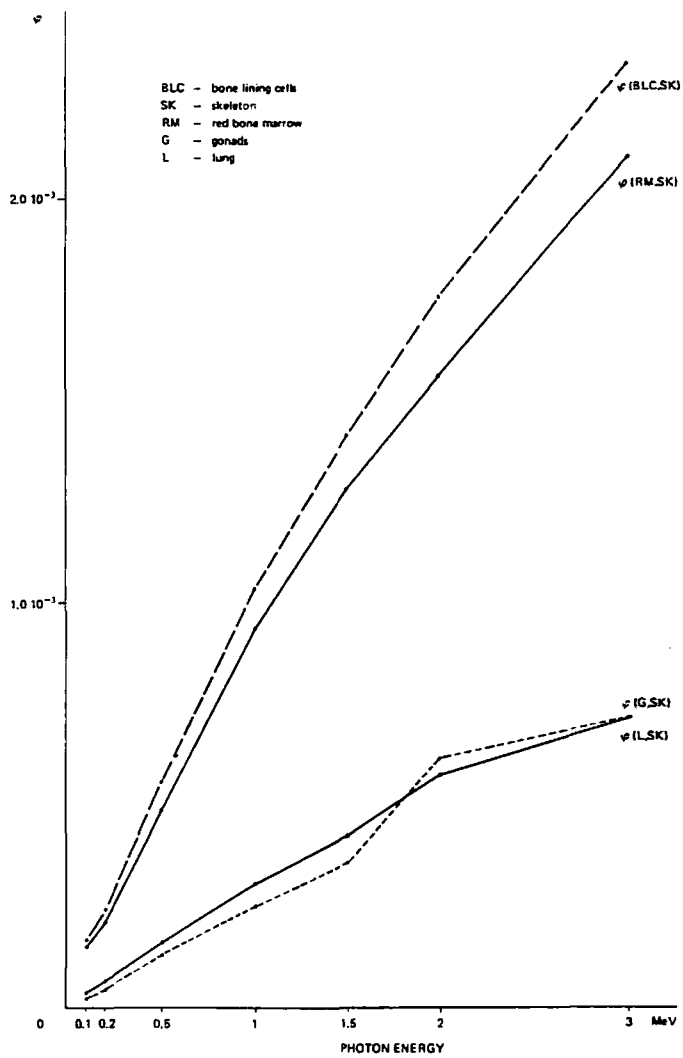

Figure XII. Dosimetric factors for several tissues for gamma-emitting radionuclides located in the skeleton (mrad y^{-1} per pCi kg^{-1})

^{14}C and ^{22}Na contribute appreciably to the dose. The production and distribution of these nuclides in the environment is presented in table 10.

1. Tritium

82. Tritium, ^{3}H, is produced naturally in the atmosphere, lithosphere and hydrosphere. The production of man-made ^{3}H in nuclear explosions and nuclear reactors is discussed in Annexes C and D. The major source of natural ^{3}H is the atmosphere, where it results from the interaction of cosmic-ray protons and neutrons with nitrogen, oxygen, and argon, the main reaction being $^{14}N + n \rightarrow {}^{12}C + {}^{3}H$ for $E_n > 4.4$ MeV. Estimates of the inventory, calculated from published values of the production rate, range from 17 to 170 MCi (table 11), the most recent estimates being 34 MCi and 28 ± 7 MCi (197, 340). It has been suggested that ^{3}H might also be ejected from the sun during solar flares (199) and from stars (83), but the contribution to the inventory from these sources has not been evaluated.

83. About 99 per cent of the ^{3}H inventory is converted to HTO and participates in the normal water cycle. According to the data contained in table 10, most of the ^{3}H inventory, which is taken to be 34 MCi, would be in the oceans, as a result of transport by rain and by

TABLE 10. DATA ON THE PRODUCTION AND DISTRIBUTION OF NATURALLY OCCURRING ^{3}H, ^{7}Be, ^{14}C AND ^{22}Na

	^{3}H	^{7}Be	^{14}C	^{22}Na
Half-life	12.3 y	53.6 d	5 730 y	2.62 y
Number of atoms produced per unit time and per unit area of the earth's surface (cm^{-2} s^{-1}) in the:				
Troposphere	$8.4\ 10^{-2}$	$2.7\ 10^{-2}$	1.1	$2.4\ 10^{-5}$
Total atmosphere	0.25	$8.1\ 10^{-2}$	2.3[a]	$8.6\ 10^{-5}$
Global inventory (MCi)	34	1	300	0.01
Distribution as a percentage of inventory in the:				
Stratosphere	6.8	60	0.3	25
Troposphere	0.4	11	1.6	1.7
Land surface and biosphere	27	8	4	21
Mixed oceanic layers	35	20	2.2	44
Deep ocean	30	0.2	92	8
Oceanic sediments			0.4	
Activity concentration in surface air (pCi m^{-3})[b]		$7\ 10^{-2}$		10^{-5}
Activity concentration in continental surface waters (pCi l^{-1})[c]	6-24			
Specific activity in terrestrial biosphere (pCi g^{-1})[d]			6.1	

Source: Reference 197.
[a] Reference 200.
[b] Reference 190.
[c] References 52, 178.
[d] Reference 330a.

TABLE 11. PUBLISHED RATES OF PRODUCTION AND CORRESPONDING INVENTORIES OF NATURAL ^{3}H

	Number of atoms produced per unit time and per unit area of the earth's surface (cm^{-2} s^{-1})	*Inventory (MCi)*	*Year of publication*	*Reference*
Atmosphere	0.10-0.20	14-28	1953	83
	0.12	17	1954	178
	0.14	20	1955	52
	1.2	170	1957	29
	1.2	170	1957	60
	1.06	150	1958	27
	0.9	130	1958	40
	0.75	100	1958	99
	0.6-1.3	80-180	1960	367
	0.25-0.35	35-150	1961	61
	0.6	80	1962	28
	0.25	34	1967	197
	0.20±0.05	28±7	1967	340
Lithosphere	10^{-3}	0.1	1954	178
Hydrosphere	10^{-6}	0.0001	1953	83

direct exchange of water vapour between air and sea water. Once in the ocean, ^{3}H is dispersed through mixing processes. Measured concentrations of natural ^{3}H in ocean surface water average about 3 pCi l^{-1} (178).

84. The land areas seem to contain about 30 per cent of the natural ^{3}H inventory (table 10). Tritium concentrations in fresh water are usually higher than in sea water. Activity concentrations of continental surface waters, measured before nuclear explosions began, were found to be in the range 6-24 pCi l^{-1} (178). Assuming that the specific activity of ^{3}H in the body is the same as that in the continental surface waters, and using the distribution of hydrogen in the Reference Man of ICRP (152), the annual doses from natural ^{3}H, calculated with the dosimetric factors given in figure X, are found to be of the order of 1 μrad in each of the four organs and tissues considered by the Committee.

2. Beryllium-7

85. Mainly because of its short half-life, most of the ^{7}Be inventory is in the atmosphere (table 10). As exemplified by measurements in the Federal Republic of Germany (190), the surface-air concentration of ^{7}Be in the temperate zones shows a regular seasonal variation with maximum values of about 100 fCi m^{-3} in spring and minimum values of about 40 fCi m^{-3} in late autumn. Using these concentrations, the annual lung absorbed dose in adults from inhalation would be about 2 μrad.

86. Reported concentrations in rain range from 2 to 130 pCi l^{-1} with an average value of about 20 pCi l^{-1} (199). In the diet, leafy vegetables have been estimated to constitute the main source of ^{7}Be, with a resulting annual whole-body absorbed dose in adults of 8 μrad (250).

3. Carbon-14

87. Natural ^{14}C is produced in the upper atmosphere by the reaction $^{14}N(n, p) \rightarrow {}^{14}C$ induced by cosmic-ray neutrons. The specific activity of biological carbon, as measured in wood samples grown in the nineteenth century, was 6.13 ± 0.03 pCi per gram of carbon (341), corresponding to an atmospheric inventory of 3.8 MCi. During the present century the specific activity of ^{14}C

in air has decreased due to the diluting effect of releases into the atmosphere of carbon dioxide from the burning of fossil fuels. By 1954 the specific activity of atmospheric carbon had been reduced some 2-5 per cent due to this process (16). The contributions of ^{14}C in the environment from nuclear explosions and from nuclear power production are discussed in Annexes C and D. According to Nydal *et al.* (260), ^{14}C activity in the human body follows that in the atmosphere with a delay of about 1.4 y.

88. Measurements of the natural ^{14}C in tree rings and in lake and ocean sediments have shown that ^{14}C levels in the atmosphere have remained fairly constant for many thousands of years, although there is a fluctuating change of 10 per cent over a period of 10 000 y (66), in addition to smaller, more random fluctuations over periods of the order of a hundred years (236). The long-term fluctuation over a period of 10 000 y is attributed to a cyclical change of the dipole strength of the earth's magnetic field, which results in a cyclical change of the cosmic-ray flux, which in turn changes the ^{14}C production rate. The causes of the fluctuations over periods of the order of a hundred years are not known.

89. Knowledge of the natural production rate of ^{14}C is useful for determining dose commitments from artificial releases into the environment. Since the Committee's 1972 report, a new estimate for the ^{14}C natural production rate has been reported. Averaged over the 11-year solar cycle, it is 2.28 atoms cm^{-2} s^{-1} (201), which is equivalent to an activity production rate of 0.038 MCi y^{-1} and is within the range of values given previously (1.6-2.5 atoms cm^{-2} s^{-1}, or 0.027-0.042 MCi y^{-1}). An independent estimate of the production rate can be computed from the total inventory of natural ^{14}C on the earth. In units of atmospheric content (which is 6.17 10^{17} g of ^{12}C), the biosphere, atmosphere and oceans contain 67 units of carbon (16). Noting that the specific activities of ^{14}C in surface ocean and deep ocean are lower than in the atmosphere by 4 and 17 per cent, respectively (46), the inventory of ^{14}C in the above reservoirs is 56 units (of the atmospheric content of ^{14}C, which is 3.8 MCi). From the estimates of Broecker (47) that the slow movement of carbon from the oceans into sediments takes place over a time scale of 100 000 years, it is inferred that about 8 per cent of the ^{14}C inventory is in sediments. The total inventory is therefore estimated to be 60 units, equivalent to some 230 MCi. This inventory is in equilibrium with a production rate of natural ^{14}C of 0.028 MCi y^{-1}. Considering the uncertainties involved in determining both the production rate and also the total ^{14}C inventory of the earth, the estimates are in reasonable agreement, particularly since no account is taken of ^{14}C entering the humus reservoir.

90. Taking the natural specific activity of ^{14}C as 6.1 pCi per gram of carbon and using the dosimetric factors presented in figure X and the concentrations of carbon, as well as the masses of organs and tissues in the Reference Man of ICRP (152), the annual absorbed doses in man are found to be 1.3 mrad in the whole body, 0.6 mrad in the lung, 0.5 mrad in the gonads, 2.0 mrad in the bone lining cells and 2.2 mrad in the red bone marrow.

4. Sodium-22

91. Even though the production rate and the atmospheric concentration of ^{22}Na are very small (table 10), the doses in man given in table 12, are higher than those arising from ^{3}H and ^{7}Be because of both the metabolic behaviour of sodium and the decay properties of ^{22}Na.

5. Annual doses from internal irradiation by cosmogenic radionuclides

92. Table 12 summarizes the data given above on the internal doses from the four cosmogenic radionuclides considered. It should be mentioned that the annual lung dose received from all the other radionuclides produced by cosmic rays has been estimated to be 10^{-3} mrad (250).

TABLE 12. ANNUAL DOSE FROM INTERNAL IRRADIATION BY COSMOGENIC ^{3}H, ^{7}Be, ^{14}C AND ^{22}Na

	Annual dose (mrad)				
Radionuclide	*Gonads*	*Lung*	*Bone lining cells*	*Red bone marrow*	*Whole-body average*
^{3}H	0.001	0.001	0.001	0.001	0.001
^{7}Be	–	0.002	–	–	0.008
^{14}C	0.5	0.6	2.0	2.2	1.3
^{22}Na	0.02	0.02	0.02	0.02	0.02

93. As can be seen from table 12, the major part of the annual dose from cosmogenic radionuclides is delivered by ^{14}C. With the present size of the world population, the annual collective dose is in the range of (2-8) 10^{6} man rad for the tissues mentioned in table 12.

B. PRIMORDIAL RADIONUCLIDES (EXCEPT RADON AND ITS SHORT-LIVED DECAY PRODUCTS)

94. The primordial radionuclides include those belonging to the ^{235}U, ^{238}U and ^{232}Th series and some other nuclides, among which only ^{40}K and ^{87}Rb are significant sources of radiation.

1. Potassium-40

95. Potassium-40, which is the major naturally occurring source of internal radiation dose, enters the body through diet. Being an essential element, potassium is under close homeostatic control in the body. The dose rates from ^{40}K can be calculated from its isotopic abundance in the biosphere and the concentration of potassium in human tissues.

96. The mass of potassium contained in the whole body varies as a function of age and sex. The mass concentration of potassium is highest in adolescent males and lowest in elderly females, the ratio of the two values being about 2. An average value for an adult male would be about 2 g of potassium per kilogram of body weight (10a, 347). According to Kaul *et al.* (179), the

mass concentration of potassium in various organs and tissues of interest to the Committee are 0.5 g kg^{-1} in bone, 4.4 g kg^{-1} in red marrow, 2.2 g kg^{-1} in lungs, 2.1 g kg^{-1} in testes and 1.35 g kg^{-1} in ovaries. The annual absorbed doses corresponding to these concentrations can be assessed using the dosimetric factors presented in figures IX to XII, the masses of organs and tissues in the Reference Man of ICRP (152) and the isotopic ratio of ^{40}K (0.0118 per cent). The annual absorbed doses are found to be 27 mrad in red bone marrow and 15-17 mrad in the lungs, gonads, bone lining cells and whole body (table 13).

TABLE 13. TISSUE CONCENTRATION AND ANNUAL ABSORBED DOSE DUE TO ^{40}K AND ^{87}Rb

	Potassium			*Rubidium*		
Organ or tissue	*Mass concentration of element (g kg^{-1})*	*Activity concentration of ^{40}K (pCi kg^{-1})*	*Annual absorbed dose (mrad)*	*Mass concentration of element (mg kg^{-1})*	*Activity concentration of ^{87}Rb (pCi kg^{-1})*	*Annual absorbed dose (mrad)*
Lung	2.1	1 700	17	9.2	220	0.4
Testes	2.1	1 700	17	20	480	0.8
Ovaries	1.35	1 100	12	–	–	–
Bone	0.5	400	–	26.7	640	–
Red marrow	4.4	3 600	27	7.8	190	0.4
Yellow marrow	0.6	500	6	7.8	190	0.3
Bone lining cells	–	–	15	–	–	0.9
Whole-body average	2	1 600	17	9.7	230	0.4

97. Yamagata (373) studied the variability of the mass of potassium in adult man. He found a normal distribution with an average of 136 g and a standard deviation of 28 g. Using these values, 95 per cent of the adult males would receive annual absorbed doses in the following ranges (mrad): gonads and endosteal cells, 9-21; lung, 10-24; red bone marrow, 16-38.

2. Rubidium-87

98. Very little is known about the behaviour of rubidium in man's environment. The doses from ^{87}Rb have been calculated from the mass concentrations of rubidium in the ICRP Reference Man (152), which are 9.2 $\mu g\ g^{-1}$ in the lung, 20 $\mu g\ g^{-1}$ in the testes and 26.7 $\mu g\ g^{-1}$ in the bone. The value for red bone marrow has been assumed to be equal to the average concentration in soft tissues, which is 7.8 $\mu g\ g^{-1}$. The annual absorbed doses obtained range from 0.4 to 0.9 mrad in the organs and tissues of interest to the Committee (table 13).

3. Uranium and thorium series

99. Uranium-238 and thorium-232 are each the head of a series of more than ten nuclides (tables 2 and 3). In the same way as in the 1972 report, the ^{238}U and the ^{232}Th series can be classified in the subseries in which the activity of the precursor to a large degree controls the activities of the decay products. For the ^{238}U series, the subseries include: (a) ^{238}U, two short-lived nuclides and ^{234}U; (b) ^{226}Ra, which is frequently separated in the environment from its precursor, ^{230}Th, of little dosimetric significance in natural background, and from its decay product, ^{222}Rn, which is an isotope of a noble gas; (c) ^{222}Rn and its short-lived decay products (through ^{214}Po) a subseries which is important both for external radiation because of the energetic gamma rays emitted through decay of ^{214}Bi, and for internal radiation, and is discussed in section C of this chapter; (d) the long-lived ^{222}Rn decay products ^{210}Pb, ^{210}Bi and ^{210}Po.

100. The ^{232}Th series has also been classified in three subseries: (a) ^{232}Th itself; (b) the sequence of ^{228}Ra, ^{228}Ac, ^{228}Th and ^{224}Ra; (c) ^{220}Rn and its decay products. Because of their similarities, ^{232}Th and ^{230}Th will be discussed together, the sequences headed by ^{228}Ra and ^{226}Ra will be treated in the same section and ^{220}Rn and its decay products will be considered with ^{222}Rn. The decay chain of ^{235}U is not of dosimetric significance and will not be dealt with here.

101. Since all the long-lived (half-life >1 y) radionuclides of the ^{238}U and ^{232}Th series are bone seekers, an important parameter for dose assessment is the average activity concentration of those radionuclides in human bone. The comparison of the reported concentrations in the skeleton is complicated since results are given per unit of various quantities such as wet, fresh, dry-fat-free, ash or calcium mass and the relationships between these quantities cannot always be readily assessed. In this report, the conversion factors that have been adopted are derived from data published by the ICRP (151, 152). The weight of the skeleton of an adult man is taken to be 10 kg (wet or fresh weight), including 5 kg of bone (dry or dry-fat-free weight), which yields 2.7 kg of ash. The total mass of calcium in the skeleton is 1 kg. Unless otherwise indicated, the activity concentrations in this document are expressed per unit mass of dry bone. The following information has also been used for dose calculations: the 5 kg of bone comprise 4 kg of compact bone and 1 kg of cancellous bone; the total bone surface in an adult man is 10 m^2 with 5 m^2 in compact bone and 5 m^2 in cancellous bone (151).

(a) *Uranium*

102. In this Annex, uranium is assumed to consist of ^{238}U in radioactive equilibrium with ^{234}Th, ^{234}Pa and ^{234}U, so that 1 g of uranium contains 0.33 μCi of each

of the four radionuclides. In fact, it is known that a disequilibrium state between ^{238}U and ^{234}U is rather common in nature. The mechanism by which the isotopes ^{238}U and ^{234}U can be fractionated in the ground is the Szilard-Chalmers effect. In the three-step decay of ^{238}U to ^{234}U, the daughter atom (^{234}U) is displaced from the crystal lattice. The recoil atom ^{234}U is liable to be oxidized to the hexavalent stage and therefore can be leached into the water phase more easily than its parent nuclide ^{238}U (56). Depending on the origin of the water sample, the ^{234}U to ^{238}U activity concentration ratio can vary greatly, and values ranging from 0.66 up to 9 have been reported (56, 337).

103. In the atmosphere, the main natural source of uranium are the dust particles resuspended from the earth. Assuming a dust loading of about 100 $\mu g\ m^{-3}$ in surface air of populated areas, and taking an average ^{238}U activity concentration in soil of 0.7 $pCi\ g^{-1}$ (table 5), the activity concentrations in air are estimated to be about $7\ 10^{-5}$ $pCi\ m^{-3}$. Measured values in ground-level air (114, 160, 226) are in good agreement with this estimate. This average concentration corresponds to a daily intake by adults through inhalation of $1.4\ 10^{-3}$ pCi.

104. The dietary intake of ^{238}U has been measured in several countries (116, 186, 259, 311, 361) and found to lie in the relatively narrow range of 0.3-0.5 $pCi\ d^{-1}$ in areas of "normal" natural radioactivity (table 14). The activity concentration of ^{238}U in tap water being usually less than 0.03 $pCi\ l^{-1}$ (14, 186), the contribution of drinking water to the total dietary intake is in general small. However, it should be mentioned that very high concentrations of uranium in tap water have been reported. In the USSR, activity concentrations as high as 70 $pCi\ l^{-1}$ have been observed (31); in Helsinki, Finland, concentrations of the order of 1000 $pCi\ l^{-1}$ have been measured in several wells, the highest concentration being about 5000 $pCi\ l^{-1}$ (176). According to the authors (176), the very high concentrations of uranium in the water of those wells are probably caused by small, localized uranium-rich deposits.

TABLE 14. URANIUM-238 IN THE HUMAN DIET AND BODY IN VARIOUS COUNTRIES

Country	*Dietary intake ($pCi\ d^{-1}$)*	*Urinary excretion ($pCi\ d^{-1}$)*	*Activity in skeleton (pCi)*	*Activity in whole body (pCi)*	*Reference*
France	0.2-0.9				311
Japan					
Kyoto and Sapporo	0.50				186
Okayama[a]	1.2	0.03			375
Control area	0.3	0.003			375
United Kingdom	0.40	0.13	21	33	69, 115, 116
United States					
New York	0.43	0.05	18	26	361
Chicago	0.46				361
San Francisco	0.43				361
USSR	about 0.3				186

[a] Mean of the values observed in two villages located near a uranium mine and its refinery.

105. There is experimental evidence (332) that the fraction of uranium absorbed in the gastro-intestinal tract is a few per cent of the amount ingested. As the intake through inhalation is only about 1 $fCi\ d^{-1}$, the blood uptake through inhalation is small compared to that from ingestion. This is confirmed by the data contained in table 14 which show that the daily urinary excretion, expected to be approximately equal to the daily uptake (145), exceeds substantially the intake by inhalation.

106. In man, the results of measurements of activity concentration of ^{238}U in soft tissues range from 0.03 to 0.3 $pCi\ kg^{-1}$, while those in bone are from 4 to 5 $pCi\ kg^{-1}$ (116, 361). From the data contained in table 14 it can be estimated that a daily dietary intake of 0.4 pCi of ^{238}U leads to concentrations in soft tissues of 0.2 $pCi\ kg^{-1}$ and to a bone concentration of 4 $pCi\ kg^{-1}$ These values have been used to calculate the absorbed doses (table 15). In bone, uranium has been taken to be homogeneously distributed throughout the volume. This has been shown to be approximately true by neutron-induced autoradiographic studies, although higher concentrations were found on bone surfaces (307, 370).

(b) *Thorium*

107. From a dust loading of 100 $\mu g\ m^{-3}$ and a ^{232}Th activity concentration in soil of 0.7 $pCi\ g^{-1}$ (table 5), the activity intake through inhalation per unit time is about 1 $fCi\ d^{-1}$. There is no direct information on the dietary activity intake of ^{232}Th per unit time but an indirect estimate of about 0.1 $pCi\ d^{-1}$ has been proposed (250). The contribution of this route to the body content is probably negligible because of the very low absorption of thorium through the gastro-intestinal tract.

TABLE 15. TISSUE ACTIVITY CONCENTRATION AND ANNUAL ABSORBED DOSE DUE TO RADIONUCLIDES OF THE ^{238}U-^{234}U SUBSERIES

Organ or tissue	Activity concentration of ^{238}U, ^{234}Th, ^{234m}Pa or ^{234}U (pCi kg^{-1})	Annual absorbed dose (mrad)					
		^{238}U	^{234}Th	^{234m}Pa	^{234}U	Total	
		(α)	(β, γ)	(β, γ)	(α)	(α)	(β, γ)
Lung	0.2	0.02	0.0002	0.003	0.02	0.04	0.003
Testes	0.2	0.02	0.0002	0.003	0.02	0.04	0.003
Ovaries	0.2	0.02	0.0002	0.003	0.02	0.04	0.003
Bone	4	–	–	–	–	–	–
Red marrow	0.2	0.02	0.0006	0.02	0.03	0.05	0.02
Yellow marrow	0.2	–	–	–	–	–	–
Bone lining cells	0.2	0.12	0.003	0.04	0.14	0.3	0.04

108. Measured levels in rib bone show a linear increase with age (216). The average activity concentration in ash would be about 1 fCi g^{-1} in adults, which is about 10 times less than the corresponding values for ^{238}U. However, thorium is known to deposit on the endosteum, and the dose rates in this tissue per unit activity of thorium in bone are much higher than those for uranium, because the latter element is distributed over the total mass of bone. The calculated dose rates to bone tissues from ^{232}Th are shown in table 16.

TABLE 16. TISSUE ACTIVITY CONCENTRATION AND ANNUAL ABSORBED DOSE DUE TO ^{230}Th AND ^{232}Th

Organ or tissue	Activity concentration of ^{230}Th or ^{232}Th (pCi kg^{-1})	Annual absorbed dose (mrad)	
		^{230}Th	^{232}Th
Lung	0.5	0.04	0.04
Gonads	0.05	0.004	0.004
Bone (average)	0.5	–	–
Trabecular bone	1.3	–	–
Red marrow	0.05	0.05	0.04
Bone lining cells	–	0.8	0.7

109. Pavlovskaya (268) measured the activity concentration of ^{232}Th in soft tissues and found it to be one fifth to one fourth of that in the skeleton and thus about one tenth of that in dry bone. Taking the activity concentration in bone to be 0.5 pCi kg^{-1}, the activity concentration in soft tissues would therefore be about 0.05 pCi kg^{-1}. It has been suggested by Wrenn (370), on the basis of Budinger's measurements (48), that the ^{232}Th concentration could be much higher in lung tissue than in the other soft tissues. Using an intake per unit time through inhalation of 1 fCi d^{-1}, a deposition of 25 per cent in the pulmonary region, and a biological half-life of 4 y, the equilibrium activity concentration in lung tissue would be about 0.5 pCi kg^{-1}. The resulting annual absorbed dose to soft tissue is presented in table 16.

110. The Committee is not aware of any study dealing with concentrations of ^{230}Th in man. However, it is likely that the ^{230}Th and the ^{232}Th levels in man are very similar, because their activity concentrations in soil are about equal and their physical half-lives are very much longer than man's life span. The annual absorbed doses in several tissues from ^{230}Th are given in table 16.

(c) *Radium*

111. Radium has 13 known radioactive isotopes, whose atomic weights range from 213 to 230 and whose radioactive half-lives range from 10^{-3} s to 1600 y. From the point of view of human radiation exposure from natural background only ^{226}Ra and ^{228}Ra, which gives rise to ^{224}Ra, are of significance.

112. *Inhalation.* As in the case of uranium and thorium, the main natural source of radium in the atmosphere is the resuspension of soil particles; this corresponds to a calculated activity intake of about 1 fCi d^{-1}.

113. *Ingestion.* Food consumption is a much more important source of radium intake and fractional blood uptake than inhalation. The average dietary activity intake per unit time of ^{226}Ra in areas of normal radiation background is of the order of 1 pCi d^{-1} (table 17). Typical ^{226}Ra levels in most components of the diet range from 0.1 to 5 pCi kg^{-1}, but some individual foods, such as Brazil nuts and Pacific salmon, contain much larger concentrations of ^{226}Ra. Although much less documented, the dietary activity intake of ^{228}Ra in areas of normal radiation background seems to be about the same as that of ^{226}Ra (278).

114. The contribution of water to the total intake is in general small when the drinking-water supplies are drawn from surface waters. However, ^{226}Ra levels of 1 to 10 pCi l^{-1} are not exceptional in well and mineral waters (5, 176, 296, 316). Available information on the concentrations of ^{228}Ra in water is limited, but it seems that they are of an order of magnitude lower than the corresponding concentrations of ^{226}Ra (14, 176).

115. Two well known populated areas with high concentrations of thorium and uranium in their soil are located along the coast of Kerala in India and in the Araxá-Tapira region in Brazil. The estimated average daily intakes of ^{226}Ra and ^{228}Ra of the Indian population along the Kerala coast are 3 and 160 pCi, respectively (58, 240). In Brazil, a survey in the

TABLE 17. RADIUM-226 IN THE HUMAN DIET AND DRY BONE IN VARIOUS AREAS

Area	Dietary intake (pCi d^{-1})	Dietary intake pCi $(gCa)^{-1}$	Mean activity concentration in dry bone[a] (pCi kg^{-1})	Bone/diet[b] pCi kg^{-1} per pCi d^{-1}	Bone/diet[b] Observed ratio	Reference
Areas of normal external radiation background						
Argentina	0.8	1.1	6.6	8.2	0.030	30
Australia			5.4			357
Canada			3.2			357
Chile			2.2			357
Congo			12			357
France	1.1	1.1				311
Germany, Fed. Rep. of			7.0			324
Guatemala			2.7			357
India						
Bombay	0.8	1.6	4.3	5.4	0.013	58
Tarapur	0.5	1.0				177
Israel			19			357
Italy	1.4	2.8				42
Japan						
Sapporo	0.4	0.8	1.6	4.0	0.016	113a
Kyoto	1.0	2.9	7.5	7.5	0.019	113a
Poland						
Eastern			7.7			163
Northern			5.3			
Southern			6.5			
Western			32.6			
Puerto Rico 1	0.7	1.3	3.4	4.8	0.013	113
Puerto Rico 2			2.7			357
South Africa			5.9			357
Ukrainian SSR			21			245
United Kingdom	1.2	1.1	8.1	6.7	0.037	357, 314
United States						
Boston			7.6			357
Houston			12			357
Illinois			20			135
New England			8.6			143
New York 1	1.7	1.7	7.2	4.2	0.021	85
New York 2			5.4			357
San Francisco	0.8	0.8	6.2	7.7	0.039	85
Wisconsin			6.5			222
Arithmetic mean	0.9	1.5	8.5	6.1	0.024	
Area of high external radiation background						
Kerala, India	3.3	6.6	77	23	0.058	58

[a] The data have been either taken directly from the references or converted in terms of dry bone using the factors of paragraph 101.

[b] The left-hand column gives the bone-to-diet quotient, the units used being pCi kg^{-1} for the activity concentration in dry bone and pCi d^{-1} for the dietary intake. The right-hand column gives the corresponding values of the bone-to-diet observed activity ratio, the unit used being pCi per gram of Ca for both bone and diet.

Araxá-Tapira region showed that, out of a population of 1670 people living in and around the radioactive anomalies of Barreiro and Tapira, only 196 individuals are ingesting alpha emitters at a level five times or more than that of a similar group living in Rio de Janeiro. Their intake of radium per unit time ranged from 10 to 40 pCi d^{-1} of ^{226}Ra and from 60 to 240 pCi d^{-1} of ^{228}Ra (347).

116. *Distribution in man and dose rates.* When radium is taken into the body, its metabolic behaviour is similar to that of calcium, and an appreciable fraction is deposited on bone surfaces and in areas of active bone turnover (82). Rowland (300) has shown that, after high intakes, approximately half of the initial activity in man is deposited in "hot spots" and half in the diffuse component. The initial deposition in hot spots is due presumably to the fact that these are areas of actively growing bone where mineralization is occurring. Even in the case of relatively low-level dietary intake, the same hot-spot accumulation is thought to occur, but at a lower activity level (125). About 70-90 per cent of the radium in the body is contained in bone (151), the remaining fraction being distributed approximately uniformly in soft tissues. In the areas of normal radiation background, the ^{226}Ra concentrations in bone range roughly from 2 to 20 pCi kg^{-1} (table 17), with an arithmetic mean of about 8 pCi kg^{-1}. Several studies

(see, for example, reference 325) have shown that the ^{226}Ra concentration in bone seems to be independent of age.

117. The relationship between the dietary intake and the skeletal content can be estimated from measurements in countries where both the concentrations in bone and the dietary intake have been published (table 17). The bone-to-diet quotient, expressed in pCi kg^{-1} per (pCi d^{-1}), ranges from 4.0 to 8.2 with an average of 6.1. The "observed ratio" between the activity per gram of calcium in the bone and in the diet ranges from 0.013 to 0.039, with an average of 0.024.

118. Another way to estimate the bone-to-diet relationship is to use the model developed by ICRP on the metabolism of alkaline earths in adult man (151). According to that model, a blood uptake of 1 pCi of ^{226}Ra yields a time-integral of the bone activity of 126.3 pCi d, and a time-integral of the whole-body activity of 143.7 pCi d. Therefore, a continuous blood uptake of 1 pCi d^{-1} would yield an equilibrium activity of 126 pCi in the skeleton corresponding to an average bone activity concentration of 25 pCi kg^{-1}. Since the fractional blood uptake for radium is 0.15-0.20 (125), an intake of about 6 pCi d^{-1} corresponds to a blood uptake of 1 pCi d^{-1}. The bone-to-diet quotient is therefore calculated to be 4.2 pCi kg^{-1} per pCi d^{-1}, which is in reasonable agreement with the value of 6.1 given in paragraph 117.

119. If all the values of the daily dietary intake and of the activity concentrations in bone shown in table 17 are taken into account, the averages are 0.9 pCi d^{-1} and 8.5 pCi kg^{-1}, respectively, corresponding to a bone-to-diet quotient of 9 pCi kg^{-1} per pCi d^{-1}, which is somewhat higher than the two estimates in the previous paragraphs. The difference may be due to the high concentrations in bone found in the Congo, Israel, western Poland, the United States (Houston and Illinois) and the Ukrainian Soviet Socialist Republic. The ^{226}Ra dietary intake in these regions might be higher than average. If they are excluded, the bone-to-diet quotient becomes 6 pCi kg^{-1} per pCi d^{-1}.

120. The fraction of ^{226}Ra distributed in the soft tissues will be taken to be 17 per cent, as given in ICRP Publication 20 (151). The average activity of human soft tissues would thus be 0.13 pCi kg^{-1}.

121. The concentration of ^{228}Ra in human bone could be expected to be lower than that of ^{226}Ra because of the shorter half-life of the former and the estimated biological half-life of radium in the body, which is of the order of 10 years (151, 363). Thus, the ^{228}Ra activity would be limited by its physical half-life to about 30 per cent of the ^{226}Ra activity. This is consistent with the ICRP model (151), from which a figure of 27 per cent can be derived. In fact, in the few studies dealing with the determination in bone of ^{228}Th, which can be assumed to be in radioactive equilibrium with ^{228}Ra, the average ratio of ^{228}Th to ^{226}Ra in bone ash was found to vary between 0.25 and 0.5 (143, 215, 324). Using a value of 0.3, the average ^{228}Ra activity in bone would be 2.4 pCi kg^{-1} in areas of normal background radiation. Since no measurement of ^{228}Ra in soft tissues could be found in the literature, the figure of 0.1 pCi kg^{-1} derived from the ICRP model (151) is used in this Annex.

122. The dose rates in bone lining cells and bone marrow presented in tables 18 and 19 have been calculated using the same assumptions as in the 1972 report: (a) an average retention factor in the skeleton and in the soft tissues of 0.33 for ^{222}Rn and of 1.0 for ^{220}Rn and (b) a uniform concentration of radium and its decay products over the total mass of mineral bone. In fact, with respect to ^{228}Ra and its decay products, it is known that a fraction of ^{228}Th, which is the long-lived alpha emitter of the radioactive sequence, migrates to the endosteum (330). Furthermore, direct intake of ^{228}Th and ^{224}Ra, although contributing to a small extent to the skeletal activity, leads to deposition of those radionuclides on bone surfaces. Because a fraction of the activity of the decay products of ^{228}Ra is surface distributed, the doses from that sequence in bone marrow and in bone lining cells may therefore be somewhat higher than indicated in table 19.

123. Data on the activity of radium in the skeleton of the populations living in the high radiation areas of Brazil and India are very scarce. In Brazil, the mean ^{226}Ra concentration in the teeth of the population living in the Araxá-Tapira region has been estimated as 85 fCi per gram of ash, which corresponds to an activity in the skeleton of about 230 pCi, if it is assumed that the concentration in teeth is the same as that in bone. In India, the analysis of a femur bone yielded a ^{226}Ra concentration per unit mass of ash of 143 fCi g^{-1}, which corresponds to a skeletal activity of about 400 pCi (58).

TABLE 18. TISSUE ACTIVITY CONCENTRATION AND ANNUAL ABSORBED DOSE DUE TO ^{226}Ra AND ITS SHORT-LIVED DECAY PRODUCTS

Organ or tissue	*Activity concentration of ^{226}Ra (pCi kg^{-1})*	*Activity concentration of the decay products of ^{226}Ra (pCi kg^{-1})*	*Annual tissue absorbed dose (mrad)*							
			^{226}Ra (α)	^{222}Rn (α)	^{218}Po (α)	^{214}Pb (β, γ)	^{214}Bi (β, γ)	^{214}Po (α)	*Total* (α)	*Total* (β, γ)
Lung	0.13	0.043	0.01	0.004	0.005	0.0003	0.001	0.006	0.03	0.001
Gonads	0.13	0.043	0.01	0.004	0.005	0.0004	0.001	0.006	0.03	0.001
Bone	8	2.6	–	–	–	–	–	–	–	–
Red marrow	0.13	0.043	0.03	0.01	0.02	0.003	0.009	0.03	0.09	0.01
Yellow marrow	0.13	0.043	–	–	–	–	–	–	–	–
Bone lining cells	–	–	0.27	0.11	0.13	0.009	0.02	0.18	0.7	0.03

TABLE 19. ANNUAL TISSUE ABSORBED DOSE

Organ or tissue[a]	^{228}Ra (β)	^{228}Ac (β, γ)	^{228}Th (α)	^{224}Ra (α)	^{220}Rn (α)	Annual
Lung	$3\ 10^{-5}$	$1\ 10^{-3}$	$1.0\ 10^{-2}$	$1.1\ 10^{-2}$	$1.2\ 10^{-2}$	
Gonads	$3\ 10^{-5}$	$1\ 10^{-3}$	$1.0\ 10^{-2}$	$1.1\ 10^{-2}$	$1.2\ 10^{-2}$	
Red marrow	$6\ 10^{-5}$	$8\ 10^{-3}$	$2.5\ 10^{-2}$	$2.8\ 10^{-2}$	$3.4\ 10^{-2}$	
Bone lining cells	$2\ 10^{-4}$	$1\ 10^{-2}$	$1.7\ 10^{-1}$	$1.8\ 10^{-1}$	$2.1\ 10^{-1}$	

[a] The activity concentration in the lung, gonads and red marrow is assumed to be 0.1 pCi kg^{-1}. The activity concentration in bone is taken to be 4 pCi kg^{-1} for cancellous bone and 2 pCi kg^{-1} for

(d) *Long-lived decay products of ^{222}Rn*

124. The ^{210}Pb-^{210}Bi-^{210}Po chain is a significant component of the dose from internal irradiation by natural alpha emitters. When the three radionuclides are in radioactive equilibrium, the dose from ^{210}Po is much higher than from ^{210}Pb and ^{210}Bi, and on this basis ^{210}Po could be considered separately. However, the activity concentrations of ^{210}Po, in the environment as well as in man, are usually closely related to those of ^{210}Pb, which is its long-lived precursor and acts as a carrier. For that reason, ^{210}Po and ^{210}Pb will be dealt with together. The half-life of ^{210}Bi is short compared to that of ^{210}Pb. Therefore, ^{210}Bi will almost always be assumed to be in equilibrium with ^{210}Pb in the various compartments of the environment and of the human body.

(i) *Sources and levels in the environment*

125. *Air.* The main source of ^{210}Pb and ^{210}Po in the atmosphere is ^{222}Rn emanation from the ground. The amount of atmospheric ^{210}Pb produced in this way has been estimated to be 0.6 MCi y^{-1} (164), which would lead to an equilibrium activity of ^{210}Pb and ^{210}Po in the atmosphere of about 20 MCi if the air concentrations were governed by radioactive decay only. However, tropospheric aerosols to which these radionuclides are attached are scavenged from the atmosphere through wash-out and dry deposition with a mean residence time of about 10 d (91). The inventories are therefore about 20 kCi for ^{210}Pb (164) and 2 kCi for ^{210}Po. The concentrations of these nuclides in surface air depend mainly on the rate of emanation of ^{222}Rn from the ground and on the latitudinal distribution of land and sea areas. Consequently, they are highest in the subtropical and temperate latitudes of the northern hemisphere, as illustrated in figure XIII for ^{210}Pb (295). In the middle latitudes of the northern hemisphere, the average concentrations of ^{210}Pb and ^{210}Po have been estimated to be 14 fCi m^{-3} (162) and 3.3 fCi m^{-3} (267), respectively. It has been suggested (244) that a significant source of ^{210}Po in surface air could be vegetative transpiration.

126. *Rain and drinking water.* The global distribution of ^{210}Pb and ^{210}Po in rain water follows the same pattern as that in surface air, being highest in the middle latitudes (fig. XIV). The annual averages of the

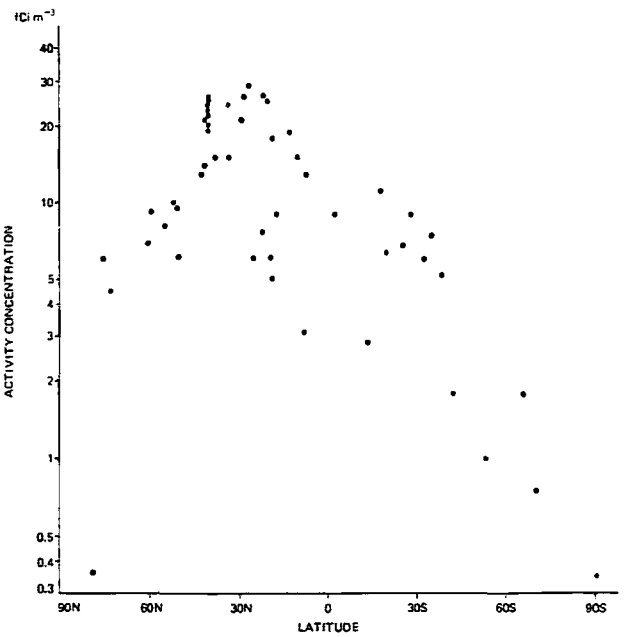

Figure XIII. Latitudinal distribution of ^{210}Pb in surface air (295)

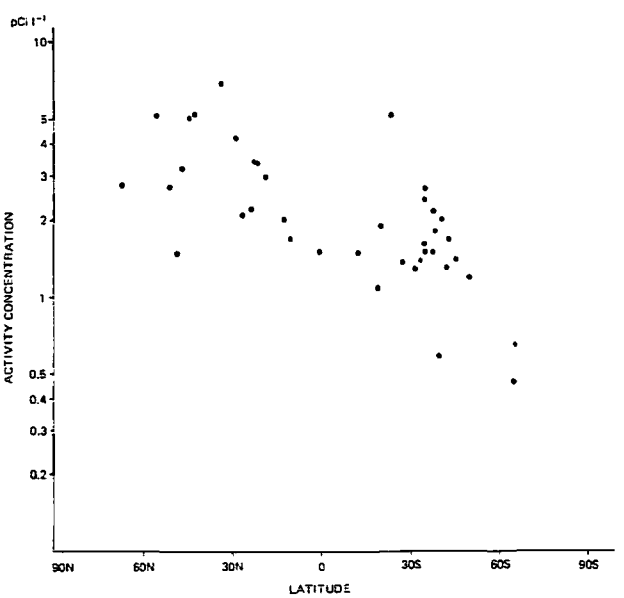

Figure XIV. Latitudinal distribution of ^{210}Pb in rain water (295)

FROM ^{228}Ra AND ITS DECAY PRODUCTS

Tissue absorbed dose (mrad)							
^{216}Po	^{212}Pb	^{212}Bi		^{212}Po	^{208}Tl	Total	
(α)	(β, γ)	(α)	(β, γ)	(α)	(β, γ)	(α)	(β, γ)
$1.3\ 10^{-2}$	$4\ 10^{-4}$	$4\ 10^{-3}$	$8\ 10^{-4}$	$1.0\ 10^{-2}$	$2\ 10^{-3}$	$6\ 10^{-2}$	$4\ 10^{-3}$
$1.3\ 10^{-2}$	$3\ 10^{-4}$	$4\ 10^{-3}$	$8\ 10^{-4}$	$1.0\ 10^{-2}$	$2\ 10^{-3}$	$6\ 10^{-2}$	$4\ 10^{-3}$
$3.9\ 10^{-2}$	$2\ 10^{-3}$	$1.2\ 10^{-2}$	$1\ 10^{-2}$	$4.3\ 10^{-2}$	$7\ 10^{-3}$	$18\ 10^{-2}$	$3\ 10^{-2}$
$2.4\ 10^{-1}$	$5\ 10^{-3}$	$6.5\ 10^{-2}$	$1.5\ 10^{-2}$	$2.1\ 10^{-1}$	$1\ 10^{-2}$	$10.8\ 10^{-1}$	$4\ 10^{-2}$

compact bone, yielding an average concentration per unit mass of bone of 2.4 pCi kg^{-1}; the activity concentration in yellow marrow is assumed to be 0.1 pCi kg^{-1}, the same as in other soft tissues.

concentration of ^{210}Pb in rain at various locations have been found to vary between 0.2 and 7 pCi l^{-1} (295), a typical value for the continental stations of the middle northern latitudes being 3 pCi l^{-1}. Reported values of the ^{210}Po/^{210}Pb activity concentration ratio in rain water range from 0.1 to 0.54 (267). Activity concentrations in drinking water are usually less than 0.1 pCi l^{-1}. However, concentrations in mineral water or in well water may reach the levels observed in rain water.

127. *Soil.* The activity concentrations of ^{210}Pb and ^{210}Po in the top layer of soil are not strictly equal to those of ^{226}Ra because (a) a fraction of ^{222}Rn diffuses through soil into the atmosphere and (b) ^{210}Pb and ^{210}Po are deposited on the soil surface through dry and wet fallout. Assuming a deposition velocity of $5\ 10^{-3}$ m s^{-1} and an atmospheric concentration of 14 fCi m^{-3}, the dry deposition of ^{210}Pb in the northern middle latitudes would occur at the rate of 2.2 mCi km^{-2} y^{-1}, corresponding to an equilibrium activity in the deposit of 68 mCi km^{-2}. With a mean annual precipitation of 800 mm and a concentration in rain or snow of 3 pCi l^{-1}, the rate of wet deposition of ^{210}Pb would be 1.2 mCi km^{-2} y^{-1}, leading to an equilibrium value of the deposit of 37 mCi km^{-2}. Assuming that the amount deposited is contained within the top 20 cm of soil, the ^{210}Pb activity concentration in that layer, at equilibrium, would be 0.2 pCi g^{-1} from dry deposition and 0.1 pCi g^{-1} from wet deposition. The average activity concentration of ^{226}Ra in soil being about 0.7 pCi g^{-1} (table 5), the activity of ^{210}Pb in the top 20 cm of soil is expected to be about 30 per cent higher than that of ^{226}Ra if the fraction of ^{222}Rn retained in soil is taken to be 0.9. Measurements of ^{210}Pb and ^{226}Ra in the top layers of soil which have been conducted in several countries confirm that the relative importance of fallout ^{210}Pb, as assessed above, is reasonably correct. In Massachusetts (United States), ^{210}Pb from fallout was found to migrate to a depth of 40 cm (121); over that depth, the average ^{210}Pb/^{226}Ra activity ratio was 1.9. In another sample of soil taken in Maryland (United States), the migration of ^{210}Pb seemed to extend up to 30 cm, the average ^{210}Pb/^{226}Ra over that layer being about 1.2 (4). In New Zealand, the results of measurements carried out on four types of soil show that that portion of ^{210}Pb which is due to fallout tends to remain within the top 15 cm of the soil and that this portion constitutes from 18 to 34 per cent of the total ^{210}Pb in this depth (17). In Poland, similar measurements, limited to a depth of 10 cm, show that in inland areas the excess ^{210}Pb is 23 per cent while in coastal areas, where the ^{210}Pb deposition is smaller, the excess ^{210}Pb is only 6 per cent over the top 10 cm of soil (166).

128. *Plants.* The concentration of ^{210}Pb and ^{210}Po in plants is a function of both direct deposition on the leaves and root uptake from the soil. The relative importance of these two pathways is controversial. Francis *et al.* (90) have studied tobacco and vegetables under greenhouse and field conditions. They found that under greenhouse conditions little ^{210}Pb or ^{210}Po was detected in the plants, while under field conditions the ^{210}Pb and ^{210}Po levels increased. They concluded that the major source of ^{210}Po in vegetation is from fallout of ^{210}Pb with decay to ^{210}Po. A similar conclusion has been reached by Hansen and Watters (118), who compared the concentrations obtained in plants grown in control soil and in $^{210}PoO_2$-contaminated soil. The ^{210}Po activity concentrations per unit mass of dry weight measured in the vegetables grown in control soil ranged from 10 to 100 pCi kg^{-1}. On the other hand, studies of tobacco by Tso *et al.* (344) suggest the source of ^{210}Po in plants may be root uptake of ^{210}Pb. Tobacco plants exposed to a 500-fold increase of ^{222}Rn in a greenhouse only exhibited a 2-fold increase in ^{210}Po content. In a study of the transfer of ^{210}Pb and ^{210}Po added to soil as nitrate, Tso and Fisenne (345) state that the principal route of entry of ^{210}Pb and ^{210}Po in the tobacco plant is probably root absorption.

(ii) *Human intake*

129. *Inhalation.* The average concentrations in surface air given above are 14 fCi m^{-3} for ^{210}Pb and 3.3 fCi m^{-3} for ^{210}Po. Assuming that an adult inhales 20 m^3 of air daily (152), the intakes of non-smokers are estimated to be 0.3 pCi d^{-1} of ^{210}Pb and 0.07 pCi d^{-1} of ^{210}Po. Since a cigarette contains about 0.6 pCi of ^{210}Pb and 0.4 pCi of ^{210}Po (267) and both nuclides are volatile at the burning temperature of tobacco, cigarette smoking will lead to a substantial increase in the intake of ^{210}Pb and ^{210}Po through inhalation. About 10 per cent of the ^{210}Pb and 20 per cent of the ^{210}Po contained in the cigarette will enter the lung with the main smoke stream (267). Therefore, for a person smoking 20 cigarettes a day, the values of the estimated intakes are 1.2 pCi for ^{210}Pb and 1.6 pCi for ^{210}Po.

However, it should be pointed out that the conditions of inhalation while smoking are very different from those in normal respiration.

130. *Ingestion.* For non-smokers, consumption of food is usually the most important route by which ^{210}Pb and ^{210}Po enter the human organism. The dietary intake is presented in table 20. In cereal products, vegetables and meat, the typical concentration of ^{210}Pb is 2-5 pCi kg^{-1}, and the ^{210}Po/^{210}Pb ratio is in the range 0.5-1.0. The concentration in milk is lower by an order of magnitude. These products are the main components of the diet in the areas of normal intake (table 20). In these areas the values of the intake of ^{210}Pb and ^{210}Po lie between 1 and 10 pCi d^{-1}, the contribution of drinking water to the intake being only a few per cent. A value of 3 pCi d^{-1} will be taken as representative of the intake of ^{210}Pb and ^{210}Po in areas of normal radiation background. The actual value of the intake in a given area depends to a certain extent upon the concentration of these nuclides in surface air and rain water. However, the published values of the dietary intake of ^{210}Pb and its average concentration in surface air and rain water in the same regions (table 21) do not seem to be correlated.

131. High concentrations of ^{210}Po are observed in the edible portions of aquatic organisms, for which it is now well established that the ^{210}Po/^{210}Pb activity concentration ratio is greater than 1 (57). The ^{210}Po concentrations in the muscles of fish and in molluscs are approximately 20 and 500 pCi kg^{-1} (267). The intakes of ^{210}Pb and ^{210}Po in populations consuming large

TABLE 20. COMPARISON OF THE DIETARY INTAKE OF ^{210}Pb AND ^{210}Po IN AREAS OF NORMAL AND HIGH INTAKE

Area	Dietary intake (pCi d^{-1}) ^{210}Pb	Dietary intake (pCi d^{-1}) ^{210}Po	Reference
Areas of normal dietary intake			
Argentina		1.3	347
Germany, Federal Republic of	4.6	4.6	347
USSR		3.8	267
Rostov	6.2	4.1	196
United Kingdom[a]	3.2	3.2	347
United States	1.4	1.8	250, 140
Areas of high dietary intake			
High seafood consumption			
Japan	17		347
High reindeer and caribou consumption			
Canada		100	132
Finland (Inari)	8.6	69	180
Sweden (Lake Rogen district)	3.6-9	72-180	276
USSR		30-70	267
Murmansk region[b]	44	79	267, 258
Yamalo-Nenetskii National Area		344	267
United States (Alaska)		60	35

[a]The range of the dietary intake of ^{210}Pb and ^{210}Po in the United Kingdom is estimated to be 1-10 pCi d^{-1} (347).

[b]The ^{210}Pb dietary intake is based on measurements of excreta (258).

TABLE 21. ACTIVITY CONCENTRATION OF ^{210}Pb IN THE ENVIRONMENT, THE HUMAN DIET AND HUMAN BONE ASH

Location	Surface air[a] (fCi m^{-3})	Rain water (pCi l^{-1})	Dietary intake (pCi d^{-1})	Human bone ash[b] (fCi g^{-1})	Reference
Continental					
Finland	7 (3-15)			78 C	180, 295
Germany, Federal Republic of	10 (3-38)	3.0	4.6	110 C	101, 137, 295
India, Bombay	18 (5-49)	3.0		321 T	182, 295
Poland				148 T	161
				91 T	32
USSR, Rostov	17	5.2[c]	6.2	134 M	196, 295
United States					
Palmer, Alaska	9 (5-16)	0.8	1.7		219, 295
Los Angeles, California	15 (6-25)	0.8, 3.2	1.5		219, 295
Chicago, Illinois	21 (11-76)	1.3-2.5	1.8	184 T 146 M 105 C	135, 219, 295
New Orleans, Louisiana	21 (12-35)		1.8		219, 295
Boston, Massachusetts	14 (10-22)		1.7		219, 295
New York, New York	21 (7-43)		1.2	200 T	39, 219, 295
Island					
Japan					
Sapporo				96 T	113a
Kyoto				218 T	113a
New Zealand	5[d]	1.4-1.8		61 M	252, 295
United Kingdom, England	6 (2-13)	2.7	3.2	96 T	134, 295
Puerto Rico	9 (4-15)	2.2[e]		118 T	137, 295
United States					
Honolulu, Hawaii	5 (4-7)	1.1	1.6		219, 295

[a]The range of observed values is given within parentheses.

[b]T = trabecular bone, C = cortical bone, M = mean bone value.

[c]Concentration measured in Moscow.

[d]Concentration measured in Melbourne.

[e]Concentration measured in Nassau.

proportions of seafood are therefore expected to be higher than those of populations with other types of diet. This assumption is confirmed by the value of the ^{210}Pb intake in Japan (table 20).

132. A well documented case of elevated intakes is that of the tens of thousands of reindeer and caribou eaters in the arctic and sub-arctic regions of the northern hemisphere. Their main food is the meat of these animals, which contains unusually high concentrations of ^{210}Po because in the winter they graze on lichens which accumulate ^{210}Pb and ^{210}Po.

133. Table 22 presents information on the concentrations of ^{210}Pb and ^{210}Po in the lichen-reindeer-man food-chain. Lichens, which do not have a root system,

TABLE 22. MEASUREMENTS OF THE CONCENTRATION OF ^{210}Pb AND ^{210}Po IN THE LICHEN-REINDEER-MAN FOOD-CHAIN

Link in chain and location of measurement	*^{210}Pb*	*^{210}Po*	*Comments*	*Reference*
Lichen	(pCi kg^{-1} dry weight)			
Canada		7 300		139
Finland, Lapland	7 900	7 300		180
Sweden	7 200	6 400		276
USSR, Murmansk	9 200			258
USA, Alaska, Bethel	5 800	5 800		35
Reindeer or caribou	(pCi kg^{-1} fresh weight)			
Bone				
Finland, Inari	4 600	2 000		180
Sweden	5 800	3 700		276
USSR, Murmansk	1 500			258
USA, Alaska, Anaktuvuk Pass		5 000		35
Meat	(pCi kg^{-1})			
Canada	11	280		139
Finland, Lapland	6	160		276
Sweden	18	360		276
USSR	38	80		293
USA, Alaska, Anaktuvuk Pass	15	200		138
Man				
Bone	(fCi g^{-1} ash)			
Finland, Inari	160	160	Levels in teeth	180
Sweden	500	370	Inferred from blood concentration	276
USSR, Nenetskii National Area	430	220		258, 267
USA, Alaska	300	220		36
Soft tissues	(pCi kg^{-1})			
Blood				
Finland	6.8	12	Concentrations measured in southern Finns are 2.7 for ^{210}Pb and 0.7 for ^{210}Po	180
Sweden	M[a] 4.7 F 3.3	M 9.4 F 5.0	Corresponding levels in "normal" populations are about 2 pCi kg^{-1}	276
Placenta				
Canada	2.5	29		139
Finland	1.9	36	Concentrations measured in southern Finns are 0.8 for ^{210}Pb and 2.9 for ^{210}Po	180

[a] M = male, F = female.

derive their nutrition preferentially from the air. As they present a high sorption area, live for a long time (as long as 300 y), and eliminate ^{210}Pb very slowly (effective half-time estimated to be 7 ± 2 y), they concentrate ^{210}Pb and ^{210}Po to much higher levels than other plants. Lichens also accumulate other long-lived natural radionuclides, such as ^{226}Ra or ^{228}Th (258), but because of their much lower concentration in surface air and rain water, the absolute concentrations reached by those radionuclides in lichens are also much lower.

134. As reindeer consume 3-4 kg of lichen per day (276, 292), their daily intake of ^{210}Pb and ^{210}Po is of the order of 10 000 pCi. The concentrations in reindeer bone and meat presented in table 22 clearly show the different biological behaviour of polonium and lead. Lead-210 concentrates in the skeleton, where it gives rise to ^{210}Po through radioactive decay. Polonium-210 concentrates mainly in the soft tissues, where it is clearly in excess of its equilibrium value with ^{210}Pb. It is worth mentioning that the ^{210}Po concentration in reindeer meat varies seasonally by a factor of 4 (180), being lowest in early autumn because of the greater availability of forage other than lichens during the warm summer months.

135. The daily intakes of ^{210}Pb and ^{210}Po by the populations living on reindeer or caribou meat are given in table 20. Most of the estimates were inferred from the measured concentration in reindeer or caribou meat, using a daily rate of consumption of 0.2-0.5 kg. The ^{210}Pb intake is not much higher than that of the populations of other areas, but the ^{210}Po intake is about one order of magnitude higher, a typical value being 100 pCi d^{-1}.

(iii) *Distribution in man and absorbed doses*

136. Lead-210, bismuth-210 and polonium-210, being the last radionuclides of the ^{226}Ra decay chain, would be present in the human body even in the absence of direct intake. However, under normal conditions, the decay of ^{226}Ra, ^{222}Rn and their short-lived products in the body does not play a major role in the accumulation of ^{210}Pb and ^{210}Po in the body (133, 135). Only in occupational exposure, such as in uranium mining, is the role of the precursors important.

137. Lead is a bone seeker which is found incorporated in bone mineral, from where it seems to be eliminated by the process of long-term skeletal remodelling (144, 162, 208). About 70 per cent of the body content of ^{210}Pb is found in the skeleton (162). According to Holtzman's study (135), in which 128 bone samples were examined for ^{210}Pb content, the concentration in males is higher than in females. In both sexes, the level in cancellous bone was found to be 70 per cent higher than in compact bone. No clear correlation could be found in that study between the age of the subject and the ^{210}Pb concentration in bone, but it is worth mentioning that stable lead concentrations increase with age (167, 308).

138. The ^{210}Pb activity concentrations in bone ash presented in table 21 show that, in continental areas of the northern latitudes, a typical value could be 0.15 pCi g^{-1}, corresponding to a skeletal content of 400 pCi. In island areas the concentrations in human bone appear to be somewhat lower than in continental regions.

139. Assuming that the rate of elimination of ^{210}Pb from bone is described by a single exponential, the total activity in the skeleton A due to both inhalation and ingestion may be estimated from the relationship

$$A = (T_e/0.693)\,(I_{inh}f_{inh} + I_{ing}f_{ing})$$

where I is the daily activity intake (I_{inh} from inhalation and I_{ing} from ingestion), f the fraction of the intake which is deposited in the skeleton, and T_e is the effective half-life of ^{210}Pb, taken here to be 3300 d (135). In the case of ingestion, assuming a blood uptake from the gastro-intestinal tract of 0.08 and a fractional deposition in the skeleton from blood of 0.28, a daily intake of 3 pCi leads to a bone deposition of 0.067 pCi d^{-1} and to a contribution to the equilibrium skeletal activity of 320 pCi. With respect to inhalation, if it is assumed that one half of the activity is deposited in the respiratory tract and that one third of the activity deposited is absorbed into the blood and the remaining two thirds are subsequently ingested, a daily intake by inhalation of 0.3 pCi d^{-1} corresponds to a bone deposition of 0.016 pCi d^{-1} and a skeletal content of 76 pCi. The sum of the contributions from inhalation and ingestion to the skeletal content is thus estimated to be about 400 pCi.

140. Polonium, in contrast to all the other natural alpha emitters, is not a bone seeker but rather accumulates in soft tissues. Therefore, the greatest part of the ^{210}Po bone activity arises from the decay of deposited ^{210}Pb (131, 370). Average measured ratios of ^{210}Po and ^{210}Pb activity concentrations in bone range from 0.5 to 1.1 (35, 135, 180, 196, 246). A value of 0.8 is assumed to be representative for the purposes of this report. Using an average ^{210}Pb activity concentration per unit mass of ash of 0.15 pCi g^{-1} and a ^{210}Po/^{210}Pb ratio of 0.8, the ^{210}Po concentration in bone ash would be 0.12 pCi g^{-1} for the populations living in continental areas in temperate regions of the northern hemisphere.

141. With respect to the soft tissues, ^{210}Pb and ^{210}Po are distributed relatively uniformly throughout the body. From measured concentrations the total amount of ^{210}Po in soft tissues has been estimated to be 72 pCi by Kauranen and Miettinen (180), 160 pCi by Parfenov (267), and 250 pCi by Ladinskaya *et al.* (196), while the corresponding estimates for ^{210}Pb were 60, 156, and 266 pCi, respectively. Although there is a factor of more than 3 between the extreme values regarding a given radionuclide, it is worth noting that in the three studies the ^{210}Po/^{210}Pb activity ratio is found to be about 1. Assuming that 70 per cent of the whole-body content of ^{210}Pb is in bone, the representative value of 400 pCi for the ^{210}Pb skeletal activity corresponds to an activity of 170 pCi of ^{210}Pb and a like amount of ^{210}Po in the soft tissues.

142. Typical concentrations of ^{210}Pb and ^{210}Po in the gonads seem to be about 6 pCi kg^{-1} (19, 35, 196). In the lung, the concentrations in non-smokers are around 3 pCi kg^{-1} for ^{210}Po and 6 pCi kg^{-1} for ^{210}Pb (35, 139). In red bone marrow, Baratta and Ferri (19) reported ^{210}Po concentrations of 26 pCi kg^{-1} in men and 21 pCi kg^{-1} in women, but a more recent study by Ladinskaya *et al.* (196) found a much lower value of 3.8 pCi kg^{-1} and a ^{210}Po/^{210}Pb activity ratio of 0.8, which will be used in this Annex for the purpose of assessing doses.

143. It is interesting to estimate how much ^{210}Po in soft tissues is due to the decay of ^{210}Pb in soft tissues, to the elimination of ^{210}Po from bone, and to the direct dietary intake of ^{210}Po. Assuming a ^{210}Po dietary

intake of 3 pCi d^{-1}, a blood uptake of 0.35 (196, 294) and an effective half-life in the body of 50 d (309), the contribution to the ^{210}Po inventory in soft tissues from the ^{210}Po dietary intake would be about 75 pCi. As inhalation of ^{210}Po, at least for non-smokers, does not lead to a substantial activity in the body, the rest of the ^{210}Po inventory would result from the decay of ^{210}Pb. An average $^{210}Po/^{210}Pb$ ratio of 0.8 in bone yields a contribution of about 30 pCi from the elimination of ^{210}Pb in bone. Finally, the decay of ^{210}Pb in soft tissues leads to an amount of 85 pCi if it is assumed that the $^{210}Po/^{210}Pb$ ratio at equilibrium in soft tissues, in the absence of any intake of ^{210}Po, is 0.5 (162). The ^{210}Po inventory in soft tissues obtained in this way is 190 pCi. Considering the uncertainties attached to the values of the parameters used, this result is in good agreement with the value of 170 pCi given in the preceding paragraphs.

144. The ^{210}Po activity in man being about 500 pCi (320 pCi in bone and 170 pCi in soft tissues) and the contribution to that activity due to the ^{210}Po dietary intake being only about 75 pCi, it is clear that the ^{210}Po activity in man depends little on the amount present in diet. It is determined mainly by the concentration of ^{210}Pb in the body, since approximately 85 per cent of the ^{210}Po body content arises from the decay of ^{210}Pb. This view has also been expressed by Holtzman (136) and by Parfenov (267).

145. Although in most of the soft tissues, the $^{210}Po/^{210}Pb$ activity concentration ratio is about 1, it is clearly greater than 1 in a few organs such as the liver and kidney. The excess ^{210}Po is probably taken up directly from food and would be partly attributable to a higher rate of incorporation for ^{210}Po than for ^{210}Pb in those organs (162). It has been suggested (80, 131) that the distribution of polonium might be similar to that of sulphur, which might be replaced by polonium in several chemical compounds of the body.

146. *Absorbed doses.* The absorbed doses from the ^{210}Pb chain depend mainly on the highly energetic alpha particles of ^{210}Po, the contribution from the beta emissions of ^{210}Pb and ^{210}Bi being at most 30 per cent of the dose from ^{210}Po. For non-smokers, the annual absorbed doses in the lungs and gonads are about 0.3 and 0.6 mrad, respectively; those in tissues in bone, calculated using the dosimetric factors presented in figures IX and X, are found to be 3 mrad for bone lining cells and 0.7 mrad for the red marrow (table 23). The annual average whole-body dose is about 0.7 mrad.

TABLE 23. ESTIMATED TISSUE CONCENTRATION AND ANNUAL ABSORBED DOSE DUE TO ^{210}Pb, ^{210}Bi AND ^{210}Po IN AREAS OF NORMAL AND HIGH DIETARY INTAKE

	Average tissue concentration (pCi kg^{-1})				*Annual tissue absorbed dose (mrad)*			
Area and radionuclide	*Gonads*	*Lung*	*Cancellous bone*	*Red bone marrow*	*Gonads*	*Lung*	*Red bone marrow*	*Bone lining cells*
Areas of normal dietary intake								
Non-smokers								
^{210}Pb	6	6	100	5	$6\ 10^{-4}$	$6\ 10^{-4}$	$5\ 10^{-4}$	$8\ 10^{-4}$
^{210}Bi	6	6	100	5	$4\ 10^{-2}$	$4\ 10^{-2}$	$2\ 10^{-1}$	$4\ 10^{-1}$
^{210}Po	6	3	80	4	$6\ 10^{-1}$	$3\ 10^{-1}$	$7\ 10^{-1}$	3
Smokers								
^{210}Pb	8	9	130	6	$8\ 10^{-4}$	$8\ 10^{-4}$	$6\ 10^{-4}$	$1\ 10^{-3}$
^{210}Bi	8	9	130	6	$6\ 10^{-2}$	$7\ 10^{-2}$	$3\ 10^{-1}$	$6\ 10^{-1}$
^{210}Po	8	9	100	5	$8\ 10^{-1}$	$9\ 10^{-1}$	$9\ 10^{-1}$	4
Areas of high dietary intake								
Reindeer or caribou eaters								
^{210}Pb	15	15	250	12	$1.4\ 10^{-3}$	$1.4\ 10^{-3}$	$1.3\ 10^{-3}$	$1.9\ 10^{-3}$
^{210}Bi	15	15	250	12	$1\ 10^{-1}$	$1\ 10^{-1}$	$6\ 10^{-1}$	1
^{210}Po	72	36	200	48	7	4	5	10

147. *Differences between smokers and non-smokers.* The additional intake due to smoking leads to increased concentrations of ^{210}Pb and ^{210}Po in organs and tissues. As expected, it is in the lung that the increase is most clearly marked. The concentrations in that organ exceed on the average the levels found in non-smokers by factors of about 1.5 for ^{210}Pb and 3 for ^{210}Po (35, 131, 267, 289). However, in spite of the fact that the daily intake from smoking is at least 20 times the natural intake from atmospheric air, the ratio of the amounts contained in the lungs of smokers and non-smokers is relatively small. This strongly suggests that ^{210}Po inhaled during smoking is rapidly removed from the lungs (267).

148. Data on the degree of non-uniformity of ^{210}Po in the individual tissues of the lungs of smokers are contradictory. One school of thought holds that ^{210}Po can be concentrated in the bronchial epithelium, particularly at points of bifurcation (207, 287), whereas the other considers that the levels in the bronchial epithelium do not exceed those in the alveolar region (131, 289). As a result, the estimates of the annual absorbed dose in the bronchial epithelium as compiled in reference (267), range from 4 to 3000 mrad.

149. The increase due to smoking is less clear in organs other than lung. Parfenov (267), summarizing the

relevant published data, shows that on the average the ^{210}Po concentrations in the soft tissues of cigarette smokers is higher than the corresponding concentrations in non-smokers by about 30 per cent, but points out that a number of studies have failed to reveal a statistically significant difference (19, 35, 206).

150. An estimate of the increase of the ^{210}Pb and ^{210}Po concentration in smokers can be made from the intake and metabolism information presented above. An additional daily intake of 1.6 pCi of ^{210}Po from smoking would yield at equilibrium an additional content of 32 pCi in the soft tissues, which would increase the average value by about 20 per cent. A more substantial increase would arise from the additional daily intake of 1.2 pCi of ^{210}Pb, which would result in an additional bone content of 300 pCi at equilibrium and in an excess of 75 per cent above the average value. It should be pointed out, however, that, under conditions of steady smoking, a few months are sufficient for ^{210}Po to approach its equilibrium value in the soft tissues, while tens of years would be required for ^{210}Pb. The full effect of cigarette smoking on the body contents of ^{210}Pb and ^{210}Po in smokers can thus only be experienced after a long period of steady smoking. Shorter periods would cause the excess to lie in the range from 20 to 95 per cent, which is in agreement with the average value of 30 per cent derived from experimental studies and used here to calculate the doses in smokers (table 23).

151. *Reindeer or caribou eaters.* Measurements carried out on the blood, placenta and bone tissue of inhabitants of the northern regions who consume caribou or reindeer meat regularly show levels higher than those in the populations of the temperate latitudes (table 22). The increase is by a factor of about 2 for ^{210}Pb in all tissues and a factor of about 10 for ^{210}Po in the placenta, which is taken to be representative of all the soft tissues. On the basis of their own measurements, Kauranen and Miettinen (180) estimated the factors of increase to be 2.5 for ^{210}Pb and 12 for ^{210}Po. The use of these values leads to the doses indicated in table 23. It is interesting to note that the factors are estimated to be 1.6 for ^{210}Pb and 14 for ^{210}Po when calculated from estimated dietary intakes of 6 pCi d^{-1} for ^{210}Pb and 100 pCi d^{-1} for ^{210}Po, using the values of the metabolism parameter indicated in previous paragraphs.

C. RADON-222, RADON-220 AND THEIR SHORT-LIVED DECAY PRODUCTS

1. Inhalation

152. In the decay chains of ^{238}U and ^{232}Th, ^{222}Rn (radon) and ^{220}Rn (thoron) are the only isotopes of noble gases. This property allows them to emanate from the ground and to be present in the atmosphere in much larger concentrations than their precursors. Exposure to the inhaled short-lived decay products of radon and thoron constitutes the main natural irradiation of the various parts of the human respiratory tract. The major part is normally caused by radon daughters rather than by thoron daughters, and by indoor exposure. Although outdoor exposure is normally smaller, the occurrence of radon and thoron and their daughters outdoors has been extensively studied since they are also of interest as tracer elements in meteorological studies. The following paragraphs summarize the data of interest on levels and doses and the factors which explain these levels and doses.

(a) *Exposure-dose relationship*

153. Radon and thoron emanate from soil, water, building materials etc. and become dispersed in the air in the gaseous phase. The decay products, radon and thoron daughters, are produced as free atoms, usually as positive ions since the alpha particles carry electrons away from the atom during the decay process. These ions tend to form clusters very rapidly with water, oxygen or other trace gases. Soon afterwards, in a matter of seconds to minutes, these clusters tend to attach themselves to aerosol particles. The dimensions of the aerosol particles being much larger than those of the clusters, the aerosols inhaled do not deposit in the same region of the respiratory tract as the clusters. It is thus important to make a distinction between the fraction of the activity of the short-lived decay products of radon carried by clusters, which is called the unattached fraction, and the fraction fixed on aerosol particles, called the attached fraction.

154. The concentration of radon and thoron daughters in air may be expressed in terms of activity concentration (unit: pCi l^{-1}), or in terms of potential alpha-energy concentration, which is defined as the total alpha energy released per unit volume by the short-lived daughters in their decay (unit: MeV l^{-1}). A unit which has been used in mines to describe the radon decay-product activities in air in terms of potential alpha energy is the working level (WL). It is defined as any combination of short-lived radon daughters (through ^{214}Po) per litre of air that will result in the emission of 1.3 10^5 MeV of alpha energy. An activity concentration of 100 pCi l^{-1} of ^{222}Rn, in equilibrium with its daughters, corresponds to a potential alpha-energy concentration of 1 WL. The WL unit could also be used for thoron daughters. In this case, 1.3 10^5 MeV of alpha energy (1 WL) is released by the thoron daughters in equilibrium with 7.5 pCi of thoron per litre. Table 24 shows the potential alpha-energy concentrations of radon and thoron daughters (157).

155. Radon and thoron daughters in air are very seldon in equilibrium with radon and thoron, respectively. The equilibrium factor F is defined as the ratio of the total potential alpha energy of the given daughter concentrations to the total potential alpha energy of the daughters if they are in equilibrium with radon and thoron, respectively.

156. It follows from the definition of the WL that the equilibrium factor F for radon or thoron (Tn) can be calculated as

$$F_{Rn} = a\langle a\rangle_{Rn}/\langle Rn\rangle;\ F_{Tn} = b\langle a\rangle_{Tn}/\langle Tn\rangle$$

where $\langle a\rangle_{Rn}$ and $\langle a\rangle_{Tn}$ are the potential alpha-energy concentrations, in WL, of Rn daughers and Tn daughters, respectively; $\langle Rn\rangle$ is the activity concentration, in pCi l^{-1}, of radon; $\langle Tn\rangle$ is the activity concentration, in pCi l^{-1}, of thoron; and a and b are constants (a = 100 pCi/WL, b = 7.5 pCi/WL).

TABLE 24. POTENTIAL ALPHA ENERGY OF THE SHORT-LIVED DECAY PRODUCTS OF ^{222}Rn AND ^{220}Rn

Radionuclide	Radioactive half-life	Number of atoms per picocurie	Potential alpha energy (MeV)		Conversion factor	
			Per atom	Per picocurie	$\frac{MeV\ l^{-1}}{pCi\ l^{-1}}$	$\frac{WL}{pCi\ l^{-1}}$
^{218}Po (Ra A)	3.05 min	9.77	13.68	134	134	0.00103
^{214}Pb (Ra B)	26.8 min	85.3	7.68	659	659	0.00507
^{214}Bi (Ra C)	19.7 min	63.1	7.68	485	485	0.00373
^{214}Po (Ra C')	$1.6\ 10^{-4}$ s	10^{-5}	7.68	$7.68\ 10^{-5}$	$7.68\ 10^{-5}$	$6\ 10^{-10}$
^{216}Po (Th A)	0.158 s	0.00844	14.57	0.123	0.123	$9.5\ 10^{-7}$
^{212}Pb (Th B)	10.6 h	2040	7.79	15 900	15 900	0.1223
^{212}Bi (Th C)	60.5 min	194	7.79	1 510	1 510	0.0116
^{212}Po (Th C')	$3\ 10^{-7}$ s	$1.6\ 10^{-8}$	8.78	$1.4\ 10^{-7}$	$1.4\ 10^{-7}$	$1\ 10^{-12}$

157. If in a given atmosphere radon (or thoron) is not in equilibrium with its daughters and the concentration of radon (or thoron) is C, the product CF corresponds to a concentration of radon (or thoron) for which the daughters in equilibrium would have the same potential alpha-energy concentration as the actual atmosphere of interest. The product CF will be referred to in this report as the equilibrium equivalent concentration of radon (or thoron).

158. For the purpose of this report, exposure to radon and its daughters is defined as the integral of the activity concentration in air over the exposure time. The unit, working level month (WLM), is often used in connection with radon in mines, and means an exposure during 170 working hours in a radon daughter concentration of 1 WL. One WLM corresponds to a time-integral of the equilibrium equivalent concentration of $1.7\ 10^4$ pCi h l^{-1} for occupational exposure in mines. For thoron daughters, 1 WLM corresponds to an exposure during 170 working hours in a thoron daughter concentration of 1 WL, which is equivalent to a time-integral of the equilibrium equivalent concentration of $1.3\ 10^3$ pCi h l^{-1} for occupational exposure in mines.

159. The deposition in the respiratory system of radon and thoron daughters attached to aerosol particles depends on, among other things, the size distribution of the radioactive aerosol, this size distribution being closely related to the size distribution of the inactive aerosol present. In both free air and room air this size distribution is relatively constant. Figure XV shows the typical size distribution of the natural aerosols carrying short-lived radon daughters (146, 242a). When these aerosols are inhaled, up to 60 per cent of the particles are deposited in different regions of the respiratory system. The attached radon and thoron daughters are mainly deposited in the pulmonary region. The unattached daughters are deposited in the upper respiratory tract on account of their high diffusion coefficient. Because of the efficient deposition of unattached daughters in the respiratory tract, experimentally proved with a model by Chamberlain and Dyson (55), the unattached fraction has since been given great attention. However, the fraction of unattached daughters in air is often small and a major proportion (up to 60-70 per cent) of the unattached daughters in the inhaled air is removed by nasal deposition (93).

160. In indoor air the degree of equilibrium between radon (or thoron) and its daughters and the fraction of

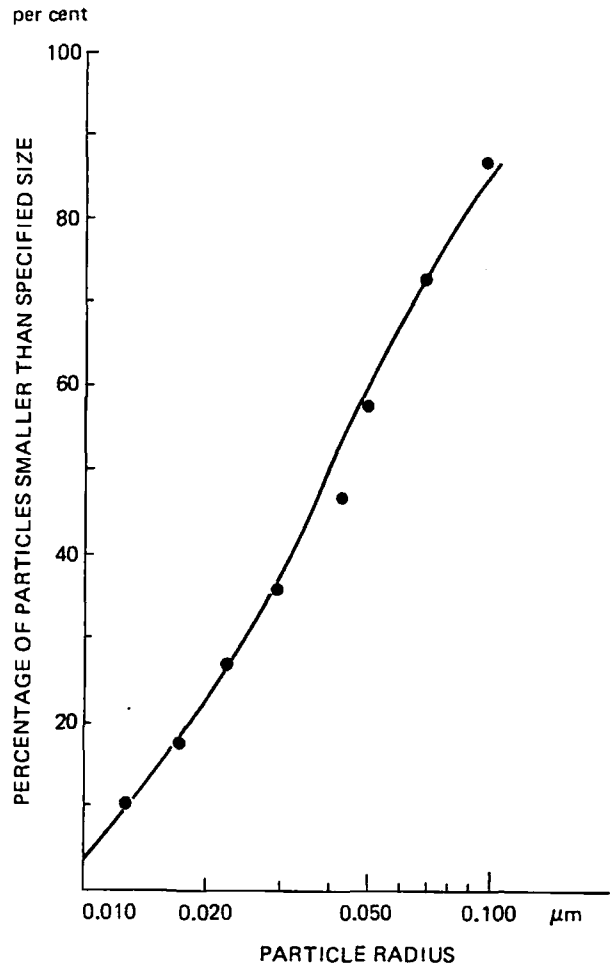

Figure XV. Size distribution of the natural carriers of ^{214}Pb and ^{214}Bi (149, 242a)

unattached daughters are affected by the ventilation rate (126), by the deposition on walls (371), and by attachment to aerosols. The relative influence of these factors has been considered on a theoretical basis by Jacobi (157). It was found that the fraction of unattached daughters increases markedly with decreasing aerosol concentration and decreasing residence time of the air. Since enhanced ventilation reduces the residence time of the air and also usually the aerosol concentration, the effect on the fraction of unattached daughters is considerable. However, the net effect of increased ventilation is a reduction of dose due to a large decrease of the potential alpha-energy concentration. In

a poorly ventilated room with a low aerosol concentration, wall deposition of unattached daughters plays an important role in reducing their concentration in air.

161. Inhalation of radon and thoron daughters results in an inhomogeneous internal irradiation of the respiratory tract, with the dose absorbed primarily in the bronchial region. The factors which influence the deposition and fate of inhaled activity and the doses, apart from the physical characteristics of the radioactive aerosol, are:

Way of breathing, i.e., mouth breathing or nose breathing and the rate and the depth of respiration

Geometrical parameters of different regions of the respiratory system

Translocation and clearance of deposited activity

Several models have been used to calculate the resultant doses in the respiratory system, assuming different characteristics of the radioactive aerosol, including the fraction of unattached activity.

162. A recent study was made by Harley and Pasternack (123), who performed experimental stopping-power measurements with tissue equivalent material using radon daughters. In the calculation of doses it was assumed, on the basis of the experimental results of Kirichenko *et al.* (184), that the activity was homogeneously distributed in the mucous layer. The lung geometry used in the calculations was based on the Weibel lung model (360), and the fractional retention was tabulated by applying the Gormley-Kennedy equations (104).

163. The removal of unattached daughters in the nose was assumed to be 60 per cent (93) and of the attached daughters, 1.3 per cent. Taking into account the deposition and translocation rates, the doses in different regions of the bronchial tree were calculated. With an aerosol size distribution with an activity median aerodynamic diameter (AMAD) of 0.3 μm, the highest regional activities were found in the segmental bronchioles (tertiary bronchi generation 4 of the Weibel model). The dose-to-exposure quotient was estimated for different depths of the airway wall. In basal cell nuclei at a depth of 22 μm, it was found to be 0.2 rad $(WLM)^{-1}$ for a breathing rate of 15 l min^{-1}, an equilibrium factor $F = 1$, and 4 per cent of unattached ^{218}Po atoms. However, if these parameters change, so also does the relationship between the dose and the exposure. For example with $F = 0.3$ and 4 per cent unattached ^{218}Po, the value is 0.4 rad $(WLM)^{-1}$.

164. Corresponding calculations concerning thoron daughters have been made (124). The highest regional activities were found in the terminal bronchioles (generation 10 of the Weibel model). For that region, and for an AMAD of 0.15 μm and 2.2 per cent unattached ^{212}Pb, a factor of 0.7 rad $(WLM)^{-1}$ may be calculated from Harley's data (124). The contribution from the unattached activity is about 20 per cent.

165. Another recent study of doses from inhaled radon and thoron daughters has been made by Jacobi (158, 159) as a continuation of his studies on the characteristics of the inhaled aerosol, activity and potential alpha-energy of radon and thoron daughters. He calculated the doses in the tracheo-bronchial region (T-B) and in the pulmonary region (P) assuming the masses to be 45 g and 955 g, respectively. The doses were derived as a function of the unattached fraction f_p of the total potential alpha energy in the inhaled air. The mean dose from alpha particles is shown in table 25 for a breathing rate of 20 l min^{-1}.

TABLE 25. MEAN DOSE FROM ALPHA PARTICLES IN THE TRACHEO-BRONCHIAL AND PULMONARY REGIONS AS A FUNCTION OF THE UNATTACHED FRACTION f_p OF THE POTENTIAL ALPHA ENERGY IN AIR

Nose breathing

	Dose-to-exposure quotient	
	Dose to time-integral of potential alpha energy (rad per WLM)	*Dose to time-integral of equilibrium equivalent concentration (rad per pCi h l^{-1})*
Tracheobronchial region		
Radon daughters	$0.31\ (1 + 6f_p)$	$1.9\ 10^{-5}\ (1 + 6f_p)$
Thoron daughters	$0.012\ (1 + 5f_p)$	$10^{-5}\ (1 + 5f_p)$
Pulmonary region		
Radon daughters	$0.16\ (1 - f_p)$	$10^{-5}\ (1 - f_p)$
Thoron daughters	$0.087\ (1 - f_p)$	$7.6\ 10^{-5}\ (1 - f_p)$

166. It was concluded that the mean dose-to-exposure quotient in the T-B region increases with increasing ventilation rate and decreases with increasing aerosol concentration. For the P region the variation is reversed. As seen in table 25, the mean dose-to-exposure quotient for thoron daughters is higher in the P region than in the T-B region with low values of f_p. A large fraction of the alpha energy deposited in the T-B region is deposited in the mucous sheet, ciliated cells and goblet cells on the bronchial epithelium. The dose in the underlying basal cells, where bronchogenic lung cancer is assumed to originate, was derived from different lung models. If the fraction f_p of the total potential alpha energy contributed by unattached radon daughters varied between 0.02 and 0.1, the factor estimated from different models covered a range from 0.2 to 10 rad

$(WLM)^{-1}$, assuming nose breathing at a rate of $20\ l\ min^{-1}$.

167. The lung cancer among uranium miners predominantly appearing in the area of the large bronchi (217) presumably originates in the basal cells in the basement membrane of the upper bronchial epithelium. It seems reasonable to regard the doses in these cells as the most relevant in the discussion of the correlation between dose and effect. However, there is still incomplete knowledge of the distribution of dose and the genesis of cancer in the basal cells and it is not yet considered appropriate to use only the dose in the basal cells as the basis for the risk assessments. As discussed in Annex G, most risk assessments are based on the direct relationship between lung cancer incidence among uranium miners and exposure as expressed in WLM. In addition, for purposes of comparison with other irradiation conditions of the lung, the mean dose in the lung is also calculated in this report.

168. The distribution of the values of the dose-to-exposure quotient for radon daughters, derived from different models is shown in table 26 (171). From the

TABLE 26. DOSE-TO-EXPOSURE QUOTIENT FOR RADON DAUGHTERS

Segmental bronchial epithelium

Relative activity concentration Rn : Ra A : Ra B : Ra C	*Equilibrium factor F*	*Exposure conditions*	*Lung model*	*Dose-to-exposure quotient (rad per WLM)*	*Reference*
10 : 10 : 10 : 10 4% free Ra A	1	0.3-μm particles	Weibel (A), 15 l min^{-1}	0.2	123
10 : 6 : 3 : 2 4% free Ra A	0.3	0.3-μm particles	Weibel (A), 15 l min^{-1}	0.4	123
10 : 9 : 6 : 4	0.6	0.3-μm particles	Landahl	1.7	123
Nonequilibrium; little free Ra A	< 1			0.5-1	247
Nonequilibrium; 1-2% free Ra A	< 1	Clean air	Revised ICRP	0.3-1	158
10 : 10 : 6 : 4	0.6	1 h^{-1} air change; 0.09-μm particles, $10^4\ cm^{-3}$	Findeisen-Landahl, 14 l min^{-1}	1.7	156
10 : 10 : 10 : 10	1	0.09-μm particles	Findeisen-Landahl, 14 l min^{-1}	2.7	156
10 : 9 : 6 : 4	0.6	0.3-μm particles	Landahl, 15 l min^{-1}, mouth breathing	2.0	217 8
10 : 9 : 6 : 4 8.5% free Ra A	0.6	0.3-μm particles	Nose breathing	1.1	8
10 : 9 : 5 : 3.5	0.5	Adequately ventilated room	Weibel, 15 l min^{-1}, mouth breathing	1.7-12	120
10 : 9 : 6 : 4	0.6	0.1-μm particles	15 l min^{-1}	2.2	49

calculations described above, it is believed (159) that in the case of mining conditions ($f_p < 0.1$) the alpha dose in the basal cell layer of the critical bronchial region lies at the lower end of the range of 0.2-10 rad $(WLM)^{-1}$ and that a value of 1 rad $(WLM)^{-1}$ could be used in the assessments of dose. One rad per WLM corresponds to 60 μrad per pCi h l^{-1} for occupational exposure in mines. In the case of exposure in houses and outdoor air, taking into account the lower mean breathing rate, the conversion factor would be 45 μrad per pCi h l^{-1}. However, it is recognized that such important parameters as the size distribution of the aerosols carrying the short-lived radon daughters, the way of breathing and the rate of ventilation might differ from what is found in mining conditions. With regard to the mean dose in the lung, from the data in table 25 a mean value of 0.2 rad $(WLM)^{-1}$ can be derived, corresponding to dose-to-exposure quotients of 9 μrad per pCi h l^{-1} in houses and outdoor air and 12 μrad per pCi h l^{-1} under occupational conditions.

169. In the case of thoron daughters, the highest doses occur in the terminal broncholi and the alveolar region. It seems reasonable therefore to estimate only the mean lung dose for the purpose of this report. From the data in table 25, a value of 0.1 rad $(WLM)^{-1}$ can be derived, corresponding to 60 μrad per pCi h l^{-1} for exposure outdoors and in houses.

(b) *Exposure outdoors*

(i) *Sources*

170. Radon and thoron in the atmosphere originate mainly from emanation from the soil. Wilkening *et al.* (366) reviewed the results of about a thousand measurements of the ^{222}Rn emanation rate from soil and obtained an overall mean value of 0.42 pCi m^{-2} s^{-1}, with a range from $6\ 10^{-3}$ to 1.4 pCi m^{-2} s^{-1}. Their world-wide estimate for the total ^{222}Rn emanation rate from the land areas of the globe is about 50 Ci s^{-1}. The contribution from the oceans is one to two orders of magnitude smaller (122, 386), the other souces are negligibly small. Even though the concentrations of ^{238}U and ^{232}Th in the soil are about the same, the emanation rate of thoron in terms of activity is about a

hundred times higher than that of radon because of its higher decay constant (33, 122).

171. The equilibrium activity of radon in the atmosphere is estimated to be 2.5 10^7 Ci (366), and the average surface air concentration, 0.07 pCi l^{-1} (122). The total inventory of thoron in the atmosphere is much less because of the short half-life of thoron. However, in the first few metres above ground level, the thoron concentrations are of the same order of magnitude as those of radon.

172. The only significant sources of radon and thoron daughters in the atmosphere are the radon and thoron in the air. The concentration of the daughter products depends on the concentration of radon and thoron, the height above earth and the meteorological conditions. Because of wash-out effects in connection with precipitation and deposition, the concentration of radon daughters is often lower than that of radon and the concentration of thoron daughters is much lower than that of thoron near the ground.

(ii) *Emanation from the soil*

173. The emanation rate of radon is influenced by the condition of the soil, its porosity, moisture content and temperature (77, 229, 285). The emanation is reduced by snow cover, increasing atmospheric pressure, and heavy rainfall (193, 229, 338). Light rainfall does not affect the emanation since it only moistens a thin surface layer of soil. Diurnal variations of the emanation, within a factor of 2, may occur with maxima at night and minima during the afternoon (310). The variations are influenced by two opposing factors. Temperature differences in the soil during the night cause convective flow in the top layer leading to an increased nocturnal emanation. On the other hand, the greater turbulent mixing in the atmosphere in daytime enhances the daytime emanation and the diurnal fluctuations are smoothed out (229, 310). The seasonal variations of the emanation rate depend on the climatic conditions. Where there is no snow and temperatures are normally above 0°C all year, only small seasonal variations have been found (229), probably because of the relatively constant moisture content of the deeper soil levels.

174. Because of the very short radioactive half-life of thoron (55s), the emanation of thoron is more dependent on the soil conditions and on meteorological factors than is that of radon. The effective emanating soil thickness is of the order of a few centimetres. The emanation decreases rapidly when the moisture increases. The thoron emanation in summer seems to be about twice that in winter mainly because of higher moisture in the soil in the winter than in the summer. When the soil surface is warmer than the air, the emanation of thoron increases because of convection. This explains the diurnal variations of the emanation of thoron on dry summer days with maxima at sunset and at night and minima at sunrise and early in the day. The variations have been found to be within 30 per cent of the mean. The influence of several other factors on the emanation rate of thoron have been reported in the literature (75, 108, 220, 229, 331).

(iii) *Variations in air concentration*

175. The concentration of radon and thoron in the air depend on their emanation rate from the soil, meteorological factors, geographical factors and the height of observation. The vertical distribution of radon and its daughters has been studied by several investigators (10, 34, 44, 183, 198, 238, 364, 365). Normally, the radon concentration decreases with increasing altitude, but there are different profiles of radon concentration at different locations and times. The reported values are in the range 0.1-0.01 pCi l^{-1} from about 0.1 km above ground to an altitude of 2-3 km; above this height the concentration is less than 0.01 pCi l^{-1}. The results of measurements of the vertical distribution of radon in Illinois (United States) are shown in figure XVI (44). Figure XVII shows a typical

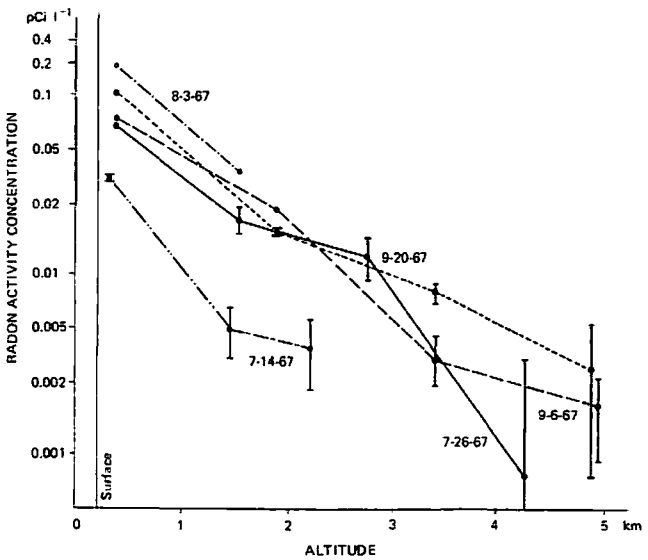

Figure XVI. Variation of radon concentration with altitude (44)

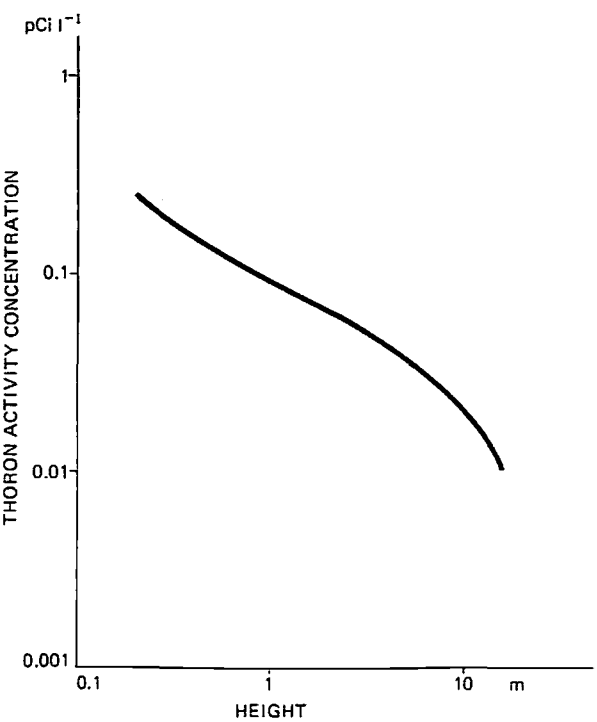

Figure XVII. Vertical profile of thoron in the atmosphere for wind speeds ranging from 4 to 12 m s^{-1} (75)

vertical profile of thoron below a height of 10 m for wind speeds ranging from 4 to 12 m s^{-1} (75). The vertical distributions of radon and thoron close to the ground are also shown in figures XVIII and XIX which

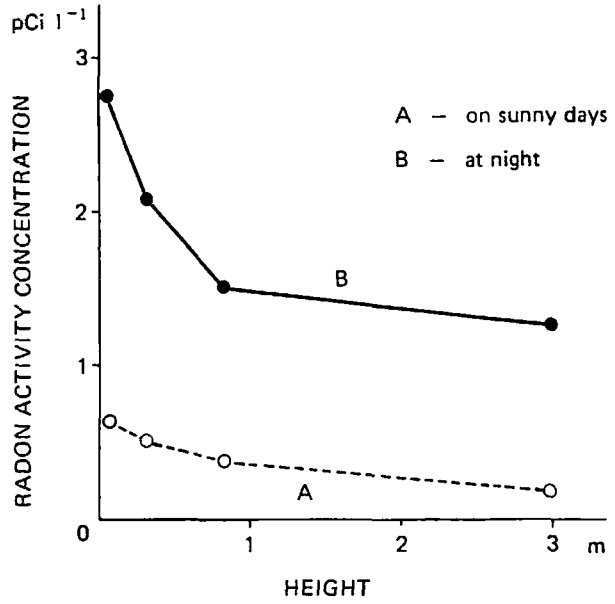

Figure XVIII. Vertical distribution of radon concentration

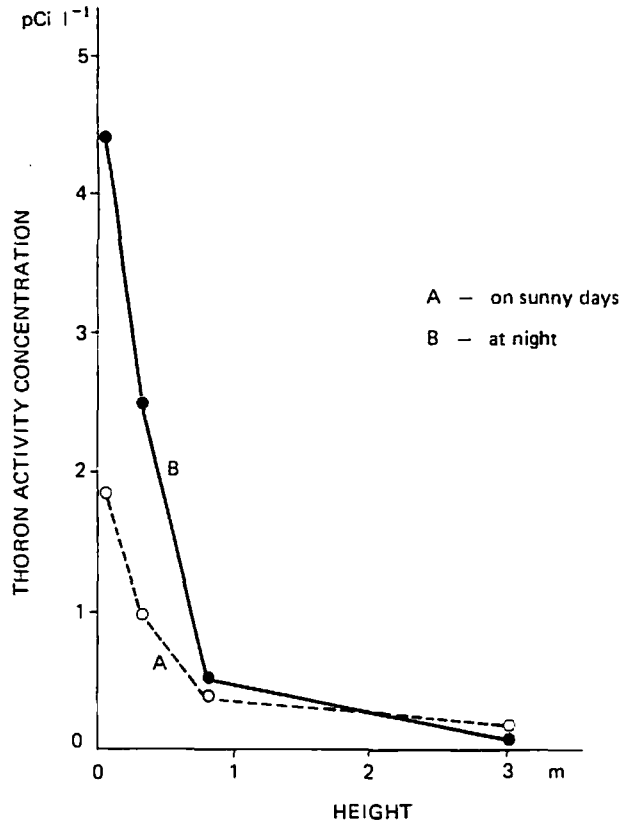

Figure XIX. Vertical distribution of thoron concentration

illustrate the influence of turbulent transfer on the radon and thoron profiles. The greater turbulence in the daytime causes smaller gradients and smaller absolute levels of radon and thoron than at night. At 1 m and above, the concentrations of thoron are about the same night and day.

176. The diurnal and seasonal variations of radon and thoron at ground level have been studied by several investigators (37, 141, 154, 155, 220, 310, 317). Eddy diffusion is the mechanism by which radon and thoron and their daughter products are transferred upward from ground level. The diurnal variation of the diffusion coefficient may be two orders of magnitude (298). The corresponding diurnal variation of radon is normally less, within one order of magnitude. As a rule, a maximum occurs towards the end of the night, and a minimum in the afternoon.

177. The seasonal variation of radon concentration depends mainly on the seasonal variation of turbulence. A maximum value of the radon concentration at ground level is reported to occur in the autumn and early winter, corresponding to a minimum in turbulent transfer. The minimum occurs in the spring. The local seasonal variations are normally less than a factor of five. The concentration of thoron in ground-level air is of the same order of magnitude as that of radon.

178. As the emanation rates of radon and thoron are much smaller over sea than over land, the concentrations of radon and thoron in ground-level air depend on the wind direction and on geographical factors. The concentration of radon at ground level is of the order of 0.1 pCi l^{-1} in continental air, 0.01 pCi l^{-1} in coastal areas and islands, and of the order of 0.001 pCi l^{-1} in oceans and arctic areas (347). In coastal areas, the diurnal variation is increased by the much smaller radon concentration during the day under sea-breeze conditions than at night with offshore winds. Inland, far away from the coast, there seems to be no correlation between radon concentration and wind direction (141). On the other hand, air which has passed over land can be identified thousands of kilometres from the coast at sea, where the emanation rates are very low (286). The concentrations of radon and thoron are reported to be very dependent on wind speed and temperature stratification (155). This correlation is probably caused by the close connection between wind speed and the intensity of turbulent transfer (141, 155). Maximum values of the radon and thoron concentrations occur during light-wind conditions, but the relation between the concentration of radon and thoron and the wind speed seems to be greatly affected by the stability of the atmosphere (146).

(iv) *Levels and doses*

179. As discussed in previous paragraphs, there are variations of the radon and thoron concentrations in air depending on local conditions. Similar variations are found for the daughters of radon and thoron, the variation being enhanced by wash-out and deposition effects. It is therefore very difficult to estimate representative values for the concentration of radon and thoron daughters in air, unless long-duration measurements are made. To estimate the resultant doses, it is also important to know the characteristics of the aerosols inhaled, and also the proportion of time spent out of doors. This proportion varies for different people depending on season, country, age, habits and type of work. For the purpose of this report it will be assumed that 20 per cent of the time is spent out of doors (4-5 h per day).

180. The equilibrium factor F for radon has been considered by several authors directly or indirectly. By comparing the activities of ^{214}Pb and ^{214}Bi and radon in the summer, autumn and winter at a height of 1 m above the ground, it was concluded that the deviation from equilibrium was less during the winter than in the autumn or summer (310). In another study (376) in Boston (United States) the concentrations of ^{218}Po, ^{214}Pb and ^{214}Bi were measured. If ^{218}Po is assumed to be in equilibrium with radon, the values of F vary between about 0.6 and 0.9 with an average of 0.8. Measurements in France in March 1970 showed that the ratio between ^{214}Pb and radon varied between about 0.6 and 0.7 at 1 m above the ground and between 0.8 and 1.0 at 13 m above the ground (41). Measurements made on the air in the city of New York (United States) from July 1973 through June 1974 gave an average radon concentration of 0.1 pCi l^{-1} (range 0.06-0.17 pCi l^{-1}), average radon-to-radon daughters ratios (^{222}Rn:^{218}Po:^{214}Pb:^{214}Bi) of 1:0.9:0.7:0.7 and an average value of F of 0.7 (84). Measurements at the same place in June and July 1972 gave an average radon concentration of 0.2 pCi l^{-1} (range 0.10-0.22 pCi l^{-1}), average radon-to-radon daughters ratios of 1:0.8:0.5:0.3 and an average value of F of 0.4 (range 0.18-0.73) (94). Similar measurements in a rural atmosphere at Sterling Forest, 80 km north of New York, in July 1972 gave an average radon concentration of 0.2 pCi l^{-1} (range 0.16-0.26 pCi l^{-1}), average radon-to-radon daughters ratios of 1:0.8:0.5:0.4, and an average value of F of 0.42 (range 0.08-0.56) (94). The lowest value, 0.08, occurred on a rainy day when the radon daughter activity dropped by a factor of almost 10.

181. The fraction of unattached radon daughters[2] out of doors varies primarily with the concentration and size distribution of the aerosols in the atmosphere. Measurements at Sutton, England (United Kingdon) indicated no consistent difference in the unattached fraction of ^{218}Po indoors and out of doors (76). It varied between 0.07 and 0.40 (relative to ^{218}Po). In two series of measurements in New York City the averages of the unattached fraction relative to radon were found to be 0.04 (range 0.01-0.06) (94) and 0.09 (range 0.05-0.12) (84). The average value for unattached ^{212}Pb was 0.02 at an average ^{212}Pb concentration of $9\ 10^{-4}$ pCi l^{-1} (84). In Sterling Forest the unattached fraction of ^{218}Po was, on the average, 0.08 relative to radon (range 0.04-0.10). The lowest value, 0.04, was found on a rainy day. The average aerosol concentration was $7.5\ 10^{3}$ particles cm^{-3} compared to $1.9\ 10^{5}$ particles cm^{-3} in New York (94).

182. As the fraction of unattached ^{218}Po is as a rule less than 0.1, it is possible to estimate the absorbed doses in the basal cells of the segmental bronchioles using a value of 45 μrad per pCi h l^{-1} for the quotient between the dose and the time-integral of the equilibrium equivalent concentration of radon (para. 168). The mean radon concentration in continental air is about 0.1 pCi l^{-1} (347), with a mean F of 0.6. Using an occupancy factor of 0.2 for outdoor exposure, the resulting annual dose in the basal cells is about 5 mrad, with a range of 1-25 mrad for different persons located in different places.

183. In order to assess the relative importance of the various natural radionuclides considered in this Annex, the doses from the radon decay products in the pulmonary region of the lung, the gonads, the bone marrow and the bone lining cells also have to be estimated. With regard to the mean dose in the lung, using a dose-to-exposure quotient of 9 μrad per pCi h l^{-1} (para. 168), an annual dose of about 1 mrad is calculated. The doses in organs and tissues outside the respiratory system have been evaluated, as in the 1972 report, from the measurements in guinea-pigs (281, 282). As the ventilation volume and the weight of blood are about the same for man and for guinea-pigs when divided by their respective body weight, the results can be taken as an estimate of the absorbed doses in man. They are calculated to be 0.007 mrad in the gonads, and 0.008 mrad in the bone marrow and the bone lining cells.

184. The thoron daughter concentration in air is mainly measured as the concentration of ^{212}Pb. In continental air the measured concentrations of ^{212}Pb are on the average about 0.001 pCi l^{-1} (37, 84, 209). This average is based on several long-term measurements (months to years) and the range of the results of these measurements is 0.0001-0.003 pCi l^{-1}. Assuming equilibrium between ^{212}Pb and ^{212}Bi, a dose-to-exposure quotient of 60 μrad per pCi h l^{-1} can be used to assess the annual absorbed dose in the whole lung (para. 169). Assuming an occupancy factor of 0.2 for outdoor exposure, the annual dose in the lung is estimated to be 0.1 mrad.

185. More than 90 per cent of the ^{212}Pb atoms deposited in the bronchial tree are eliminated by swallowing before their decay. Those deposited in the pulmonary region are transferred to the blood with a biological half-life of around 10 h, which means that about 50 per cent of the potential decay energy of ^{212}Pb is released outside the lung, whereas the corresponding figure for ^{214}Pb is only 4 per cent (347). The annual doses in tissues outside the respiratory system, as estimated from experiments on guinea-pigs, are $2\ 10^{-4}$ mrad in the gonads and $3\ 10^{-3}$ mrad in bone marrow and in bone lining cells.

(c) *Exposure indoors*

186. As the indoor concentrations of thoron daughters are low compared to those of radon daughters, the main emphasis in this Annex will be on radon. The main contribution to radon indoors is from the building materials. Other sources of significance may be the soil under the building, natural gas and radon-rich water. The radon level outdoors may sometimes also be of significance for the radon level indoors. Even if many measurements have been made on natural radiation

[2] The unattached fraction of ^{218}Po is either expressed relative to the total number of atoms of ^{218}Po measured in the atmosphere ("relative to ^{218}Po") or to the total number of atoms of ^{218}Po that would be present at equilibrium with ^{222}Rn ("relative to ^{222}Rn"). Since the atmospheric activity concentration of ^{218}Po is usually more than 80 per cent of its equilibrium value with ^{222}Rn, the difference between the two values of the unattached fraction of ^{218}Po is at most 25 per cent.

indoors, most indoor measurements have been concerned with the external irradiation and there are only a few extensive surveys of radon and radon daughter levels indoors.

(i) *Sources*

187. *Factors influencing radon levels in a room.* The radium content of the building materials constitutes the source of the emanation of radon. High radon levels may be found in buildings with high radium content in the building materials (142), and it has been shown that particularly low radium contents result in low levels (205).

188. However, it is not possible, on a general basis, to correlate the radon levels in a building to the radium content of the building material, mostly because of the strong influence of ventilation conditions. Furthermore, variations may occur even with the same building material, depending on the distance from the ground level (342) and whether there is a cellar or not. The higher radon levels in cellars and lower storeys are believed to be due to radon emanation from the soil, but they may also be influenced by the lower ventilation. It is not unusual for different building materials with different radium contents to be used in houses, for outer walls, for inner walls and for insulation.

189. The diffusion of radon from the building materials into a room is influenced by the moisture content of the material, its density, whether or not sealants are used and the nature of the material itself. When the moisture content in concrete increases by a factor of 2 from about 3 to 7 per cent by weight, the radon emanation may increase by 10 to 20 per cent (15). This effect has also been found with soil samples (230) and it depends on a decreased adsorption power of the particles in the soil and concrete. If, however, the moisture content increases further, the emanation rate decreases. The temperature effect between 20° and 45°C on the emanation rate from concrete has been found to be insignificant (15). At temperatures lower than 0°C the emanation of radon is expected to decrease (21). It has been suggested (119) that the diurnal variations of radon levels found in some buildings depend on the higher temperature during the afternoon, causing higher emanation rates of radon from the walls than during the night. A possible dependence of the radon emanation rate on the atmospheric pressure has also been suggested (170).

190. Few data for the rate of emanation from building materials can be found in the literature. They are presented as diffusion coefficient (unit: $cm^2\ s^{-1}$), as emanation rate per unit area ($pCi\ m^{-2}\ s^{-1}$) or as fractional escape (pCi escaped per pCi produced). However, both the fractional escape and the emanation per unit area depend on the thickness of the material. As a rule of thumb the fractional escape is of the order of 1 per cent for building materials in walls and ceilings. Table 27 shows the estimated emanation rate per unit activity concentration of ^{226}Ra of different materials based on data given in the references.

TABLE 27. RADON EMANATION RATES OF VARIOUS MATERIALS

Material	*Emanation rate of ^{222}Rn per unit activity concentration of ^{226}Ra ($pCi\ m^{-2}\ s^{-1}$ per $pCi\ g^{-1}$)*	*Comments*	*Reference*
By-product gypsum	0.01	Internal walls 76 mm thick	265
By-product gypsum	0.001	Ceilings 13 mm thick	265
Concrete	0.005	10 cm thick	306
Uranium mill tailings	0.2	10 cm thick	306
Uranium mill tailings	1.6	"Infinite" thickness	306
Soil	0.5	"Infinite" thickness	33
Light concrete	0.02	20 cm thick	195
Heavy concrete	0.01	8 cm thick	195

191. The effect of paints and sealants on the emanation rate is quite variable. Cement plaster and asphalt coating on the walls does not reduce the emanation rate (15). However, by heavily coating with epoxy paint the emanation rate can be reduced by a factor of 4. Furthermore, three layers of oil paint reduce the radon emanation rate by about an order of magnitude (195). Several sealants have been tested both in the uranium industry (297) as well as for buildings incorporating uranium mill tailings in the construction (64).

192. The most effective factor influencing the radon level in houses is the ventilation rate, defined as the fractional change of air per unit time. The equilibrium radon concentration in a room varies with the ventilation rate λ_v (unit: air changes per hour, h^{-1}) according to the formula

$$C = C_0 + eT/(\lambda_v + \lambda)V$$

where e is the emanation rate (in $pCi\ m^{-2}\ h^{-1}$); T, the area (in m^2) of the emanating surfaces; V, the volume

(in m^3) of the room; λ, the decay constant ($0.00755\ h^{-1}$); and C_0, radon concentration (in $pCi\ m^{-3}$) of the ventilation air (outdoor air). Changes in the ventilation of a poorly ventilated room influence the radon level considerably. Conversely, the radon level in a room in which the ventilation ceases may increase to 100 times an earlier level obtained with an air change rate of $1\ h^{-1}$. For example, in a room with $V = 30\ m^3$, $T = 50\ m^2$ (walls and ceiling), $\lambda_v = 1\ h^{-1}$, $e = 0.005\ pCi\ m^{-2}\ s^{-1}$ per picocurie of ^{226}Ra in each gram of concrete (table 27), and concrete with a ^{226}Ra content of $5\ pCi\ g^{-1}$, the radon activity concentration will be about $0.15\ pCi\ l^{-1}$. If the room is unventilated, the radon activity concentration increases to about $20\ pCi\ l^{-1}$.

193. The ventilation differs in different types of houses, depending on age, number of storeys and number of apartments, and in different parts of a building. It is frequently found that the basement of a house has less ventilation than the higher floors and that consequently the radon levels are higher. The ventilation rate in houses is different in different countries owing to differences in climate, heating systems and building standards. Air change rates of $2\text{-}5\ h^{-1}$ are not unusual in many countries (347). However, in countries with cold climates the ventilation rate may be much less; it has been found to be in the range $0.1\text{-}0.9\ h^{-1}$ in central Sweden in houses built after 1970 (251). Central heating and good insulation reduce air exchange rates and increase radon concentrations. In some houses, there is often only natural draught ventilation, which is less efficient than the forced ventilation found in tall buildings. In the case of recirculated forced-air heating or recirculation of ventilation air, only a fraction p of fresh air is admitted, and the true air exchange rate will be reduced to $\lambda_v p$.

194. Diurnal variations of the indoor radon levels may occur because of variations in the outdoor concentration and the opening or closing of windows. In measurements in residential structures in Grand Junction (United States), diurnal variations of a factor of 2-3 were found (322). Variations occurred even in vacant houses, with maxima in the afternoon and decreasing levels during the night, and no correlation was found with either the barometric pressure or the indoor and outdoor temperatures. Other long-term measurements of radon concentrations in a house have shown an increase of radon level during the night up to levels much greater than those outdoors (67). The great effect of closing and opening doors between rooms has also been demonstrated in apartments with natural, as well as forced, ventilation (333). Opening doors could lead to reductions in the radon levels by a factor of 5.

195. Temperature, wind direction and wind speed influence the ventilation rate. It has been shown that a mere change in wind direction to a direction at right angles to the outer wall of a badly ventilated room reduces the radon level by a factor of 3 (333). In rooms with open vents the reduction is even greater (73). If the radon levels indoors are of the same order as the levels outdoors, the variation indoors follow the pattern outdoors, but the variations are smaller (119).

196. *Levels and doses.* For the estimation of doses, use has to be made of the results of a limited number of measurements. Since large variations may occur, as already described, it may be very difficult to judge how representative the results are. It has been suggested (369), as a criterion for determining the radon daughters concentration, that four to six samples of several weeks' duration spread throughout the year should be necessary to provide representative values. Results of radon and radon daughter measurements are shown in table 28. The measurements by Fisenne, Harley and George (84, 94) show the effect of recirculation (high fraction of unattached Ra A, low value of F) and show that even with a low ventilation rate the value of F is fairly low (0.4). The radon activity concentrations in the Hungarian houses (342) are assumed to be numerically equal to the ^{218}Po activity concentrations (according to the reference). This results in a rather high value of F.

197. There are no direct measurements reported on radon and radon daughters in houses which give values of F higher than 0.5. This value is used in this report for the purpose of assessing doses in cases in which only the radon values have been given. As indicated in paragraph 168, the quotient of bronchial dose to the time-integral of the equilibrium equivalent concentration of radon is taken to be 45 μrad per $pCi\ h\ l^{-1}$, as the unattached fraction is of the order of 0.1 or less. The occupancy factor is assumed to be 0.8.

198. The difficulty in estimating mean annual bronchial doses to the population is illustrated by the Hungarian and the Swedish values. As regards the Hungarian data, the weighted mean dose, taking into account the use of different types of apartments, differs a great deal from the unweighted mean. The weighted mean annual dose is 1050 mrad while the unweighted mean annual dose is 700 mrad. Regarding the Swedish data, the mean annual dose obtained from the levels of radon and radon daughters measured in the "new buildings" (houses built after 1970) is 480 mrad, which is twice the result obtained from the measurements performed in the "old buildings" (houses built before 1956). Possible reasons for that difference are that, in modern houses, (a) the ventilation rate is lower, (b) more concrete is used, and (c) the activity concentration of ^{226}Ra in the concrete is higher (334). Taking into account the proportion of the "new buildings", the mean annual dose in the segmental bronchial epithelium is estimated to be about 320 mrad.

199. The differences between the doses calculated in this chapter (and in table 29) and those given in the references depend on different assumptions concerning the occupancy factors and the dose-to-exposure quotients. The arithmetic mean of the annual doses obtained for the five countries listed in table 29 is about 250 mrad. Since a substantial fraction of the measurements were taken in unventilated buildings, this mean is believed to be an overestimate of the average dose.

200. Another estimate can be tentatively derived from the information contained in table 28 and the paragraphs above. Assuming that a representative value of the average ^{222}Rn concentration indoors is $1\ pCi\ l^{-1}$

TABLE 28. RADON LEVELS IN HOUSES AND WORKING PLACES IN VARIOUS COUNTRIES

Country	Number of buildings investigated[a]	Type of building and material	Ventilation	Radon concentration mean and range[b] (pCi l^{-1})	Ratios (average) Rn : Ra A : Ra B : Ra C[c]	Unattached fraction of Ra A (mean)[d]	Equilibrium factor[e] F	Equilibrium equivalent concentration[f] (pCi l^{-1})	Proportion of dwellers[g] (per cent)	Type of occupancy[h]	Reference
Hungary	42	Ground floor, stone, no cellar	Unventilated for 8 h	(5.8)	1 : 1 : 0.8 : 0.8	–	(0.8)	4.8	5.5	H	342
	11	Ground floor, stone, with cellar		(2.3)	1 : 1 : 0.8 : 0.7	–	(0.8)	1.8	1.3	H	
	252	Ground floor, adobe and other, no cellar		(5.3)	1 : 1 : 0.9 : 0.8	–	(0.9)	4.6	40.6	H	
	62	Ground floor, adobe and other, with cellar		(3.6)	1 : 1 : 0.8 : 0.8	–	(0.8)	2.9	9.5	H	
	27	Higher floors, other materials		(1.0)	1 : 1 : 0.9 : 0.9	–	(0.9)	0.9	1.0	H	
	158	Ground floor, brick, no cellar		(2.9)	1 : 1 : 0.8 : 0.8	–	(0.8)	2.4	33.4	H	
	66	Ground floor, brick, with cellar		(1.5)	1 : 1 : 0.9 : 0.8	–	(0.9)	1.3	7.9	H	
	185	Higher floors, brick		(0.7)	1 : 1 : 0.8 : 0.8	–	(0.8)	0.6	0.8	H	
	30	Higher floors, concrete and block panel		(0.7)	1 : 1 : 1 : 0.9	–	(0.9)	0.7		H	
Poland	28	Apartment, concrete	Unventilated for 8 h	0.44 0.14-2.14	–	–	(0.5)	0.22		H	271
		Aggregate		0.35 0.26-1.10	–	–	(0.5)	0.18		H	
		Brick	Unventilated	0.19 0.08-0.37	–	–	(0.5)	0.10		H	
Sweden[i]	60	House, wood		0.41 0.03-1.7	–	–	(0.5)	0.21		H	142
	115	House, brick		1.08 0.06-8.2	–	–	(0.5)	0.54		H	
	109	House, concrete including alum shale		3.13 0.07-16	–	–	(0.5)	1.57		H	
USSR		Silicate brick		0.12-4.3	–	–					347
		Red brick		0.19-1.10	–	–					
		Concrete		0.4	–	–					
		Adobe		0.3-10	–	–					
		Slag		4.0-8.0	–	–					
United Kingdom	1	House	Adequate	0.16 0.016-0.3	–	–	(0.5)	(0.08)		H	119
	1	House	Inadequate	0.4 0.2-0.7	–	–	(0.5)	(0.2)		H	
	6	Industrial	Poor	0.09 0.005-1.2	–	–	(0.5)	(0.05)		W	
	4	Office	Air conditioning	0.17 0.06-0.35	–	–	(0.5)	(0.09)		W	

TABLE 28 *(continued)*

Country	*Number of buildings investigated*[a]	*Type of building and material*	*Ventilation*	*Radon concentration mean and range*[b] *(pCi l⁻¹)*	*Ratios (average) Rn : Ra A : Ra B : Ra C*[c]	*Unattached fraction of Ra A (mean)*[d]	*Equilibrium factor*[e] *F and mean range*	*Equilibrium equivalent concentration*[f] *(pCi l⁻¹)*	*Proportion of dwellers*[g] *(per cent)*	*Type of occupancy*[h]	*Reference*
United States											
New York	1 (long-term measure)	Instrument room, cinder-block walls	Poor Recirculation	0.2 0.1-0.3	1 : 0.5 : 0.3 : 0.2	0.07 0.02 (^{212}Pb)	0.3	0.06		W	84, 94
	1	Chemical laboratory	Good, filtration of ventilation air	~ 0.1	1 : 0.7 : 0.5 : 0.3	–	0.5	0.05		W	
	1 (11 measurements)	Basement in laboratory[j]	Low	6.0 3.6-7.8	1 : 0.9 : 0.4 : 0.2	0.04 (0.3-0.5)	0.4	2.3		W	
	1	Fifth floor in laboratory[k]	Normal	0.26	1 : 0.9 : 0.4 : 0.2	0.07	0.4 0.2-0.5	0.1		W	
Boston area	7	One-family house, wooden frame, first floor	2-6 h^{-1}	(0.07) (0.005-0.23)	1 : 1 : 0.9 : 0.8	–	(0.9)	0.07		H	376
	7	One-family house, concrete basement	1-3 h^{-1}	(0.4) (0.1-0.94)	1 : 1 : 1 : 0.7	–	(0.9)	0.4		H	347
	3	Apartment, brick	5-9 h^{-1}	(0.09) (0.01-0.19)	1 : 1 : 1 : 0.6	–	(0.8)	0.07		H	
	4	Office and laboratory, concrete and cinder block	6-14 h^{-1}	(0.05) (0.02-0.1)	1 : 1 : 0.9 : 0.8	–	(0.9)	0.05		W	
Tennessee	15	Houses, most of them of concrete construction		(1.4) (0.13-4.8)	1 : 0.9 : 0.6 : 0.4	–	(0.6)	0.8		H	212
Florida	16	Houses, most of them of concrete construction		(1.3) (0.03-3.6)	1 : 0.9 : 0.6 : 0.4	–	(0.6)	0.7		H	347

[a] Rooms in the case of Hungary.

[b] Some authors have not measured the Rn concentration. In those cases it is assumed that Rn : Ra A = 1 : 1, and the Rn value is given in parentheses.

[c] Relative to Rn.

[d] Relative to Rn, i.e., to the number of Ra A atoms in radioactive equilibrium with the Rn concentration.

[e] $F = (A_0 E_0)^{-1} \sum_{i=1}^{3} A_i E_i$, where A_i is, in turn, the activity concentration (pCi l^{-1}) of ^{218}Po, ^{214}Pb and ^{214}Bi; E_i is, in turn, the potential alpha energy (MeV pCi^{-1}) of ^{218}Po, ^{214}Pb and ^{214}Bi (see table 24); A_0 is the activity concentration of ^{222}Rn (pCi l^{-1}); and $E_0 = 1.3\ 10^3$ MeV.

[f] Calculated as Rn concentration times F.

[g] Proportion of dwellers in these exposure conditions.

[h] H = home; W = work. Only home values have been used to calculate the doses presented in table 29.

[i] More recent measurements in Sweden in modern houses with ventilation rates in the range of 0.2-0.9 h^{-1} have shown Rn concentrations ranging from 0.8-19 pCi l^{-1} with F = 0.5-0.7 (251). The corresponding average equilibrium equivalent concentration is about twice that obtained from the results given in the table, which were published in 1956.

[j] Aerosol particle concentration $N = (48 \pm 8)\ 10^4$ cm^{-3}; activity median diameter AMD = 0.11 ± 0.03.

[k] $N = (48 \pm 7)\ 10^4$ cm^{-3} : AMD = 0.11 ± 0.03.

TABLE 29. ESTIMATED ANNUAL INDOORS ABSORBED DOSE DUE TO RADON DAUGHTERS IN THE RESPIRATORY SYSTEM IN FIVE OF THE COUNTRIES LISTED IN TABLE 28

Country	*Annual indoor absorbed dose (mrad)*	
	Segmental bronchial epithelium	*Whole lung*
Hungary	700	140
Poland	52	10
Sweden	320	65
United Kingdom	44	9
United States	130	26

and using an equilibrium factor of 0.5, the annual absorbed dose in the basal cells of the bronchial epithelium can be roughly estimated to be about 160 mrad for indoor conditions. The annual dose in the whole lung would be around 30 mrad, and the annual doses in the gonads, the bone marrow and the bone lining cells would be of the order of 0.3 mrad.

201. Few data on the concentrations of thoron decay products in buildings have been published. Harley and Pasternack (124) reported average concentrations of $3.6\ 10^{-3}$ pCi l^{-1} of ^{212}Pb and of $2.7\ 10^{-3}$ pCi l^{-1} of ^{212}Bi in a laboratory in New York (United States). In Salzburg (Austria), Steinhäusler *et al.* (326) found a mean ^{212}Pb concentration of $24\ 10^{-3}$ pCi l^{-1}, the extreme values being $0.1\ 10^{-3}$ and $62\ 10^{-3}$ pCi l^{-1}. Taking a typical ^{212}Pb concentration to be 10^{-2} pCi l^{-1} and assuming radioactive equilibrium between ^{212}Pb and ^{212}Bi, the absorbed dose rate in the basal cells of the terminal bronchioles is estimated to be 8 μrad h^{-1}, corresponding to an annual dose of around 60 mrad. The annual absorbed dose in the whole lung would be about 5 mrad. The annual doses in the gonads, the bone marrow and the bone lining cells would be 0.008, 0.1 and 0.1 mrad, respectively.

202. *Future trend of indoor exposures to radon.* There are several factors which will probably influence the exposure to radon indoors. These include: (a) the development of international and national agreements on limits for ^{226}Ra and ^{232}Th (and ^{40}K) concentrations in building materials; (b) increasing use of central heating, which will probably have the effect of decreasing the ventilation of houses; (c) energy economizing programmes, which will involve an increased use of recirculation, resulting in an increased build-up of radon. However, because of the filtration system, the activity of the radon daughters might decrease and the unattached fraction might increase so that it is not certain whether the net effect of the increasing use of recirculation will be an increase or a decrease in the lung doses. In summary, factor (a) will probably lead to lower indoor exposures to radon, factor (b) to higher exposures, while the net effect of factor (c) is not clear. It is therefore difficult to predict the future trend of indoor exposures to radon.

(ii) *Radon in water*

203. Another source of radon in homes is the use of radon-rich water. There are many private and communal wells with radon concentrations in the water far exceeding 20 pCi l^{-1} (176, 316), and radon concentration in the water of the order of 1000 pCi l^{-1} is not unusual. While there are many measurements of radon in water, there is no information available on the inhalation exposure resulting from the use of radon-rich water. Assuming that (a) the radon concentration in water is 1000 pCi l^{-1} and is completely released into the air, (b) a normal rate of water consumption in a house with four persons is about 1000 l per day, and (c) the house has a volume of 230 m^3 and is ventilated at a rate of 1 h^{-1}, the average concentration of radon from this source in the air of such a house can be roughly estimated at 0.2 pCi l^{-1}. Using an equilibrium factor of 0.5 and an occupancy factor of 0.8, the corresponding annual dose in the bronchial epithelium is about 30 mrad. Further studies on the significance of this radon source in different countries would be of great interest.

204. In certain special areas there may be very high radon concentrations in the water. The highly radioactive spas at Badgastein (Austria) have been used for many years as part of a treatment in "thermal galleries" with radon inhalation facilities. The radon concentration of the water varies between 0.5 and 120 nCi l^{-1} with a mean value of 40 nCi l^{-1}. The total amount of radon released into the air in this area by the daily use of 21 springs has been estimated to be about 200 mCi per day (283). The radon concentrations in the air are of the order of 1 pCi l^{-1} in open air and of the order of 10 pCi l^{-1} in room air. The radon concentration in the air of a thermal gallery is 3000 pCi l^{-1}. The concentration of ^{212}Pb is about 0.01 pCi l^{-1} indoors and 0.001 pCi l^{-1} outdoors.

(d) *Recapitulation of tissue absorbed doses from ^{222}Rn, ^{220}Rn and their short-lived decay products*

205. The annual dose arising from inhalation of radon and thoron decay products can be obtained by adding the results corresponding to open air and to indoor conditions (table 30). In fact, since the concentrations and occupancy factor are much higher in houses than outdoors, the outdoor exposure leads to doses which can usually be neglected in comparison with those from indoor exposure. The main contributions to indoor exposure appears to be due to the ^{226}Ra and ^{232}Th content of building materials. The resulting annual tissue absorbed doses are estimated in this document to be about 160 mrad in the segmental bronchioles and 30 mrad in the whole lung from exposure to the ^{222}Rn short-lived decay products, and about 30 mrad in the terminal bronchioles and 4 mrad in the whole lung from exposure to the ^{220}Rn decay products. The doses in tissues and organs outside the respiratory system are expected to be lower by at least an order of magnitude.

206. The contribution to indoor exposure arising from the consumption of water has been considered. From fragmentary information it seems that the use of radon-rich water in homes might in some cases contribute significantly to the absorbed doses.

207. It is very difficult to assess the annual collective dose due to radon owing to the large diversity of housing

TABLE 30. ESTIMATED ANNUAL TISSUE ABSORBED DOSE ARISING FROM INHALATION OF ^{222}Rn AND ^{220}Rn SHORT-LIVED DECAY PRODUCTS[a]

Source of irradiation	*Equilibrium equivalent concentration ($pCi\ l^{-1}$)*	*Annual tissue absorbed dose (mrad)*				
		Segmental bronchial epithelium	*Lung*	*Gonads*	*Bone marrow*	*Bone lining cells*
^{222}Rn short-lived decay products						
Outdoor exposure	0.06	5 (1-25)	1 (0.2-5)	0.007 (0.001-0.08)	0.008 (0.002-0.04)	0.008 (0.002-0.04)
Indoor exposure						
Building materials	0.5 (0.05-5)	160 (20-2 000)	30 (3-300)	0.2 (0.02-2)	0.3 (0.03-3)	0.3 (0.03-3)
Water	(10^{-4}-1)	(0.03-300)	(0.006-60)	($5\ 10^{-5}$-0.5)	($5\ 10^{-5}$-0.5)	($5\ 10^{-5}$-0.5)
^{220}Rn decay products						
Outdoor exposure	0.001		0.1	$2\ 10^{-4}$	0.003	0.003
Indoor exposure						
Building materials	0.01 (0.001-0.06)		4 (0.4-20)	($8\ 10^{-4}$-0.05)	0.1 (0.01-0.6)	0.1 (0.01-0.6)

[a]The expected ranges of the concentration or the dose are given within parentheses.

characteristics, materials and building techniques. It would appear, however, that the order of magnitude of the annual collective dose to the lung is 10^8 man rad. As this collective dose is delivered by alpha particles, it can not be readily compared with the other collective doses from natural sources.

2. Ingestion

208. Small absorbed doses in human tissues are also incurred as a result of ingestion of ^{222}Rn with water. The presence of ^{222}Rn in water has already been mentioned in paragraph 203, and is due to activity transfer from soils. Radon-222 concentrations in fresh water vary from less than 1 $pCi\ l^{-1}$ up to the order of 10^6 $pCi\ l^{-1}$ (346). Levels less than 10 $pCi\ l^{-1}$ are found in lakes and rivers, and concentrations in the range 10^2-10^4 $pCi\ l^{-1}$ have been reported for ground waters; even higher concentrations can be found in deep wells, and the highest reported values have been observed in some spas.

209. As mentioned in paragraph 203, concentrations of the order of 10^3 $pCi\ l^{-1}$ are frequently seen in tap water from ground-water supplies. Assuming a consumption of 0.3 l per day of water containing 10^3 $pCi\ l^{-1}$ of ^{222}Rn, the estimated annual absorbed dose in the stomach is about 2 mrad, while the average dose in the whole body is lower by a factor of 100.

III. RECAPITULATION OF TISSUE ABSORBED DOSES

210. Table 31 summarizes the contribution of natural sources to the radiation exposure of human populations living in areas of normal radiation background. The four tissues considered in table 31 are the gonads, the lung, the bone lining cells and the red bone marrow. In those tissues, the annual average absorbed dose from natural sources is estimated to be of the order of 100 mrad. For comparison purposes, table 31 includes the estimates for the gonads, the bone lining cells and the bone marrow given in the 1972 report. The new estimates of the total doses are a few per cent lower than the previous ones for the gonads and the bone lining cells, and a few per cent higher for red bone marrow. The difference is mainly due to a better knowledge of the terrestrial doses, which are now estimated to be about 30 per cent lower than indicated in the 1972 report. The increase of the dose in the red bone marrow results from a much higher estimate of the contribution from ^{40}K than in the 1972 report.

211. As a result of inhalation of ^{222}Rn and ^{220}Rn short-lived decay products, the dose in the entire lung, which has been assessed for the first time by the Committee, is due primarily to alpha particles and is more than 30 per cent higher than the doses in the three other tissues. It is worth mentioning that, in addition to the doses included in table 31, yearly doses of the order of 200 mrad are received by the basal epithelial cells of the tracheo-bronchial tree.

212. The most important components of the total absorbed dose in gonads, bone lining cells and red bone marrow are the ionizing component of the cosmic radiation, the terrestrial gamma radiation, and ^{40}K, which together amount to 90 per cent or more of the total dose. Neglecting the variability of the dose from cosmic rays and considering only the variability of the annual doses from ^{40}K and from terrestrial gamma radiation given earlier in this Annex, it can be estimated that the annual doses from natural sources received by 95 per cent of the population are in the range of 70-92 mrad in the gonads, 77-110 mrad in the bone lining cells, and 67-120 mrad in the red bone marrow. In the lung, an important contribution to the dose arises from ^{222}Rn and its short-lived decay products. The expected range of the annual dose in the lung from ^{222}Rn and its short-lived decay products is fairly large, extending from 4 to almost 400 mrad (table 30). If this large variability were confirmed in large-scale surveys, it would make the variability of the other contributions to the lung dose from natural sources unimportant.

TABLE 31. ESTIMATED ANNUAL TISSUE ABSORBED DOSE FROM NATURAL SOURCES IN "NORMAL" AREAS

Compared with the estimates of the 1972 report (in parentheses)

Source of irradiation	*Annual tissue absorbed dose (mrad)*							
	Gonads		*Lung*	*Bone lining cells*		*Red bone marrow*	
External irradiation							
Cosmic rays:							
Ionizing component	28	(28)	28	28	(28)	28	(28)
Neutron component	0.35	(0.35)	0.35	0.35	(0.35)	0.35	(0.35)
Terrestrial radiation: (γ)	32	(44)	32	32	(44)	32	(44)
Internal irradiation							
Cosmogenic radionuclides:							
^{3}H (β)	0.001	(0.001)	0.001	0.001	(0.001)	0.001	(0.001)
^{7}Be (γ)	–	–	0.002	–	–	–	–
^{14}C (β)	0.5	(0.7)	0.6	2.0	(0.8)	2.2	(0.7)
^{22}Na ($\beta+\gamma$)	0.02	–	0.02	0.02	–	0.02	–
Primordial radionuclides:							
^{40}K ($\beta+\gamma$)	15	(19)	17	15	(15)	27	(15)
^{87}Rb (β)	0.8	(0.3)	0.4	0.9	(0.6)	0.4	(0.6)
^{238}U-^{234}U (α)	0.04	(0.03)	0.04	0.3	(0.3)	0.07	(0.06)
^{230}Th (α)	0.004	–	0.04	0.8	–	0.05	–
^{226}Ra-^{214}Po (α)	0.03	(0.02)	0.03	0.7	(0.6)	0.1	(0.1)
^{210}Pb-^{210}Po ($\alpha+\beta$)	0.6	(0.6)	0.3	3.4	(1.6)	0.9	(0.3)
^{222}Rn-^{214}Po (α) inhalation	0.2	(0.07)	30	0.3	(0.08)	0.3	(0.08)
^{232}Th (α)	0.004	–	0.04	0.7	–	0.04	–
^{228}Ra-^{208}Tl (α)	0.06	(0.03)	0.06	1.1	(0.3)	0.2	(0.06)
^{220}Rn-^{208}Tl (α) inhalation	0.008	(0.003)	4	0.1	(0.05)	0.1	(0.05)
Total (rounded)	78	(93)	110	86	(92)	92	(89)
Fraction of absorbed doses delivered by alpha particles or neutrons (%)	1.2	(1.3)	31	8.5	(4.1)	2.1	(1.2)

213. Much higher doses from external radiation are received by population groups living at high altitudes or in regions of high natural radioactivity. A number of population groups are exposed to elevated internal absorbed doses, such as the caribou or reindeer eaters, or people living in houses with a low rate of ventilation. The importance of the contribution of areas of high natural radiation to the global collective dose cannot yet be assessed. As a first approximation the global annual collective dose from natural radiation sources is estimated to be of the order of $3\ 10^{8}$ man rad for the gonads, bone marrow and bone lining cells, and about 30 per cent higher for the lung.

IV. TECHNOLOGICALLY ENHANCED EXPOSURES TO NATURAL RADIATION

214. The exposures to natural sources of radiation discussed in the previous sections are those to which man has always been subjected, namely exposures to cosmic rays at ground level and to naturally occurring radionuclides in soil, air, water and food. The present habits of human societies have also been taken into account, in particular when the doses received indoors have been estimated. This has been done because the vast majority of the population spends most of its time in buildings, where the radiation environment differs appreciably from that found outdoors.

215. There are other circumstances where man finds himself in a natural radiation environment to which he would not be exposed if some kind of technology had not been developed. Examples of such circumstances are travelling by air, using natural gas for cooking or heating purposes, or living in the neighbourhood of a coal-fired power plant. The resulting exposures have been labelled "technologically enhanced natural radiation" (TENR) exposures by Gesell and Prichard (97a), who define them as exposures to truly natural sources of radiation (that is, naturally occurring radionuclides and cosmic radiation) which would not occur without (or are increased by) some technological activity not expressly designed to produce radiation. This section deals with these enhanced exposures and presents some assessments of the doses arising from such exposures.

216. According to the definition given above, the mere fact of being in a building would constitute a TENR exposure, since both the absorbed dose in air and the tissue absorbed dose from inhalation are on average higher indoors than outdoors. However, since the indoor exposures have been abundantly discussed earlier in this Annex, the only building materials that will be considered in this section are industrial waste products and raw materials containing relatively high concentrations of natural radionuclides.

217. The exposures from widely used consumer products containing radionuclides are also dealt with in the appendix to this Annex. They do not qualify as

technologically enhanced exposures for several reasons, the main one being that the radionuclides are deliberately incorporated into the products. However, these consumer products present enough similarities with the TENR sources to justify the inclusion of the appendix, particularly because the majority of the radionuclides used are naturally occurring, and most of the users of the products are not aware that they constitute a source of radiation.

A. ENHANCED EXPOSURES TO COSMIC RAYS

1. Passengers in aircraft

218. The number of passenger kilometres flown annually throughout the world (not including data from China) is approaching 10^{12} (149a).

Year	*Passenger kilometres (10^{12})*
1970	0.460
1971	0.494
1972	0.560
1973	0.617
1974	0.654
1975	0.676

The average speed is about 600 km h^{-1}, which means that a total of about 10^9 passenger hours are spent travelling each year. Under average solar conditions, the absorbed dose index rate at the altitude of subsonic flights is about 0.3 mrad h^{-1} (fig. II), and therefore, the annual collective dose from these flights is about 3.4 10^5 man rad (with the 1975 data).

219. The prospect of the development of a supersonic aircraft transport (SST) system on a large scale during the next decade poses the question of the cosmic-ray absorbed dose index rates to which passengers and crews will be exposed and of the contribution of this to the collective dose to the world population. The first generation of supersonic aircraft flies at altitudes ranging up to 20 km, compared with at most 12 km for standard jet aircraft. The absorbed doses in human tissues received in a particular flight will depend markedly on the duration of the flight and on the altitude and geomagnetic latitude of the flight; for example, the doses will be much higher at latitudes above 50°.

220. When considering dose rates in persons exposed at such high altitudes, it is necessary to discuss separately two contributions. The first of these is due to the galactic cosmic rays, ever present, which vary in intensity by a factor of about two during the sun's 11-year solar cycle. Secondly, there may occasionally be large short-term increases in the radiation as a result of energetic solar protons originating from solar flares.

221. Estimates of the absorbed dose index rates from both the ionizing and neutron components of galactic cosmic rays at high latitude and at altitudes of 12 and 20 km can be obtained from figure II. During the time of solar activity minimum, when cosmic-ray flux densities are at maximum, the absorbed dose index rates are: at 12 km, 300 μrad h^{-1} from the ionizing component and 20 μrad h^{-1} from neutrons: at 20 km, 600 μrad h^{-1} from the ionizing component and 30 μrad h^{-1} from the neutron component.

222. The estimates of absorbed dose index rates from the ionizing component given above probably do not include the contribution resulting from local nuclear interactions of high-energy primary cosmic rays in tissue (called nuclear disintegration stars). A number of measurements of absorbed dose rate in tissue at supersonic transport altitudes have been reported, some of which include information on absorbed dose rates from nuclear stars.

223. Some of these measurements have been made with instruments calibrated in terms of the dose equivalent (expressed in rem), equal to the absorbed dose multiplied by a mean quality factor. In these cases the absorbed dose has been inferred from the reported dose equivalent and quality factor.

224. Fuller and Clarke (92) made measurements from balloons at 20 km over Fort Churchill, Canada, in July 1964, near solar minimum. Their measurements correspond to an absorbed dose index rate from the ionizing component of 750 μrad h^{-1}. An average quality factor of 1.5 was calculated for this ionizing component from a study of tracks recorded in nuclear emulsion plates. The neutron "rem counter" indicated a dose-equivalent rate from neutrons of 500 μrem h^{-1}. O'Brien and McLaughlin (263) concluded that this neutron dose-equivalent measurement corresponded to a surface dose in a phantom irradiated isotropically from above. The dose-equivalent rate for a flux density of 1 neutron cm^{-2} s^{-1} at the surface of a 30 cm slab for monolateral isotropic incidence is 68 μrem h^{-1} (112). The corresponding figure averaged through the 30 cm slab for bilateral isotropic incidence is 29 μrem h^{-1}. The 500 μrem h^{-1} of Fuller and Clarke (92) reduces to 210 μrem h^{-1} for bilateral isotropic incidence averaged through 30 cm. For the neutron energy spectrum, the quality factor, averaged over 15 cm, is estimated to be about 6. The absorbed dose rate therefore corresponds to 35 μrad h^{-1}, in reasonable agreement with figure II.

225. Fuller and Clarke (92) estimated the absorbed dose rate in tissue from nuclear stars recorded in the nuclear emulsion plates as 64 μrad h^{-1} (with an average quality factor of 8.5). These authors were not certain whether all or part of the dose rate from nuclear stars was recorded in the ionization chamber measurements or not. At most, failure to subtract the contribution of stars from the ionizing component would over-estimate the absorbed dose in tissue by 10 per cent. The measurements by Davison (68) at an altitude of 20 km agree well with those of Fuller and Clarke for all three components (ionizing, neutron and tissue stars) (6, 68).

226. Between 1968 and 1971, measurements were made at a geomagnetic latitude of 70°N by the United States Air Force (2). The instrumentation consisted of a Rossi-type LET spectrometric chamber, a 10-channel pulse-height analyser and a Geiger counter. The average absorbed dose rate at SST altitudes was 450 ± 90 μrad h^{-1}. On some of these missions nuclear emulsions were exposed for some 40 h. Nuclear-track analysis indicated

a tissue absorbed dose rate of 580 μrad h^{-1}, with a quality factor of 1.8. In addition, there was a contribution from nuclear stars of 70 μrad h^{-1}, in good agreement with the measurements of Fuller and Clarke.

227. Measurements made with a BNL dose-equivalent meter at a number of altitudes near geomagnetic latitude 70°N in 1971 correspond to absorbed dose index rates of 603 ± 100 and 288 ± 50 μrad h^{-1} at altitudes of 20 and 12.7 km, respectively. Absorbed dose index rates measured with this same instrument at several altitudes and geomagnetic latitudes are plotted in figure XX (2).

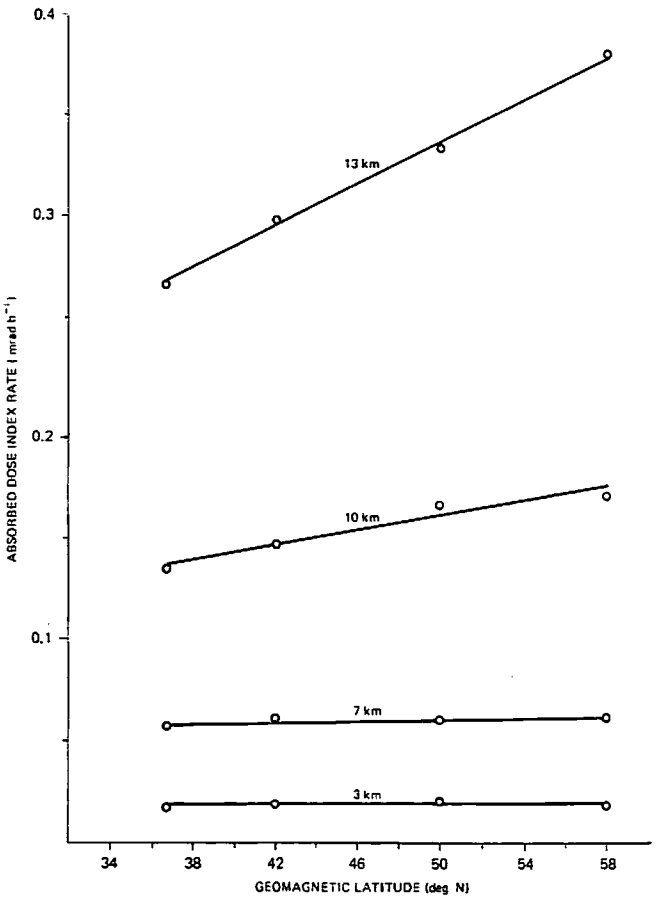

Figure XX. Galactic cosmic radiation absorbed dose index rate at four different altitudes as a function of latitude

228. Foelsche *et al.* (88) determined galactic cosmic-ray dose rates in the centre of a body phantom at SST altitudes from measurements made in balloon flights over Minnesota (United States; geomagnetic latitude 55°) and over Fort Churchill (Canada; geomagnetic latitude 69°) from 1965 to 1968. At 20 km altitude the ionizing component of the absorbed dose rate was in the range 470-730 μrad h^{-1}, the neutron dose-equivalent rate, 320-550 μrem h^{-1}; and that from nuclear stars, 100-180 μrem h^{-1}. Considering that there are considerable changes in dose rates with latitude and altitude and also that there is some uncertainty about the quality factor to use in relating dose equivalent to absorbed dose or dose index, all the measured dose rates reported above are in reasonable agreement with each other and with the estimates given in paragraph 221 based upon cosmic-ray flux densities.

229. There is general agreement between calculated and measured values. At solar minimum and high latitude, absorbed dose index rates at an altitude of 20 km are estimated to be about 600 μrad h^{-1} from the ionizing component, 30 μrad h^{-1} from neutrons and about 60 μrad h^{-1} from nuclear stars. At an altitude of 12 km they are about 300 μrad h^{-1} from the ionizing component, 20 μrad h^{-1} from neutrons and little from nuclear stars.

230. In an attempt to gain data on absorbed doses received by passengers of transport aircraft, thermoluminescent dosimeters and films sensitive to β and γ radiation were repeatedly sent by airmail between San Francisco, Washington, Tokyo, Buenos Aires, Rio de Janeiro (356). The doses to a passenger for a round trip, assessed from the films and TLD devices, are compared with the values computed for average solar activity conditions in table 32. It should be pointed out that the individual experimental results are quite variable, their average for a given route being only a rough estimate of the dose to the passenger. The values are in reasonable agreement.

TABLE 32. ESTIMATED COSMIC RAY DOSE TO A PERSON FLYING IN CONVENTIONAL JET AIRCRAFT

Average solar conditions

	Dose per round trip (mrad)		
	Experimental assessment		
Destination from San Francisco	*β and γ film*	*TLD*	*Calculated*[a]
Washington	3.4	3.0	3.1
Tokyo	3.5	3.8	3.3
Buenos Aires	4.1	4.4	8.7
Rio de Janeiro	5.4	6.9	6.4

Source: Reference 356.

[a] Including neutron contribution.

231. Wallace (356) used the same computer code to calculate absorbed doses to passengers for a round trip, for both subsonic and supersonic transport between various city pairs. Some of these estimates are shown in table 33. Doses for a round trip in supersonic aircraft are approximately 70 per cent of those for subsonic speeds, because of the shorter flying time. However, the dose rates in supersonic aircraft are about twice as high as in subsonic aircraft. For a round trip across the Atlantic, the tissue absorbed doses in passengers may be estimated at about 2 mrad and 3 mrad for an SST and a subsonic

TABLE 33. COMPARISON OF CALCULATED COSMIC-RAY DOSES TO A PERSON FLYING IN SUBSONIC AND SUPERSONIC AIRCRAFT

Average solar conditions

	Subsonic flight at 11 km		*Supersonic flight at 19 km*	
Route	*Flight duration (h)*	*Dose per round trip (mrad)*	*Flight duration (h)*	*Dose per round trip (mrad)*
Los Angeles-Paris	11.1	4.8	3.8	3.7
Chicago-Paris	8.3	3.6	2.8	2.6
New York-Paris	7.4	3.1	2.6	2.4
New York-London	7.0	2.9	2.4	2.2
Los Angeles-New York	5.2	1.9	1.9	1.3
Sydney-Acapulco	17.4	4.4	6.2	2.1

Source: Reference 356.

aircraft, respectively, under average solar activity conditions. Estimates of 4 mrad and 5.6 mrad, respectively, were given in the 1972 report of the Committee for solar minimum conditions when cosmic-ray intensities are highest (with the exception of solar flares).

232. Measurements of absorbed dose rates on board the Concorde aircraft have been reported (70, 242c). The decrease of the absorbed dose index rate as a function of the geomagnetic latitude, is illustrated in figures XXI and XXII, which show the results of a continuous

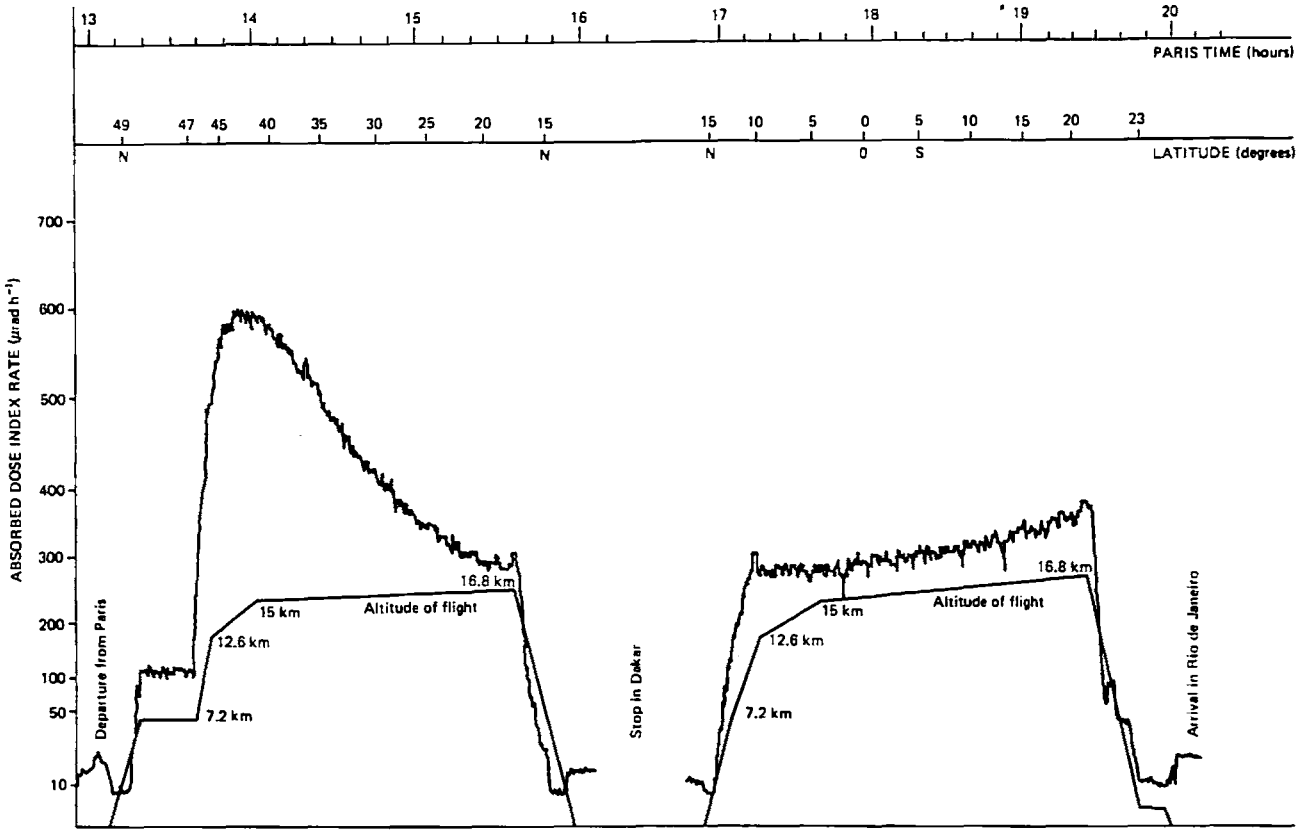

Figure XXI. Recording of the absorbed dose index rate on a flight from Paris to Rio de Janeiro, February 1976

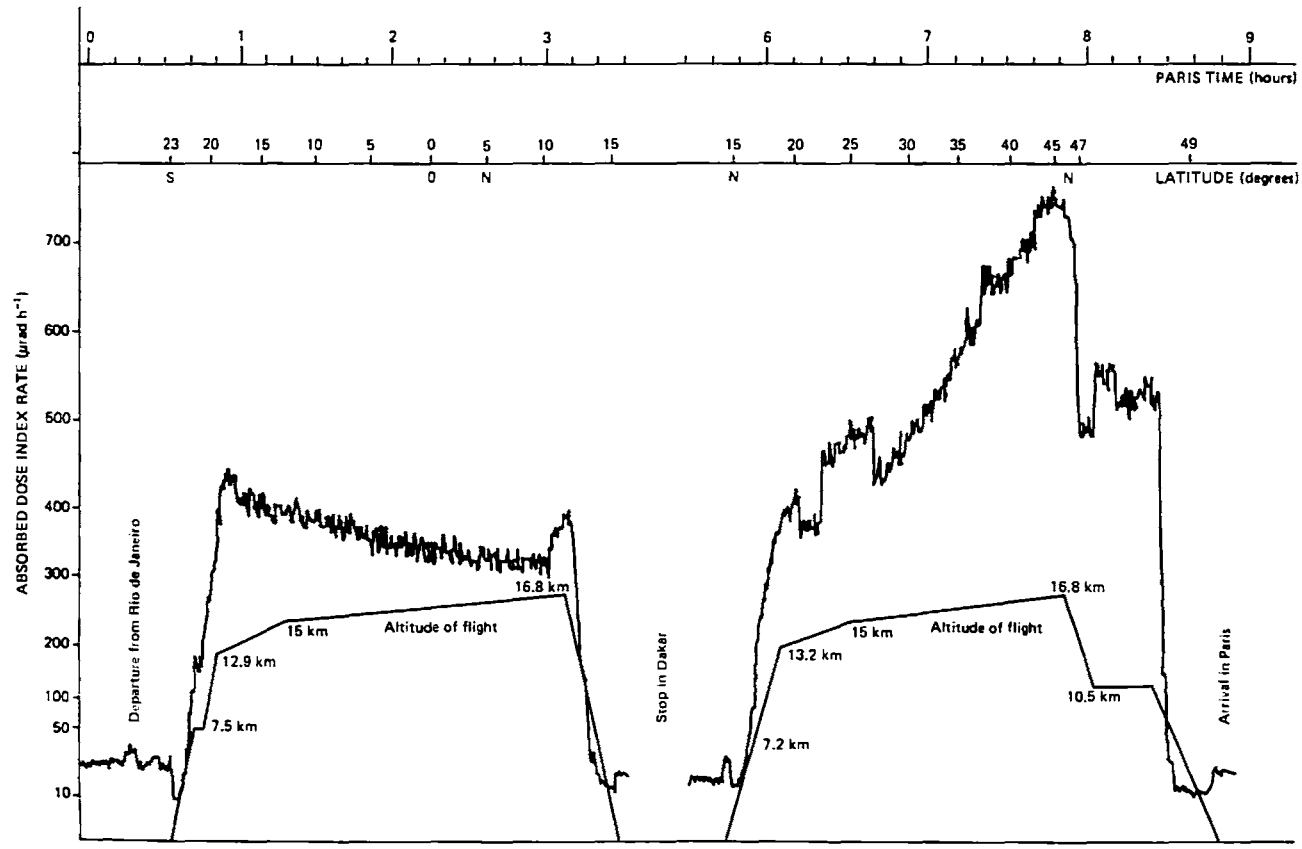

Figure XXII. Recording of the absorbed dose index rate on a flight from Rio de Janeiro to Paris, February 1976

recording carried out in February 1976 by Moroni *et al.* (242c) during a Paris-Rio de Janeiro-Paris flight. During the Paris-Rio de Janeiro portion of the flight (fig. XXI), a plateau at the level of 100 μrad h^{-1} was observed between Paris and Nantes when the aircraft was flying at subsonic speed at an altitude of 7.2 km. Between Nantes and Dakar, now at supersonic speed at an altitude of 16 km, the absorbed dose index rate reached 620 μrad h^{-1} at latitude 45°N, then decreased with latitude down to 300 μrad h^{-1} at 25°N. From Dakar to Rio, in low-latitude regions, the absorbed dose index rate changed very little. On the return flight, the recording of the absorbed dose index rate (fig. XXII) shows a few irregularities between Dakar and Paris, which coincide with the rising of the sun (242c). The absorbed dose index for the passengers and the crew during the round trip did not exceed 5 millirad.

233. From dose-rate values given in the 1972 report, the average absorbed dose index rate from solar radiation can be estimated to be 4 μrad h^{-1} at 12 km and 90 μrad h^{-1} at 20 km. The 1972 values had been obtained by an ICRP working group by averaging the effects of solar flares over the period 1952-1960 (150). It can be seen that at these altitudes the average contribution from this source is small compared with that from galactic cosmic rays.

234. Although radiation of solar origin does not contribute significantly to the average absorbed dose index rate, during an occasional intense solar flare radiation levels at these altitudes may increase by several orders of magnitude. The absorbed dose index rates at different altitudes have been estimated for the large solar flare event on 23 February 1956 (7, 12, 368). Estimates of the peak absorbed dose index rates in polar regions at different altitudes during this flare are shown in figure XXIII (12). The radiation at these altitudes from solar flares is very latitude-dependent and the absorbed dose index rates are more than 10 times smaller at latitudes below 50° (110). SST aircraft carry radiation monitors, and the pilots will move the aircraft to lower altitudes when the dose rate reaches a prescribed level. The giant solar flare events last only for about 10 h and occur a few times in each solar cycle, and therefore are not likely to add significantly to the collective dose of the world population.

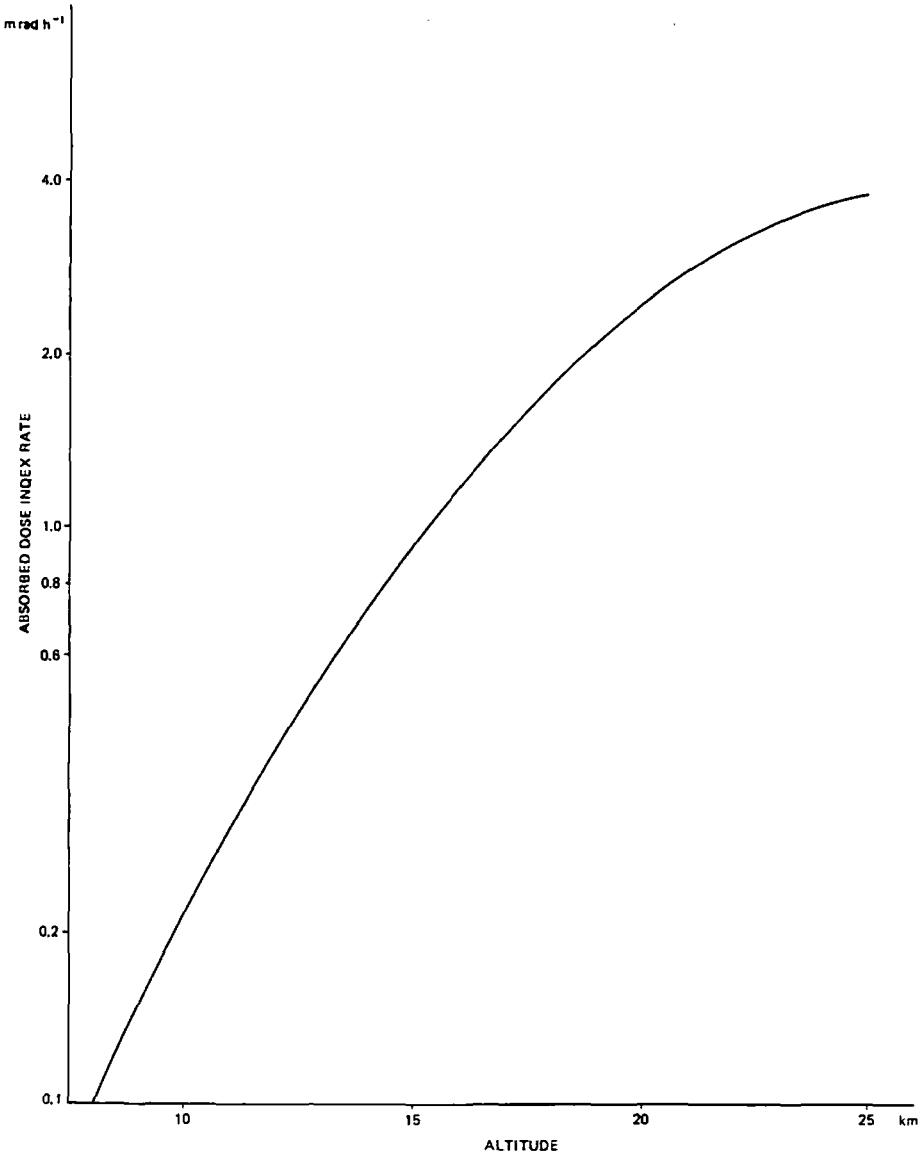

Figure XXIII. Estimated absorbed dose index rate as a function of altitude at high latitudes during the large solar flare of 23 February 1956

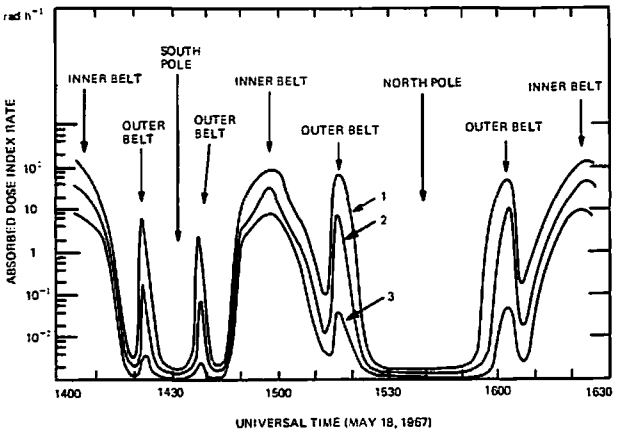

Figure XXIV. Absorbed dose index rate measured by the three tissue-equivalent ionization chambers aboard the OVI-9 satellite on a polar orbit during a period of no solar activity. Chamber 3 was the most heavily shielded (65, 290)

2. Astronauts

235. When travelling into space, astronauts are subjected to primary cosmic-ray particles, the radiation from solar flares, and also the intense radiation present in the two radiation belts. Savun *et al.* (303) have reported measurements in the radiation belts in 1971. Measurements inside a 0.7 g cm^{-2} shield indicate that the maximum absorbed dose index rate crossing the inner belt was 22 rad h^{-1} and crossing the outer belt belt 5.4 rad h^{-1}. Dose rates in tissue-equivalent ionization chambers were measured aboard the OVI-9 satellite with different amounts of shielding. Dose index rates based upon these measurements are shown in figure XXIV.

236. Estimated absorbed doses in the chests of the astronauts on five Apollo missions (average for the three occupants) based upon dosimeter measurements are shown in table 34 (65, 290). A large part of this dose was received while the spacecraft was passing through the earth's radiation belts. For example, the higher dose received on the Apollo X mission was largely due to a different trajectory through the radiation belts. Analogous data in table 34 from USSR space flights (Vostok, Voskhad and Soyuz series) indicate doses of comparable magnitude (106a). In outer space, remote from the shielding influence of the earth's magnetic field, the absorbed dose index rate from solar protons emitted during solar flares is very high. For example, it has been estimated that the absorbed dose indices in outer space from the solar proton event of 10 July 1959 were: from protons 360, 170 and 40 rad behind shielding of 1, 2 and 5 g cm^{-2}, respectively, and from alpha particles the corresponding values were 150, 30 and 5 rad, respectively (65).

TABLE 34. ABSORBED DOSE IN THE CHESTS OF ASTRONAUTS ON SPACE MISSIONS

Mission or mission series	*Launch date (Year-month-day)*	*Duration of mission (h)*	*Type of orbit*	*Dose (mrad)*
Apollo VII	1968-08-11	260	Earth orbital	157
Apollo VIII	1968-12-21	147	Circumlunar	150
Apollo IX	1969-02-03	241	Earth orbital	196
Apollo X	1969-05-18	192	Circumlunar	480
Apollo XI	1969-07-16	195	Lunar landing	179
Vostok 1-6			Earth orbital	2-80
Voskhad 1, 2			Earth orbital	30, 70
Soyuz 3-9			Earth orbital	62-234

Sources: References 65, 106a, 290.

B. ENHANCED EXPOSURES TO NATURALLY OCCURRING RADIONUCLIDES

1. Radiation exposures due to coal-fired power plants

237. Burning of coal is one of the sources of enhanced exposures to natural radionuclides. Large coal-fired power stations burn pulverized coal, the combustion products of which, both in gaseous and particulate form, are discharged into the atmosphere. There is more particulate emission during combustion of coal than any other fuel because of its high ash content (typically, 5-10 per cent) (20, 79). It is estimated that annual world coal consumption is approaching 3 10^9 tonnes (t) (185). The combustion of about 3 10^3 t of coal is required to produce an electrical energy of one megawatt-year (23, 79, 175, 185).

238. Most industrially consumed coal is burned at central power plants where the elements entering the boiler in the coal stream are partitioned between a bottom-ash (or slag) stream, and a flue-gas stream containing suspended fly ash and the vapours of volatile elements or compounds. A further partitioning of the flue-gas stream takes place in the particulate emission control devices (electrostatic precipitators or scrubbers) that efficiently remove larger fly-ash particles but are less efficient for vapours and finer particles, which are thus discharged into the atmosphere. Ash from the boiler and ash removed by the precipitators are flushed with water to ash ponds. The disposal of the very large quantities of ash produced, or their utilization in making concrete, can also lead to human exposure.

239. Studies relative to the flow of trace elements through coal-fired power plants (175, 185) indicate that radium and thorium are at essentially the same concentration in coal ash, slag, and fly ash while the concentration of lead increases progressively in fly ash collected downstream from the burner toward the stack. The behaviour of uranium seems to be intermediate between that of lead and that of radium and thorium. Reported activity concentrations of natural radionuclides in samples of coal, slag and fly ash from several countries are presented in table 35.

TABLE 35. ACTIVITY CONCENTRATION OF RADIONUCLIDES IN COAL AND COAL RESIDUES

(pCi g^{-1})

Type of coal or coal residue and its origin	^{40}K	^{238}U	^{226}Ra	^{210}Pb	^{228}Ra	^{228}Th	^{232}Th	*Reference*
Coal								
Australia			0.8-1.3					23
Czechoslovakia (brown)			0.11, 0.35					165
Germany, Fed. Rep. of	< 2.5		< 0.7				< 0.6	307a
Hungary (bituminous)			0.04					165
Poland (bituminous)			0.048-0.94					165
Poland (brown)			0.90					165
United States								
Illinois	2.5		0.6[a]			0.04[b]		20
Montana	0.7		0.3[a]			0.07[b]		20
North Dakota	2.2		0.2[a]			0.02		20
United States		0.7					0.2	185
United States			0.014	0.28				175
Coal ash (laboratory processing)								
Australia			4.7-8.3					23
Germany, Fed. Rep. of			6.2[c]			2.6		172
	19		5.8				3.4	307a
Japan								
Central			0.10	19.8	1.15	15.3		257
Southern			0.98	8.16	0.46	2.35		257
Northern			0.63	105.0	1.45	6.79		257
United States (semi-bituminous)			3.8		2.4	2.6		79
Slag								
Poland	17.3		4.3[a]			1.2[b]		272
United States	26		4.5[a]			0.5[b]		20
United States		4.9					1.5	185
United States			0.55	1.0				175
Fly ash								
Australia			14.0					23
Hungary			0.6-15					204
Poland			1.0					165
Poland	22.5		6.4[a]			1.1[b]		272
Poland (bituminous)		1.5, 2.8	0.61, 4.18	4.4, 6.7			0.18. 0.22	166
Poland (lignite)			0.91					166
United States		10					2.6	185
United States			0.4	17.3				175
United States	11		3.1[a]			0.4[b]		20

[a] Assumed equal to activity concentration of ^{214}Bi.
[b] Assumed equal to activity concentration of ^{208}Tl.
[c] Including activity concentration of ^{228}Ra.

240. The activity of a given radionuclide discharged into the atmosphere can be evaluated from the activity concentration of that radionuclide in fly ash and the flow of fly ash through the stack. On the basis of the results presented in table 35 it will be assumed that representative values of activity concentrations in fly ash are 1 pCi g^{-1} for ^{226}Ra, ^{228}Ra, ^{228}Th and ^{232}Th, 5 pCi g^{-1} for ^{238}U, 10 pCi g^{-1} for ^{210}Pb and 15 pCi g^{-1} for ^{40}K. It will be noted that the activity concentrations of ^{40}K, ^{226}Ra, ^{228}Th and ^{232}Th are about the same as in average soil, while those of ^{238}U and ^{210}Pb are much higher. This results from the enrichment of lead and uranium in fly ash relative to slag and coal ash.

241. Estimates of the flow of fly ash through the stack per megawatt-year of electrical energy produced (23, 172, 175, 185) range from 0.7 to 30 t. Taking a value of 10 t to be representative, the activities discharged per megawatt-year produced would amount to 10^{-5} Ci for ^{226}Ra, ^{228}Ra, ^{228}Th and ^{232}Th, 5 10^{-5} Ci for ^{238}U, 10^{-4} Ci for ^{210}Pb, and 1.5 10^{-4} Ci for ^{40}K.

242. The activity of ^{222}Rn released per megawatt-year has been estimated to be about 10^{-3} Ci on the basis of the following assumptions: (a) ^{222}Rn is in radioactive equilibrium with ^{226}Ra in coal and is discharged in its entirety when coal is burned, (b) the average activity concentration of ^{226}Ra in coal is 0.3 pCi g^{-1} (table 35), and (c) the combustion of 3 10^3 t of coal is required to produce an electrical energy of 1 MW y.

243. Measurements in environmental samples around coal-fired power plants clearly show the presence of enhanced concentrations of these nuclides. In air, Martin *et al.* (221) measured, at a point 6 km downwind of a coal power plant, concentrations of 6 10^{-16} Ci m^{-3} of ^{226}Ra, 3 10^{-16} Ci m^{-3} of ^{232}Th, and 2 10^{-15} Ci m^{-3} of ^{238}U, compared with the "normal" concentrations of 7 10^{-17} Ci m^{-3} for each of the three radionuclides. In snow, the ^{226}Ra concentrations found by Jaworowski *et al.* (164) ranged up to 1.7 10^{-15} Ci g^{-1} and were related to the distance from the power plants. Studies of a glacier 150 km for an industrial centre revealed a 50-fold increase in ^{226}Ra concentration over the

preceding 80 years (164). In soils of industrial areas, the concentrations of ^{226}Ra, uranium and thorium were found to be higher in the upper 5-cm layer than in the 5-10 cm layer, while this effect was not observed in rural soils (166).

244. The main pathways through which the populations living around coal-fired power plants are exposed to enhanced levels of natural radionuclides are inhalation and ingestion of the activity discharged into the atmosphere. The collective dose commitments due to inhalation during the passage of the cloud have been estimated using the following assumptions:

(a) The average dilution factor is $1.6\ 10^{-8}$ s m^{-3} at a distance $\rho_1 = 10$ km from the stack;

(b) The variation of the concentration as a function of the distance ρ is of the form $\rho^{-1.5}$;

(c) Practically all of the activity is deposited within a circle of 500 km radius;

(d) The human population density δ is uniform and equal to 100 km^{-2} around the plant.

245. Assumption (a) takes into account that stacks of coal-fired power plants may be as tall as 200 m. The ground-level air concentration of the pollutants released from such tall stacks increases as a function of distance up to a few kilometres, reaches a maximum, then decreases according to a function that can be approximated by a power law. The fraction of the collective dose commitments due to the short distances (<10 km), where the stack height has an influence on the ground-level air concentrations, is small and has been neglected. The figure of $1.6\ 10^{-8}$ s m^{-3} for the average dilution factor is derived from the value of $5\ 10^{-7}$ s m^{-3} at 1 km adopted in Annex D in the case of releases from nuclear reactors and from assumption (b). With regard to assumption (c), all of the activity released will be deposited within a circle of 500 km radius if a value of $8\ 10^{-3}$ m s^{-1} is adopted for the deposition velocity of aerosols under dry weather conditions.

246. The collective dose commitment due to inhalation can be expressed in the form

$$S^c = \int_{10}^{500} D_1 \left(\frac{\rho}{\rho_1}\right)^{-1.5} \delta 2\pi\rho d\rho$$

where D_1 is the dose commitment per MW(e)y at the reference distance $\rho_1 = 10$ km. The results for the natural radionuclides considered are presented in table 36.

TABLE 36. ESTIMATES OF COLLECTIVE DOSE COMMITMENT DUE TO ATMOSPHERIC RELEASES FROM COAL-FIRED POWER PLANTS

(man rad per MW(e) y)

	Collective dose commitment arising from inhalation during the cloud passage[b]			*Incomplete collective dose commitment due to the activity deposited*			
Radio-nuclide[a]	*Lung*	*Bone marrow*	*Bone lining cells*	*Lung*	*Gonads*	*Bone marrow*	*Bone lining cells*
^{238}U[c]	$3\ 10^{-4}$	$2\ 10^{-5}$	$7\ 10^{-5}$	$5\ 10^{-4}$	$5\ 10^{-4}$	$8.5\ 10^{-4}$	$3.6\ 10^{-3}$
^{226}Ra	$2\ 10^{-4}$	$4\ 10^{-6}$	$3\ 10^{-5}$	$7\ 10^{-5}$	$7\ 10^{-5}$	$2\ 10^{-4}$	$2\ 10^{-3}$
^{210}Pb	$9\ 10^{-4}$	$4\ 10^{-4}$	10^{-3}	10^{-3}	$2\ 10^{-3}$	$2\ 10^{-3}$	10^{-2}
^{228}Ra[d]	$5\ 10^{-4}$	$8\ 10^{-6}$	$4\ 10^{-5}$	$1.5\ 10^{-4}$	$1.5\ 10^{-4}$	$5\ 10^{-4}$	$3\ 10^{-3}$
^{228}Th	$7\ 10^{-3}$	$6\ 10^{-4}$	$9\ 10^{-3}$	–	–	–	–
^{232}Th	$9\ 10^{-4}$	$6\ 10^{-4}$	10^{-2}	10^{-4}	10^{-5}	10^{-4}	$2\ 10^{-3}$
Total	10^{-2}	$2\ 10^{-3}$	$2\ 10^{-2}$	$2\ 10^{-3}$	$3\ 10^{-3}$	$4\ 10^{-3}$	$2\ 10^{-2}$

[a] The collective dose commitments from ^{40}K have not been estimated; they are expected to be very small since (a) the activity concentration in fly ash is about the same as in soil, (b) potassium compounds are very soluble in the lung, and (c) the concentration of potassium in the body is homeostatically controlled.

[b] The collective dose commitments arising from inhalation of ^{222}Rn and its short-lived decay products have been estimated to be about $3\ 10^{-5}$ man rad/MW(e) y in the lung and negligible in bone tissues. The collective dose commitments due to all the radionuclides contained in the table are calculated assuming that all the fly-ash particles are in the respirable range.

[c] Uranium-238 is assumed to be in radioactive equilibrium with ^{234}Th, ^{234m}Pa and ^{234}U.

[d] The collective dose commitments due to ^{228}Ra include the contribution of its decay products, which are assumed to be in radioactive equilibrium with ^{228}Ra in the body. When the activity is deposited on the soil, the doses due to the intake of ^{228}Th are small compared to those from ^{228}Ra. When inhaled, the doses from ^{228}Th are much higher than those from ^{228}Ra because of the long biological half-life of thorium in lung and bone, and because of its deposition on bone surfaces.

247. The incomplete collective dose commitments (Annex A) incurred after deposition can be evaluated by comparison with the natural soil activity concentrations and the corresponding tissue dose rates discussed earlier in this Annex for "normal" levels of natural radionuclides. Making the conservative assumption that the deposited activity only becomes unavailable to the vegetation by radioactive decay and that only the upper 20 cm of soil are involved in the uptake of radionuclides by vegetation, the incomplete collective dose commitments per unit energy generated, S_1^τ, due to deposition can be assessed as

$$S_1^\tau = \frac{A\dot{D}_N \delta \tau}{SC_N}$$

where A is the activity discharged per unit energy generated, $\dot{D}_N$ is the natural tissue dose rate due to the radionuclide under consideration, δ is the population density, τ is the expected duration of the practice, taken to be 500 years, S is the thickness of soil involved; expressed as mass per unit area (assumed to be $3\ 10^5$ g m^{-2}), and C_N is the natural concentration of the nuclide in the soil.

248. The results obtained in this way are presented in table 36. On the basis of these tentative estimates, ^{210}Pb, ^{228}Th, and ^{232}Th appear to be the most important contributors to the collective dose commitments due to atmospheric releases from coal-fired power plants. Most of the dose is due to alpha radiation.

2. Radiation exposures due to the industrial use of phosphate products

249. Phosphate deposits usually contain relatively high concentrations of the naturally occurring radionuclides of the ^{238}U series. In the United States alone, 130 10^6 t of phosphate rock were mined in 1973, yielding 38 10^6 t of marketable rock (109). About half of the marketable rock is converted to fertilizer, the other half being used to produce other commodities, such as phosphoric acid (244). Mining and processing phosphate ores redistributes ^{238}U and its decay products among the various products, by-products, and wastes of the phosphate industry. The dispersal of the wastes in the environment as well as the use of phosphate fertilizers in agriculture and of chemical gypsum as a building material are possible sources of exposure to the public.

250. Table 37 presents the results of a survey of uranium, thorium and radium contents of phosphate rock samples collected from all major phosphate-producing areas of the world (232). The average activity concentrations obtained range up to 130 pCi g^{-1} for ^{238}U and ^{226}Ra, which are generally found to be in radioactive equilibrium, and up to 4.4 pCi g^{-1} for ^{232}Th. The activity concentrations of ^{238}U vary widely from area to area but are usually much higher than those of ^{232}Th, which are comparable to those observed normally in soil.

251. The products and by-products of the phosphate industry contain various fractions of the uranium, radium and thorium originally present in the rock, depending on the manufacturing process. In the wet process, the marketable ore is combined with sulphuric

TABLE 37. ACTIVITY CONCENTRATION OF ^{226}Ra, ^{238}U, AND ^{232}Th IN PHOSPHATE ROCK

Origin and type of rock	*Number of samples*	*Average activity concentration (pCi g^{-1})*		
		^{226}Ra	*^{238}U*	*^{232}Th*
Algeria	12	31	35	1.5
Australia	6	11	10	0.5
Brazil, apatite	6	1	3	3.8
Brazil (Olinda)	4	96	91	4.4
Christmas Island	5	9	9	0.2
Curaçao	9	5	5	0.1
Chile and Ecuador islands	9	1	1	0.7
Egypt	6	37	41	0.7
Guatemala and Mexico	5	12	9	0.4
India, China and south-east Asia	5	4	4	0.7
Jordan and Turkey	6	25	16	[a]
Makatea	3	32	34	0.5
Morocco	5	46	47	0.9
Nauru	4	23	22	0.2
Ocean Island	5	32	33	0.4
Peru	14	30	45	1.0
Poland and USSR, phosphorite	5	15	17	0.8
Senegal and other African countries	6	37	36	1.8
Seychelles, guano	4	4	7	0.2
Spain and other western European countries	5	[a]	2	0.4
Tunisia	6	14	16	2.5
USSR, apatite	5	2	2	2.5
United States				
Arkansas	13	11	10	1.4
Florida, land pebble and soft phosphate	48	54	52	1.6
Idaho	5	49	50	0.9
Montana	10	41	38	0.7
North Carolina	3	18	26	1.0
Oklahoma	5	10	8	0.8
South Carolina	11	130	130	2.1
Tennessee, brown rock, blue rock, white rock and phosphatic limestone	38	4	4	0.5
Utah	9	50	43	0.8
Wyoming	4	62	61	1.3
Venezuela	4	27	24	1.3
West Indies	12	3	3	1.5

Source: Reference 232.
[a] Not detectable.

acid, and phosphoric acid and gypsum result. This mixture is called normal superphosphate. By separation, phosphoric acid is obtained, and gypsum is sent to a waste pile (351). Most of the uranium and much of the thorium is transferred to the phosphoric acid during the separation process, whereas most of the radium remains with the gypsum by-product. The phosphoric acid obtained can subsequently be used to prepare various phosphate fertilizers. For example, when combined with ammonia, phosphoric acid produces diammonium phosphate fertilizer, which is expected to have the low concentrations of ^{226}Ra and the high concentrations of ^{238}U characteristic of the phosphoric acid. Triple superphosphate, which is obtained by combining phosphoric acid with marketable ore, shows both the high concentrations of ^{226}Ra characteristic of the phosphate rock and the high concentrations of ^{238}U characteristic of the phosphoric acid. In the dry furnace process, the marketable ore is combined with coke and silica to produce phosphorus and phosphoric acid. In that process, almost all of the ^{226}Ra activity is retained by the calcium silicate by-product, with very little entering the other products (109). Therefore, a large fraction of the ^{226}Ra activity that enters either the electric furnace plant or the wet-process installation is found in the by-products slag and gypsum, respectively.

252. The activity concentrations of ^{226}Ra, ^{238}U, and ^{232}Th in various products and by-products of the phosphate industry obtained using ore from the same origin, namely Florida (United States), are presented in table 38. The variations in the concentrations of ^{226}Ra and ^{238}U from one product to another are those expected from the above discussion.

TABLE 38. ACTIVITY CONCENTRATION OF ^{226}Ra, ^{238}U, AND ^{232}Th IN PHOSPHATE ROCK AND IN PRODUCTS DERIVED FROM IT

Marketable rock produced in Florida (United States)

Sample	*Production in the United States in 1973*[a] *(10^6 t)*		*Activity concentration ($pCi\ g^{-1}$)*		
	Amount	*P_2O_5 content*	*^{226}Ra*	*^{238}U*	*^{232}Th*
Marketable rock	38	–	42	41	0.4
Wet process products					
Normal superphosphate	3.1	0.6	25	[b]	–
Triple superphosphate	3.4	1.6	21	57	0.4
Ammonium phosphate	5.3	2.4	5.7	63	0.4
Phosphoric acid	10.0	5.1	0.6	–	–
Gypsum	23.0	–	3.3	6.1	0.3
Electric furnace process products					
Slag	–	–	56[c]	–	–

Source: Reference 109.

[a] Florida accounts for 82 per cent of the marketable rock production of the United States.

[b] The activity concentration of ^{238}U in normal superphosphate is expected to be equal to that of ^{226}Ra.

[c] The ^{226}Ra activity concentration in the input feed ore was 60 $pCi\ g^{-1}$.

253. The use of phosphate fertilizers in agriculture, resulting in uptake by the food crops of natural radionuclides from soil, and of chemical gypsum as a building material are possible sources of exposure to the public. Other pathways of exposure include external irradiation over fertilized fields, in fertilizer storehouses and in fertilizer production plants, and inhalation of radon decay products in houses built over land reclaimed after phosphate mining.

(a) *Doses arising from the use of phosphate fertilizers*

254. The world production of phosphate ferilizers was 94 10^6 t in 1972 (205a). The amount of fertilizer used each year in agricultural land is about 60 kg of P_2O_5 per hectare (325a).

255. Measured activity concentrations of naturally occurring radionuclides in phosphate fertilizers from several countries are summarized in table 39. For a given radionuclide and type of fertilizer the concentrations vary markedly from one country to another, depending probably on the origin of the ore and on the type of manufacturing process used. Some of the general features are (a) the concentrations of ^{232}Th are always low; (b) with the exception of the potassium fertilizers, the concentrations of potassium (and thus ^{40}K) are also generally low; (c) the concentrations of ^{226}Ra do not exceed 25 $pCi\ g^{-1}$; and (d) ^{210}Pb and ^{210}Po are generally close to radioactive equilibrium with ^{226}Ra. For the purpose of estimating the doses, it will be assumed that the average activity concentrations of natural radionuclides in phosphate fertilizers are 15 $pCi\ g^{-1}$ for ^{238}U and 10 $pCi\ g^{-1}$ for ^{226}Ra and for each of its decay products. The doses from ^{40}K and from the radionuclides of the ^{232}Th series will be neglected.

256. Taking the example of the United States (table 38), a production of 38 10^6 t of marketable rock yields 11.8 10^6 t of phosphate fertilizer. Therefore, 1 t of marketable rock produces 0.3 t of phosphate fertilizer containing 5 μCi of ^{238}U and 3 μCi of ^{226}Ra and each f its decay products. It is assumed that the total

TABLE 39. ACTIVITY CONCENTRATION OF NATURALLY OCCURRING RADIONUCLIDES IN PHOSPHATE FERTILIZERS

(pCi g^{-1})

Type of fertilizer	*Country*	^{238}U	^{226}Ra	^{210}Pb	^{210}Po	^{232}Th	^{40}K	*Reference*
Apatite	USSR		0.8	0.7	0.8	1.5	2.6	105
Phosphorite dust	USSR		10.6	10.2	13.1	0.7	6.2	105
"Thomasphosphat"	FRG	< 1.0	0.2			0.1	<0.1	279
Phosphate rock, calcined, soft, partly converted[a]	FRG	18.0	13.0			0.7	3.1	279
Superphosphate	FRG	14	14.1			0.4	3.7	279
Superphosphate	USSR		3.1	8.0	4.1	1.2	3.2	105
Normal superphosphate	USA		25					109
Triple superphosphate	USA	57	21			0.4		109
Triple superphosphate	FRG	21.7	6.3			1.2[b]	1.4	279
Ammonium phosphate	USSR		2.7			0.4		105
Ammonium phosphate	USA	63	5.7			0.4		109
Nitro phosphate	USSR		23	23.6	25			105
Nitroammonium phosphate	USSR			0.4	0.4			105
NPK	USSR		0.2	0.4	0.5	1.4	33	105
NPK[c]	FRG	12	7.2			0.4	140	279
PK[d]	FRG	11	10			0.4	160	279
NP[a]	FRG	25	8.5			0.8	1.1	279
Enriched concentrate	USSR		11.5	10.6	7.9	0.6	2.0	105
Phosphate without fluor	USSR		0.9				0.9	105

[a] Assuming a P_2O_5-to-fertilizer mass concentration ratio of 0.28.
[b] Assuming that ^{232}Th is in radioactive equilibrium with ^{228}Th.
[c] Assuming a P_2O_5-to-fertilizer mass concentration ratio of 0.13.
[d] Assuming a P_2O_5-to-fertilizer mass concentration ratio of 0.16.

production of phosphate fertilizers is used in agriculture to improve crops. Assuming, as is done in the section on coal power plants, that the ploughed layer of soil is about 20 cm deep, that the availability to plants of natural radionuclides is the same whether in fertilizer or in the normal constituents of the soil and is only reduced by radioactive decay, and that the human population density is 100 km^{-2}, and furthermore assuming that the practice of producing phosphate fertilizers will continue for the order of a century, the incomplete collective dose commitments arising from the decision to use 1 t of marketable rock to produce phosphate fertilizers can be crudely estimated from the comparison between the normal concentration of natural radionuclides in soil and the resulting doses. Table 40 shows the results obtained.

(b) *Doses arising from the use of waste gypsum as a building material*

257. As shown in table 41, the waste gypsum from the phosphate industry, also called phosphogypsum, contains concentrations of ^{226}Ra of about 25 pCi g^{-1}.

TABLE 40. INCOMPLETE COLLECTIVE DOSE COMMITMENT PER UNIT MASS OF MARKETABLE ROCK ARISING FROM THE USE OF PRODUCTS DERIVED FROM IT

	Incomplete collective dose commitment per unit practice (man rad per tonne)				
Product and type of irradiation	*Tracheo-bronchial tree*	*Lung*	*Gonads*	*Red bone marrow*	*Bone lining cells*
Phosphate fertilizer					
^{238}U	–	$1\ 10^{-5}$	$1\ 10^{-5}$	$2\ 10^{-5}$	$7\ 10^{-5}$
^{226}Ra	–	$4\ 10^{-6}$	$4\ 10^{-6}$	$1\ 10^{-5}$	$1\ 10^{-4}$
^{210}Pb	–	$5\ 10^{-5}$	$9\ 10^{-5}$	$1\ 10^{-4}$	$5\ 10^{-4}$
Total		$6\ 10^{-5}$	$1\ 10^{-4}$	$1\ 10^{-4}$	$7\ 10^{-4}$
Phosphogypsum (as building material)					
External irradiation	1	1	1	1	1
Inhalation	$9\ 10^{-1}$	$2\ 10^{-1}$	$7\ 10^{-4}$	$7\ 10^{-4}$	$7\ 10^{-4}$
Total	2	1	1	1	1

TABLE 41. ACTIVITY CONCENTRATION OF NATURALLY OCCURRING RADIONUCLIDES IN PHOSPHOGYPSUM

Origin of sample	Number of samples	Activity concentration ($pCi\ g^{-1}$)				Reference
		^{40}K	^{238}U	^{226}Ra	^{232}Th	
Germany, Fed. Rep. of						
Apatite	2	< 1	–	1.5	< 0.5	327
Phosphorite	39	3	–	16	< 0.4	327
Unknown origin	7	2	–	< 0.5	< 0.7	327
United Kingdom	6	2	3.5	21	0.5	265
United States	–	–	5.5	40	0.2	105

Phosphogypsum can replace natural gypsum in the building industry and thus be used to make blocks and plasterboard, partition systems and also cement (265). One tonne of marketable ore produces 0.6 t of gypsum (table 38). The practice of using this waste product has been considered attractive, since overall building costs are reduced, natural resources are preserved, and environmental pollution is decreased. On the other hand, since phosphogypsum contains a much higher concentration of ^{226}Ra than its natural counterpart, its use increases the radiation doses to the public.

258. O'Riordan *et al.* (265) estimated the doses that would be received by the occupants of a residential building in which 4.2 t of by-product gypsum (considered to be a high, but realistic amount) would have replaced the established materials. Assuming the ^{226}Ra concentration of phosphogypsum to be 25 $pCi\ g^{-1}$, they estimated the absorbed dose rate in air to be 7 $\mu rad\ h^{-1}$, and the radon concentration, using a ventilation rate of 1 h^{-1} to be 0.2 $pCi\ l^{-1}$.

259. If it is assumed that all the phosphogypsum produced by 1 t of marketable ore is used in the building industry, that on the average, four persons live in the dwellings so constructed, and that the mean life of the dwelling is 50 y, the collective dose commitments can be evaluated from the estimates provided by O'Riordan *et al.* (265). The results obtained are presented in table 40.

(c) *Other pathways of exposure*

260. The average addition from phosphate fertilizers to the soil activity of agricultural areas in the Federal Republic of Germany during the period 1973-1974, was estimated to be ($nCi\ m^{-2}$): ^{238}U, 9; ^{226}Ra, 6; ^{232}Th, 0.3; ^{40}K, 90 (279). The corresponding absorbed dose rate in air is about 0.02 $\mu rad\ h^{-1}$ (314). Assuming that the rate of the addition of activity to the soil has been constant for the last 80 y, and that there has been no removal of the added radionuclides by water erosion, the absorbed dose rate in air would attain a value of about 0.3 $\mu rad\ h^{-1}$ at the present time. Fertilizer application therefore results in a small increase of the external radiation exposure (232, 280). It is worth mentioning, however, that absorbed dose rates in air of about 50 $\mu rad\ h^{-1}$ have been measured in fertilizer storehouses and that similar values are expected in fertilizer production plants (280).

261. In Florida, much land on which phosphate mining operations have been completed has been reclaimed and some is being developed for residential use. The ^{226}Ra activity concentration in the land fill is about one order of magnitude higher than in ordinary soil (214). In a preliminary study of buildings on the reclaimed land, elevated gamma-ray and ^{222}Rn decay-product exposures were discovered (350).

3. Exposure to ^{222}Rn in natural gas and natural-gas products

262. Natural gas used for kitchen ranges and space heaters is a source of radon in buildings. The radon which is produced in the ground diffuses through the geological formations into the natural gas wells. A summary of reported data on radon concentrations in natural gas at production wells is given in table 42.

TABLE 42. RADON CONCENTRATION IN NATURAL GAS AT THE WELL

Location of well	Radon concentration ($pCi\ l^{-1}$)		Reference
	Average	Range	
Borneo			
Ampa field	...	1.5-3.2	352
Canada			
Alberta	62	10-205	
British Columbia	473	390-540	302
Ontario	169	4-800	
Germany, Federal Rep. of	...	1.0-9.6	352
Netherlands			
Slochteren	...	1.1-2.8	352
Other fields	...	3.7-44.7	
Nigeria			
Niger delta	...	0.9-2.9	352
North Sea			
Leman field	...	2.0-3.8	352
Indefatigable field	1.8	...	
United States			
Colorado, New Mexico	25	0.2-160	171
Texas, Kansas, Oklahoma	< 100	5-1 450	
Texas Panhandle	...	10-520	
Colorado	25.4	11-45	
Project Gasbuggy area	15.8	...	
California	...	1-100	
Kansas	100	...	
Wyoming	10	...	
Gulf Coast (Louisiana, Texas)	5	...	
California, Louisiana, Oklahoma, Texas	...	1-120	98

263. The concentration of radon remaining in the gas when it reaches the consumer depends on many factors, including the concentration at the well-head, dilution, gas processing, transmission time, and storage time. The processing includes fractionation, which mainly separates out methane (the principal constituent), ethane, propane and heavier hydrocarbons, which are bottled as liquefied gas. This process may remove more than half the radon content of the natural gas. However, the radon removed will appear in the liquefied gas sold by retailers and thus constitute a potential cause of radon exposure in homes. Storage of gas in reservoirs prior to consumption reduces the radon concentration by decay. This may lead to seasonal variations depending on the consumption rate, with maximum concentrations during winter (22). For liquefied gas, minimum concentration during winter has been reported because higher consumption leads to the introduction into the market of previously stored gas (47).

264. There are very few data on radon levels caused by natural gas consumption in homes. Table 43 summarizes the results of measurements made on natural gas

TABLE 43. RADON CONCENTRATION IN NATURAL GAS IN THE DISTRIBUTION LINE

	Radon concentration (pCi l^{-1})	
Area	*Average*	*Range*
Poland (Warsaw)	8	4-14
United States		
Chicago	14.4	2.3-31.3
New York City	1.5	0.5-3.8
Denver	50.5	1.2-119
West coast	15	1-100
Colorado	25	6.5-43
Nevada	8	5.8-10.4
New Mexico	45	10-53
Houston	8	1.4-14.3

Sources: Poland, 359; United States, 171.

distribution lines in Poland and the United States. In the estimation of the resultant exposure due to radon daughters in homes supplied with natural gas, the following factors have to be considered: the concentration of radon and radon daughters in the gas, the volume of gas used, and the volume and ventilation rate of the house. The resultant doses to the bronchial epithelium have been calculated (22), assuming that the radon concentration in the gas is 20 pCi l^{-1} and that 0.8 m^3 of gas is consumed per day in a kitchen range in a 230-m^3 house with an air change rate of 1 h^{-1}. This leads to an average radon concentration in the house of 0.0028 pCi l^{-1}. If there are no radon daughters in the released gas, the estimated annual absorbed dose to the basal cells of the bronchial epithelium is 0.6 mrad, assuming an occupancy factor of 0.8 and the dose-to-exposure quotient discussed in paragraphs 153-169. With other assumptions, the annual dose in the bronchial epithelium has been estimated to be about 1.5 mrad (22). If the radon daughters are in equilibrium with the radon in the gas, the equilibrium factor of the radon daughters in the air will be higher, so that the corresponding doses will be about twice as great. It should be pointed out, however, that during the use of the kitchen range the heat build-up and the depletion of air might lead the user to increase the ventilation rate, so that the radon concentration would drop sharply instead of increasing slightly (352).

265. The doses caused by the gas consumed in space heaters have not been calculated specifically because a typical individual could not be defined (171). However, by indirect methods the average individual annual dose in the bronchial epithelium (T-B) was estimated by the author to be 5.4 mrad, a value which corresponds to 2 mrad if the dosimetric parameters used in this Annex are applied.

266. The occupation exposure to ^{222}Rn and its decay products in the natural gas industry has been examined (98, 352). External radiation surveys were conducted in nine gas processing plants of the United States (98). The exposure rates obtained at the equipment surfaces ranged from background to 8 mR h^{-1}. The highest values were found at the surface of the various product pumps. As the equipment is in low occupancy areas, the tissue absorbed dose rates would be less than 2 mrad h^{-1}. The long-lived decay products of ^{222}Rn which are likely to be concentrated on the inner surfaces of the pumps do not contribute to the external absorbed dose while the pumps remain closed, but if the pumps are opened for repair or maintenance, an opportunity exists for inhalation of ^{210}Pb and ^{210}Po (98).

4. Exposure due to the use of building materials containing higher-than-average concentrations of naturally occurring radionuclides

267. As exemplified in table 44, the use of some building materials may lead to elevated indoor radiation levels. The building materials may be of natural origin, such as pumice stone, (Federal Republic of Germany and USSR), concrete containing alum shale (Sweden), and granite wherever it is used. They may also result from industrial processes. In the non-uranium industries, the use of phosphogypsum, a waste product of the manufacture of phosphoric acid, has already been discussed. Other by-products that were shown to contain relatively high concentrations of naturally occurring radionuclides were red slime, a waste product of aluminium mills, and blast furnace slag, a by-product of iron manufacture (192).

268. In its recommendations, the National Commission of Radiation Protection of the USSR (195) used a dosimetric relationship. If the concentrations of ^{40}K, ^{226}Ra and ^{232}Th, expressed in pCi g^{-1}, in building materials made of industrial wastes satisfy the expression

$$\frac{C(^{40}\mathrm{K})}{130} + \frac{C(^{226}\mathrm{Ra})}{10} + \frac{C(^{232}\mathrm{Th})}{7} \leqslant 1$$

the authors (195) estimate that the increase of the gonad absorbed dose indoors over background is less than 150 mrad in a year. They also examined the question of

TABLE 44. ACTIVITY CONCENTRATION OF NATURALLY OCCURRING RADIONUCLIDES IN BUILDING MATERIALS EXPECTED TO GIVE RISE TO HIGHER-THAN-AVERAGE EXTERNAL ABSORBED DOSES

Type of building material	*Country*	*Number of samples*	*Average activity concentration (pCi g^{-1})*			*Absorbed dose rate in air[a] (μrad h^{-1})*	*Reference*
			^{40}K	^{226}Ra	^{232}Th		
Granite	FRG	34	33	2.6	2.2	30	327
Granite bricks	UK	7	28	2.4	2.3	28	117
Granite	USSR	2	40	3.0	4.5	46	194
Pumice stone	FRG	20	29	3.0	3.4	35	327
Concrete containing alum shale	Sweden	83	23	40.4	2.0	145	335
Phosphogypsum							
From apatite	FRG	2	< 1	1.5	< 0.5	< 8	327
From phosphorite	FRG	39	3	16	< 0.4	54	327
Of unknown origin	FRG	7	2	< 0.5	< 0.7	< 6	327
Phosphogypsum	UK	6	2	21	0.5	68	117
Phosphogypsum	USA	–	–	40	0.2	126	105
Red-slime bricks	FRG	23	9	7.6	6.3	58	327
Fly ash	FRG	28	19	5.7	3.5	42	327
Fly ash[b]							
Type 1	UK	1	15	0.2	1.0	10	117
Type 2	UK	1	15	3.7	0.9	20	117
Type 3	UK	1	6	1.4	1.2	12	117
Blast-furnace slags	USSR	29	6.6	1.8	0.5	10	194

[a] The absorbed dose rates in air have been calculated assuming a 4π geometry and an infinite thickness, and using the conversion factors given in table 6. The values obtained are an index allowing the comparison between building materials and not an estimate of the doses that would be received in dwellings constructed with those building materials.

[b] Mixture of coal clinker, ash and cement.

exposure to ^{222}Rn short-lived decay products and estimated that a ^{226}Ra activity concentration of 10 pCi g^{-1} in a building material would result in an increase in the concentrations of the ^{222}Rn decay products of less than 0.03 WL.

269. The measurements of activity concentrations of naturally occurring radionuclides in building materials in the USSR (195) showed that only a few materials would cause higher exposures than those quoted above, while in the Federal Republic of Germany it was found that 12 per cent of the analysed samples would cause such higher exposures (192).

270. It should be pointed out that the average absorbed dose rates in air measured in buildings using these materials are much lower than what would be expected from the radioactive content of the materials considered, because materials usually less active are also used in the same buildings. For example, the average absorbed dose rate derived from measurements carried out in Swedish houses made of concrete containing alum shale is about 18 μrad h^{-1} (241), while the value given in table 44, calculated from the activity concentrations of radionuclides in that type of concrete, using very pessimistic assumptions, is 145 μrad h^{-1} (335).

271. Use has also been made of waste products of the uranium and radium industry. In the United States, notably in Grand Junction, Colorado, tailings from uranium mills were used during the period 1952-1966 as fill material under houses and as building materials (348a). Remedial action was deemed necessary by the national authorities.

272. In the town of Port Hope, Ontario, Canada, another type of problem arose from a plant which had recovered radium in the 1930s and the 1940s from pitchblende-radium-silver ores (323). In this particular case, the management of the waste material resulting from the plant demolition was inadequate and much contaminated construction and fill material was used in and around the houses in the town. As in the case of Grand Junction, remedial action was deemed necessary by the national authorities.

C. SUMMARY AND CONCLUSIONS

273. This section has dealt with the examples of technologically enhanced exposures to natural radiation (TENR) which have been brought to the attention of the Committee. It should be stressed that it is very likely that those examples do not present the complete picture of TENR. From the assessments presented, TENR does not add significantly to the collective dose on the global scale but may give rise, in localized areas or for people exposed under extreme conditions, to appreciable increases in individual doses from natural radiation. The present state of knowledge does not allow an accurate estimate of the collective dose from TENR to be made, and further research is required in this field.

Appendix

RADIATION EXPOSURES FROM CONSUMER PRODUCTS

Introduction

274. A wide variety of consumer products contain radioactive nuclides that have been deliberately incorporated to satisfy a specific purpose. Table 45 presents a list of such products classified into six categories, namely

1. Radioluminous products
2. Electronic and electrical devices
3. Antistatic devices
4. Gas and aerosol (smoke) detectors
5. Ceramic, glassware, alloys etc. containing uranium or thorium
6. Other devices, including scientific instruments

TABLE 45. CURRENTLY AVAILABLE PRODUCTS CONTAINING RADIONUCLIDES

Products	*Nuclide*	*Activity or mass per product (range of approximate values)*
1. Radioluminous products		
(a) Radionuclide contained in paint or plastic		
(1) Timepieces	^{3}H	1-25 mCi
	^{147}Pm	65-200 μCi
	^{226}Ra	0.1-3 μCi
(2) Aircraft instruments	^{3}H	⩽ 10 Ci
	^{147}Pm	⩽ 0.3 Ci
	^{226}Ra	⩽ 20μCi
(3) Compasses	^{3}H	5-50 mCi
	^{147}Pm	10 μCi
(4) Instrument dials and markers	^{3}H	25 mCi
(5) Instruments, signs and indicators	^{147}Pm	0.75 Ci
(6) Thermostat dials and pointers	^{3}H	25 mCi
(7) Automobile lock illuminators	^{3}H	2-15 mCi
	^{147}Pm	2 mCi
(8) Automobile shift quadrants	^{3}H	25 mCi
(9) Bell pushes	^{3}H	0.3 mCi
(10) Speedometers	^{147}Pm	0.1 mCi
(11) Rims for underwater watches	^{3}H	0.3 mCi
(12) Fishing lights	^{14}C	3-4 mCi
(13) Spirit levels	^{3}H	5-25 mCi
(b) Radionuclide contained in sealed tubes		
(1) Timepieces	^{3}H	0.2-0.4 Ci
(2) Ordinary compasses		0.2-0.4 Ci
(3) Marine compass		0.2-2 Ci
(4) Marine navigational instruments		0.25 Ci
(5) Markers	^{3}H	4 Ci
	^{85}Kr	0.3 Ci
(6) Instruments, signs and indicators	^{3}H	2 Ci
	^{85}Kr	0.25 Ci
(7) Exit signs for commercial buildings	^{3}H	15 Ci
(8) Large signs		30 Ci
(9) Small exit signs		2 Ci
(10) Step markers		2 Ci
(11) Mooring buoys and lights		2 Ci
(12) Public telephone dials		0.5 Ci
(13) Light switch markers		0.2 Ci
(14) Bell pushes		10 mCi
(15) Miniature light sources		20 mCi
2. Electronic and electrical devices		
(a) Electronic tubes	^{3}H	1-10^{4} μCi
	^{63}Ni	1-5 μCi
	^{147}Pm	1 μCi
	^{85}Kr	1-5 μCi
	^{60}Co	0.15-5 μCi
	^{226}Ra	0.1 μCi
	^{137}Cs	5 μCi
(b) Glow-discharge tubes	^{85}Kr	0.01-10 μCi
(c) Voltage-discharge tubes	^{147}Pm	3 μCi
(d) Cold-cathode tubes	^{3}H	90 μCi
(e) Fluorescent lamp starters	^{226}Ra	1 μCi
(f) Gas-discharge lamps (high-pressure mercury-vapour lamps)	Natural Th	6 nCi
(g) Vacuum tubes		0.8-1.2 wt%
(h) Electric lamps		50 mg
(i) Germicidal lamps, sun lamps, lamps for outdoor and industrial lighting		2 g
(j) Glow lamps	^{3}H	0.01 mCi
(k) Spark-gap tubes	^{147}Pm	30 μCi
	^{60}Co	5 μCi
	^{63}Ni	5 μCi
	^{137}Cs	5 μCi
(l) High-voltage protection devices	^{147}Pm	3 μCi
(m)Low-voltage fuses	^{147}Pm	3 μCi
3. Antistatic devices		
(a) Lightning rod	^{226}Ra	0.2-1 mCi
	^{241}Am	0.06-0.7 mCi
(b) Antistatic devices contained in instruments	^{226}Ra	10 μCi
(c) Antistatic brushes	^{210}Po	0.05-0.5 mCi
	^{241}Am	2-25 μCi
(d) Antistatic devices contained in precision balances	^{3}H	1 mCi
4. Gas and aerosol (smoke) detectors		
Smoke and fire detectors	^{241}Am	1-100 μCi
	^{226}Ra	0.01-15 μCi
	^{85}Kr	7 mCi
	Natural or depleted U	7.5 mg
	^{238}Pu	20 μCi
5. Ceramic, glassware, alloys etc. containing uranium or thorium		
(a) Chinaware	Natural U	10^{-2} μCi cm^{-2} surface
(b) Ceramic tableware glaze	Natural Th	20 wt% (glaze)
	Natural or depleted U	20 wt% (glaze)

TABLE 45 *(continued)*

Products	*Nuclide*	*Activity mass per product (range of approximate values)*
5. *Ceramic, glassware, alloys etc. containing uranium or thorium* (continued)		
(c) Glassware, glass enamel, glass-enamel frit	Natural Th	10 wt%
	Natural or depleted U	10 wt%
(d) Optical lenses		⩽ 30 wt%
(e) Incandescent gas mantles	Natural Th	⩽ 0.5 g
(f) Magnesium-thorium alloys		⩽ 4 wt%
(g) Products containing rare earths: arc carbons, lighter flints, metallurgical additives, precision lenses, television tubes, electronic ceramics, microwave devices etc.	Natural Th	0.25 wt%
	Natural or depleted U	0.25 wt%
(h) Welding rods	Natural Th	1-2 wt%
6. *Other devices, including scientific instruments*		
(a) Gas chromatographs	^{3}H	250 mCi
	^{63}Ni	12 mCi
(b) Static meters	^{241}Am	0.5-50 μCi
(c) Vending-machine coins	^{14}C	2 μCi
(d) Bank cheques	^{14}C	0.01 μCi

Sources: References 81, 359a.

275. The radionuclides and the approximate range of activities used are also given in table 45. It must be pointed out, however, that accurate information on the activities contained in the consumer products and on the number of products manufactured is sometimes difficult to obtain (355).

276. The purpose of this appendix is to review what has recently been published in the scientific literature on the uses of radionuclides in consumer products and on the resulting doses to the public.

1. Radioluminous timepieces

277. Radium-226, promethium-147, and tritium have been used extensively in the dial-painting industry for the illumination of timepieces, the radiation emitted by those radionuclides being converted into light by a scintillator, which is usually zinc sulfide containing small amounts of copper or silver. From the public health point of view, one of the major disadvantages of radium is its inherent emission of a great deal of penetrating radiation which is not useful for the production of light yet irradiates the whole body of the watch wearer. Radium tends to be replaced by ^{3}H and ^{147}Pm, which are soft beta emitters and thus cause much smaller external radiation doses to the watch users.

278. Table 46 presents the number of luminous timepieces distributed in the United States in 1971, 1972 and 1973. It is clear from the table that, although only a few radium watches have been sold in the United States in recent years, radium continues, in that country, to be heavily used in clocks. A small survey in Tennessee showed that, out of a total of 227 clocks reported in 48 households, 35 were luminescent, 17 of which contained radium (51).

TABLE 46. TYPES AND QUANTITIES OF LUMINOUS TIMEPIECES DISTRIBUTED IN THE UNITED STATES, 1971-1973

(Thousands of units)

Type of timepiece and activator	*1971*	*1972*	*1973*
Wrist-watches			
Tritium			
Domestic	2 710	2 330	1 800
Imported	5 670	6 540	3 600
Promethium			
Domestic	negligible		
Imported	620	770	900
Radium-226	negligible		
Clocks			
Tritium			
Domestic	18	10	20
Imported	500	190	240
Promethium			
Domestic	negligible		
Imported	1 470	970	1 370
Radium-226	2 800	2 800	2 800

Source: Reference 242.

279. The activities of ^{3}H and ^{147}Pm which produce the same brightness as 1 μCi of ^{226}Ra have been estimated to be 5000 μCi of ^{3}H and 170 μCi of ^{147}Pm for a newly manufactured timepiece (148). However, owing to radioactive decay, release of activity and deterioration of the phosphor, the brightness decreases continuously over the useful life of the timepiece at a rate that depends upon the radionuclide used. The activities of ^{3}H and ^{147}Pm required to produce the same average brightness as 1 μCi of ^{226}Ra over the useful life of the timepiece, assumed to be five years, have been estimated as 11 000 μCi of ^{3}H and 390 μCi of ^{147}Pm (242).

(a) *Absorbed doses from ^{226}Ra-activated timepieces*

280. The absorbed doses from ^{226}Ra-activated timepieces result mainly from external irradiation. Joyet (173, 174), who made comprehensive measurements of the external radiation dose from ^{226}Ra-activated timepieces, suggested an annual gonad dose of about 60 mrad μCi^{-1} for wrist-watches worn continuously. According to the recommendations issued by a joint group of experts from the OECD and the IAEA (148), the total activity of ^{226}Ra should be limited to 0.1 μCi per wrist-watch. That limit corresponds to a gonad absorbed dose in a year of 6 mrad.

281. Pocket watches are worn closer to the gonads and thus the dose rate is higher. If it is assumed that the pocket watch is worn 16 h per day at a distance from

the gonads of 0.25 m, the annual dose can be estimated to be about 80 mrad μCi^{-1} if the dose rate for a source-to-target distance of 1 m is taken to be 0.34 $\mu rad\ h^{-1}\ pCi^{-1}$ (242).

282. The use of ^{226}Ra in pocket watches has not been permitted in most countries since 1966 (148). Assuming that in older pocket watches the total activity of ^{226}Ra is 0.1 μCi, the corresponding gonad absorbed dose would be about 8 mrad in a year.

283. The external radiation dose to the user of a ^{226}Ra activated alarm clock can be estimated in the same way. Assuming an exposure of 8 h per day at a distance of 2 m and an activity of 0.15 μCi, which is the limit recommended by the joint group of experts from the OECD and the IAEA (148), the annual gonad dose would be about 0.1 mrad.

284. The user of a radium-dial timepiece is also exposed to an inhalation dose from ^{222}Rn leaking out of it. As indicated in the 1972 report, radon emissions from watches and clocks vary widely. The radon content measured after a build-up of 10 h in an air-tight box was found to range from around 0.1 to 30 nCi per μCi of ^{226}Ra for new, water-tight watches and for loosely sealed, old watches, respectively (78). Assuming a leakage rate of 1 $nCi\ h^{-1}$ of ^{222}Rn per μCi of ^{226}Ra, the average ^{222}Rn concentration in a 300 m^3 house ventilated at a rate of 1 h^{-1} would be about 3 $fCi\ l^{-1}$, corresponding to an annual absorbed dose in the lungs of the order of 0.1 mrad.

(b) *Absorbed doses from ^{3}H-activated timepieces*

285. The casing of timepieces being at least 50 $mg\ cm^{-2}$ thick, no external dose results from luminous watches containing tritium, since the beta particles that are emitted by that radionuclide have a maximum range of 0.6 $mg\ cm^{-2}$. However, tritiated water or tritiated organic molecules evolve slowly from the tritium paints leading to internal absorbed doses to wearers from inhalation and skin absorption.

286. The determination of ^{3}H concentration in the body water of users of ^{3}H-painted watches has been carried out in at least two studies. Fitzsimmons *et al.* (87), measuring the ^{3}H activity in urine of eight persons wearing ^{3}H-painted watches, found concentrations ranging from 0.5 to 11 $nCi\ l^{-1}$ above background, with an average of 3.2 $nCi\ l^{-1}$. The corresponding whole-body absorbed doses in a year range from 0.05 to 1.1 mrad with an average of 0.3 mrad. Schell and Payne (305), investigating the origin of a relatively high ^{3}H concentration in a laboratory, found the source to be an employee's wrist-watch. The whole-body absorbed dose that this employee would receive in a year if he wore his watch 24 h a day was estimated to about 0.3 mrad.

287. The relationship between the ^{3}H activity in watches and the resulting whole-body absorbed dose has been studied under controlled conditions by Moghissi and Carter (242). The average dose in a year per millicurie of tritium paint was found to be 0.03 mrad, the range being 0.012-0.044 mrad.

288. If that result is applied to the results reported by Fitzsimmons (87) and by Schell *et al.* (305), it would appear that the watches in these two studies had an average tritium activity of 10 mCi. This finding is not consistent with either the observations of Bradley *et al.* (43), whose survey of the storage areas of nine wholesale importers and two retailers of self-luminous watches in the New York City area suggested values ranging from 1 to 5.6 mCi per watch, or with the maximum tritium activity of 7.5 mCi per watch recommended by IAEA and OECD. It would therefore seem more reasonable to adopt a figure of 0.1 mrad mCi^{-1} as a conservative estimate of the whole-body dose. This value would give a calculated annual whole-body dose of 0.5 mrad to a person continuously wearing a ^{3}H-activated watch luminized with the average activity of 5 mCi recommended by IAEA and OECD.

(c) *Absorbed doses from ^{147}Pm-activated wrist-watches*

289. Since promethium is a rare earth, it does not evolve from a watch under normal conditions of usage, so that the risk of external radiation is the only one that has to be considered. Promethium-147 is a pure beta emitter. The maximum energy of its beta particles is 224 keV, corresponding to a range of 46 $mg\ cm^{-2}$. Since the standards set by the OECD and the IAEA recommend a minimum thickness of 50 $mg\ cm^{-2}$ for the casing of timepieces, no exposure hazard from beta radiation should exist. However, a low external radiation dose from bremsstrahlung has to be expected. Moghissi and Carter (242) estimated that the gonad absorbed dose in a year could be about 5 mrad mCi^{-1}. However, more recent measurements on compasses radioluminized with ^{147}Pm have suggested that a more appropriate figure for the annual gonad dose from a watch would be about 1 mrad mCi^{-1} (372a). Taking an intermediate value of 3 mrad mCi^{-1} would give a calculated annual gonad dose of 0.3 mrad to a person continuously wearing a ^{147}Pm-activated wrist-watch luminized with the average activity of 0.1 mCi recommended by IAEA and OECD.

(d) *Absorbed doses from wrist-watches luminized by ^{3}H in sealed tubes*

290. With the advent of liquid-crystal displays, the use of gaseous tritium light sources to illuminate digital watches is being investigated. The external bremsstrahlung dose rate from a well-designed watch of this type will be very small; measurements of prototypes containing 300 mCi of ^{3}H in the form of several sealed tubes have shown that external surface dose rates in air as low as 5 $\mu rad\ h^{-1}$ are achievable (372a). There would be some internal dose to a person breaking one of the sources, but that is unlikely to be a frequent occurrence as the sources are usually sealed in a metal or glass capsule with the liquid-crystal display and are not accessible to the wearer.

(e) *Collective dose from radioluminous timepieces*

291. Estimates of the collective dose from radioluminous timepieces have been reported for the population of two countries. For the population of the United States, a minimum value of 6100 man rad has

been proposed for the exposure during the year 1973 (242). The population of the United States being about $2\ 10^8$, the average absorbed dose would be 0.03 mrad in a year. The annual collective dose to the population of the United Kingdom has been assessed to be about 10^4 man rad from ^{226}Ra luminous watches and about 10^3 man rad from ^{3}H luminous watches (339), corresponding to an average absorbed dose of about 0.2 mrad in a year. If it could be extrapolated that those values are representative of the situation in the world's most populated countries, the collective dose to the world population would lie in the range from 10^5 to 10^6 man rad in a year.

2. *Other self-luminous devices*

292. It is known that radioluminous materials are being used in exit signs, compasses, gun sights, and many other devices (see table 45), but there is not enough information available to make a reasonable estimate of the doses arising from their use. However, it is likely that the resulting collective dose is insignificant in comparison to that from radioluminous timepieces.

3. *Uses of uranium and thorium*

293. The main uses of uranium in consumer products are either as a pigment (328) or in applications making use of its high density. Thorium is used in incandescent mantles and in certain optical lenses.

294. The principal hazard from the uses of uranium and thorium under normal conditions is the somatic dose from the beta-emitting decay products. In general, doses received will be small due to substantial attenuation over the distance between the device and the exposed person. In particular cases, this may not apply, however. Some optical lenses containing up to 30 per cent by weight of uranium or thorium may deliver substantial doses to the lens of the eye (372). The air absorbed dose rate at a surface of a lens which contained 18 per cent thorium by weight was measured by thermoluminescent dosimetry to be 1 mrad h^{-1} (228).

295. Another example which has attracted interest is the practice of incorporating uranium in the porcelains used in restorative and prosthetic dentistry. In the United Kingdom, it is estimated that about one in nine adults has artificial porcelain teeth (266); in the United States, that proportion is likely to be even higher (315). A combination of uranium and cerium compounds is incorporated in the majority of modern porcelains in order to simulate the fluorescence of natural teeth in daylight and in artificial light. As all the isotopes of uranium are radioactive, the tissues of the mouth are exposed to ionizing radiation from fluorescent porcelains.

296. In the Federal Republic of Germany and the United States, the two countries where most of the dental porcelain seems to be manufactured, the mass concentration of uranium is limited by law. The uranium content of porcelain powders and artificial teeth should not exceed 0.1 per cent by weight in the Federal Republic of Germany and 0.05 per cent in the United States.

297. An analysis performed by O'Riordan and Hunt (266) on 20 porcelain powders under five brand names showed that 17 of the powders contained uranium, on the average 0.041 weight per cent, with 2 having about 0.1 per cent. It is estimated in that study that for people with fluorescent porcelain teeth, the absorbed dose from external irradiation in the basal layer of the oral epithelium wold be the limiting factor. Assuming a mass concentration of depleted uranium in the porcelain of 0.1 per cent, the absorbed dose in that basal layer, taken to be at a distance of 30 μm from the interface, was found to be of the order of 3 rad in a year. As the ranges of the alpha particles emitted by the isotopes of uranium are less than 30 μm in soft tissues, most of the absorbed dose is due to beta radiation.

298. On the basis of that estimate, the National Radiological Protection Board has recommended that the use of radioactive fluorescers in dental porcelain be discontinued in the United Kingdom (328). Following that decision, the false-teeth industry in the United States has voluntarily agreed to standardize the level of use of uranium at 250-300 μg per gram of porcelain (372).

4. *Electronic and electrical equipment*

299. Electronic and electrical equipment may give rise to radiation exposure if they contain radioactive substances or if they emit x radiation owing to the acceleration of electrons.

300. Radioactive materials provide pre-ionization in gases for the purpose of passing an electric current, so that the equipment reads faster and more reliably, or displays more constant characteristics (72). Examples of application are starters for tubular fluorescent lamps, trigger tubes in electrical appliances and excess-voltage protection devices. In fire alarms and smoke detectors the radioactive materials are used to provide a sufficient rate of ionization in gases. The radionuclides mainly used for that purpose are ^{3}H, ^{63}Ni, ^{147}Pm, and ^{241}Am. The doses resulting from the normal use of such equipment can be expected to be very small. It is only in the event of breakage through accident or disposal that the radiation exposure could be significant.

301. The absorbed doses from the normal use of ionization-chamber smoke detectors (ICSDs) have been estimated (242b). The use of ICSDs is widespread in industrial, commercial and public buildings, and also, at least in the United States in private homes. Although some of the ICSDs now on the market contain ^{226}Ra, ^{238}Pu, ^{85}Kr, and ^{63}Ni, the preferred radionuclide seems to be ^{241}Am. During normal use of ICSDs, the doses to members of the public are virtually limited to those resulting from external irradiation. Assuming that in some countries the total number of ICSDs now installed in industrial, commercial and public buildings corresponds to one for every hundred members of the population and that each ICSD contains 60 μCi ^{241}Am, the consequential average whole-body absorbed dose received in a year by individuals in those buildings has been estimated to be about 60 μrad while the *per caput* whole-body dose would be about 1 μrad (242b). In private homes equipped with smoke detectors, the

average whole-body dose received in a year by the occupants would be of the order of 1 μrad if the activity of ^{241}Am contained in each smoke detector is taken to be 1 μCi; assuming that 1 house in 20 is equipped with such a smoke detector, the corresponding *per caput* whole-body dose would be about 0.05 μrad in a year (242b).

302. Household colour television receivers are the most common electronic product with the potential of exposing the general public to x radiation. As indicated in the 1972 report, several surveys conducted in the 1960s showed that a small proportion of the colour television sets emitted x radiation in excess of the limit recommended by the ICRP, that is 0.5 mR h^{-1} at 5 cm from the surface of the television receiver. Since then, more stringent regulations became effective in the United States, and more and more solid-state circuitry has been employed, so that it is likely that the x-ray emission from recently built colour television receivers is negligible under conditions of normal operation and proper servicing. The assumption is supported by the results of measurements recently conducted in the Federal Republic of Germany (192a) and in the island of Taiwan (358). In the first of these surveys, conducted in 1972, it was found that the average exposure rate 5 cm from the surface of the colour television receivers was 0.1 mR h^{-1} and that the estimated annual gonad dose, under normal viewing conditions, was of the order of 1 millirad. In the second the exposure rate at the surface of 28 randomly chosen colour television receivers was found to vary from 0.001 to 0.076 mR h^{-1} under normal working conditions.

5. *Absorbed doses from disposal of consumer products as waste*

303. Although in many countries the use and eventual disposal as waste of consumer products containing relatively high levels of radioactivity are subject to various forms of control, the vast majority of these products are likely to be disposed of as household refuse, without control. The normal subsequent disposal of this refuse is by dumping on land or by incineration. Dumping on land will result in the radioactivity being more isolated from man than when the product containing it was in use, so that doses from this type of disposal will on the average be less than from normal use of the product. No data are available on the likely proportion of these products that might be incinerated. If it is assumed that 10 per cent of the ^{3}H-radioluminized wrist-watches distributed in the United States are disposed of in this way after they have been in use for 10 y and that the average activity per watch at this time is 2.5 mCi, then the disposal would give rise to approximately 1000 Ci of airborne tritium distributed more or less uniformly over the country. Further assuming that this would give rise to doses of a similar magnitude as those resulting from airborne tritium discharges from nuclear reactors, i.e., a collective dose per unit activity released of 3 10^{-3} man rad Ci^{-1} (see Annex D), then the annual collective dose would be about 0.3 man rad. This value is negligible relative to the collective dose resulting from the wearing of wrist-watches (para. 291).

6. *Conclusions*

304. Many millions of units of various types of consumer products containing deliberately incorporated radionuclides are in everyday use around the world. Estimates of doses in individuals resulting from the use of such products show that in all cases these doses are small. The highest calculated whole-body doses result from the wearing of radioluminous watches, which are the most widespread radioactive consumer product. The assessment of the global collective dose from these sources is hampered by wide gaps in the knowledge of important factors such as the activities involved, the number of products on the market, and the problems related to the disposal of those devices. Even for the most common product, watches, the data are not always available since watches are generally not subject to control. Nevertheless, owing to international recommendations, and national regulations in some countries, there is a gradual improvement of control. It is likely that the average annual gonad dose due to the use of consumer products is less than 1 mrad, almost entirely due to radioluminous timepieces. However, in view of the growing number and diversity of consumer products, it is important to ensure that proper control is maintained over their use and disposal.

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ANNEX C

Radioactive contamination due to nuclear explosions

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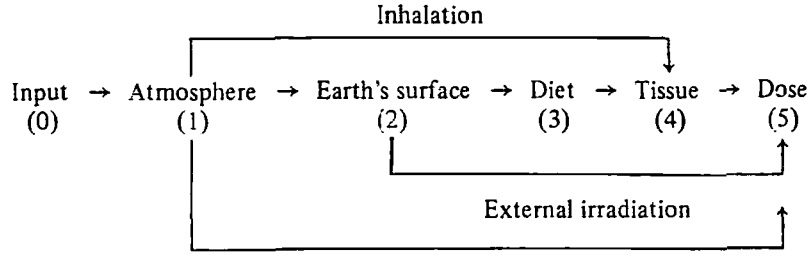
Introduction

1. During the period reviewed in this report (January 1972 to December 1976) a number of nuclear tests have been reported, including 20 atmospheric tests, 6 of which were in the northern hemisphere and 14 in the southern hemisphere. In this Annex, therefore, the total inventory of radionuclides from nuclear tests has been reassessed and the consequential changes in the dose commitments have been evaluated.

2. This Annex also discusses improvements in the knowledge of the parameters involved in the assessment of dose commitments, particularly those factors related to the transfer of radioactivity between compartments

of the environment linking the input of radionuclides to the subsequent dose in man. The compartment model used by the Committee in its assessments can be represented schematically as follows:



This model does not include all possible pathways of human exposure, but only those relevant to the assessments presented in this Annex. Procedures for the use of the model are described in Annex A.

3. Where sufficient information is available, assessments of collective dose commitments per unit activity release are presented. It should be noted that the bulk of the radionuclides from atmospheric nuclear explosions was injected into the atmosphere at high altitude. For this reason many of these commitments per unit activity do not apply to other situations of environmental releases of radioactive materials.

I. TRANSPORT OF RADIOACTIVE DEBRIS WITHIN THE ATMOSPHERE

4. During a nuclear explosion, the fission products, residual fissile material and structural materials associated with the device are raised to sufficiently high temperatures to be present in gaseous form. For explosions detonated in the atmosphere near the surface of the earth, a considerable amount of volatilized soil or rock material may also be entrained in the fireball.

5. After the explosion in the atmosphere, the fireball expands rapidly and rises due to buoyancy. As it rises, cooling causes the volatilized debris to condense, forming an aerosol with a wide distribution in particle size (245).

6. The height to which the aerosol cloud rises increases with explosion yield. Since the height of the tropopause is lower in polar regions than near the equator, the extent to which the cloud enters the stratosphere will depend on both latitude and yield (201).

7. During the initial expansion of the fireball, some tens of seconds after detonation, particles composed of iron and aluminium oxides and of other refractory materials are formed, with diameters in the range 0.4-4.0 μm (81, 223). The radionuclides having the more refractory oxides (i.e., oxides with high boiling points), tend to be incorporated into these particles, while those that have low boiling point oxides tend to be excluded. When the refractory material has condensed out, the gaseous remainder, enriched in the more volatile radionuclides and in radionuclides with volatile precursors, condenses into small particles (diameter < 0.4 μm). This separation of the radionuclides between aerosol particles in the two size ranges is usually known as fractionation. Because the larger aerosol particles are subjected to significant gravitational settling, they are more likely to be deposited upon the earth near the explosion site, whereas the smaller aerosol particles remain at greater altitudes for a longer time and are distributed over a wider area (95).

8. When nuclear explosions are detonated on or near the ground, large amounts of soil or rock materials are drawn into the fireball. On cooling, these tend to form large aerosol particles; so for surface detonations much of the radioactive material is present in relatively large aerosol particles.

9. Radioactivity present in large aerosol particles will fall out within a few hundred kilometres, constituting the "local fallout"; smaller aerosol particles injected into the lower troposphere can be transported around the earth in the same hemisphere, and will be deposited from hundreds to many thousands of kilometres from the detonation site, constituting the "tropospheric fallout". Aerosol particles carried up into the stratosphere give rise to fallout with a world-wide distribution, the major part of which is in the hemisphere of injection. This fallout is known as global or "stratospheric" fallout.

10. Most of the world-wide contamination of long-lived fission products has been from the stratospheric fallout resulting from large thermonuclear tests. On the other hand, tropospheric fallout accounts for much of the contamination from short-lived radionuclides, during the first few months after a test.

11. Our knowledge of mixing processes and air movements in the stratosphere is still incomplete, although many of the gross features are now known from studies of radionuclide concentrations. Detailed descriptions of the atmospheric movement of radionuclides were given in the Committee's 1964 and 1972 reports (242, 245). Mixing processes in the stratosphere are generally slower than in the troposphere, most of the movement being due to horizontal diffusion with considerable downward motion at higher latitudes in the winter hemisphere (153).

12. Several mechanisms account for the transfer of particulate radioactivity from the stratosphere to the troposphere. Prominent among these is the horizontal transfer through the subtropical tropopause gap. This

transfer process reaches a maximum in late winter and gives rise to the well known spring maximum in the fallout rate (141).

13. The mean residence time of a radionuclide in the stratosphere, defined as the average time spent by atoms of that radionuclide in the stratosphere before transfer to the troposphere, depends on the latitude and altitude of injection and also on the time of the year at which the injection is made. Between 15 and 25 km altitude, the mean residence time can vary from 0.3 to 2 y, depending upon altitude and latitude (212). For ^{90}Sr, the mean residence time in the stratosphere is typically of the order of 1 y (242). The long effective mean residence time in the stratosphere observed for some radionuclides such as ^{14}C is due to the fact that these radionuclides are not removed rapidly from the troposphere and are recycled back into the stratosphere (211).

14. After the radioactive debris has entered the troposphere, it is rapidly dispersed throughout the hemisphere. For particulate radioactivity, the troposphere is rapidly depleted by essentially three processes: *(a)* rain-out caused by droplet formation within clouds, *(b)* wash-out by falling raindrops picking up radioactivity, and *(c)* dry deposition on land surfaces or plant cover, this last process being of more importance in dry regions (85, 140). The resulting residence time for particulate radioactivity in the troposphere is about 30 d (98, 154, 176). Because of this rapid removal, very little particulate activity moves from the troposphere of one hemisphere to the troposphere of the other. On the other hand, gaseous radionuclides in the troposphere, such as ^{85}Kr, mix between hemispheres with a mean exchange time of 1.5 y (242).

II. INTERNAL IRRADIATION

A. TRITIUM

15. Tritium, a radioactive isotope of hydrogen, is a pure beta emitter with maximum energy of 0.018 MeV and a half-life of 12.3 y. It occurs naturally on the earth's surface, being produced in the stratosphere by reactions induced by cosmic rays (Annex B). Man-made tritium, in amounts substantially larger than the natural inventory, has been injected into the stratosphere by thermonuclear explosions. Most of this tritium is in the form of water (as HTO) and, after a mean residence time of about a year, enters the troposphere, and then the hydrological cycle. Tritium has been extensively monitored in precipitation and natural waters. In 1961, IAEA established a world-wide network for monitoring the ^{3}H concentration in precipitation (133).

1. Tritium inventory

16. From a study of ^{3}H concentrations in profiles in the Pacific Ocean at stations from latitude 60° S to 51° N, Michel (167) has estimated the world's ^{3}H inventory in 1970 to be 2900 MCi, which when corrected for decay using the annual deposition of ^{90}Sr as a guide, gives a total injection of ^{3}H of 4500 MCi. According to Michel's estimates, about 20 per cent of this is in the southern hemisphere, so it is estimated that 3600 MCi and 900 MCi of ^{3}H were released into the northern and southern hemisphere, respectively. It is also possible to estimate the ^{3}H inventory from measured ^{3}H and ^{90}Sr activities in ocean waters. Bowen and Roether (46) have reported total ^{3}H and ^{90}Sr inventories in the profiles at five sites in the Atlantic Ocean between latitude 35° and 45°. The average ^{3}H-to-^{90}Sr activity ratio at these five sites was 325.6. The cumulative deposit of ^{90}Sr in the northern hemisphere in 1970 was 9.37 MCi, and since the ocean makes up 56 per cent of the area of the northern hemisphere, 5.25 MCi of ^{90}Sr will be in the northern hemisphere oceans. Using the above value for the $^{3}H/^{90}Sr$ ratio, it is estimated that $5.25 \times 325.6 = 1708$ MCi of ^{3}H were present in oceans of the northern hemisphere in 1970. Correcting for radioactive decay it is estimated that some 2740 MCi of ^{3}H were released in the northern hemisphere, since it can be assumed that most fallout tritium on land has been washed into the oceans. Using the partitioning of ^{90}Sr between hemispheres as a guide, the inventory of ^{3}H in the southern hemisphere is estimated to be 820 MCi.

17. Both the above estimates are larger than that of Eriksson (1900 MCi) reported in the Committee's 1972 report, but much lower than the 8000 MCi reported by Miskel (84, 173). the latitudinal distribution of tritium in surface waters of the Pacific between 1965 and 1972 is shown in figure I (167). From concentrations in precipitation at stations in the IAEA network, Schell *et al.* (20) estimated the deposition between 1963 and 1969 to be 1780 MCi in the northern hemisphere and about 400 MCi in the southern hemisphere. Using the annual global deposition of ^{90}Sr as a guide, these results indicate that the total injection of ^{3}H up to 1970 was about 4500 MCi, in agreement with the estimate from Michel's data.

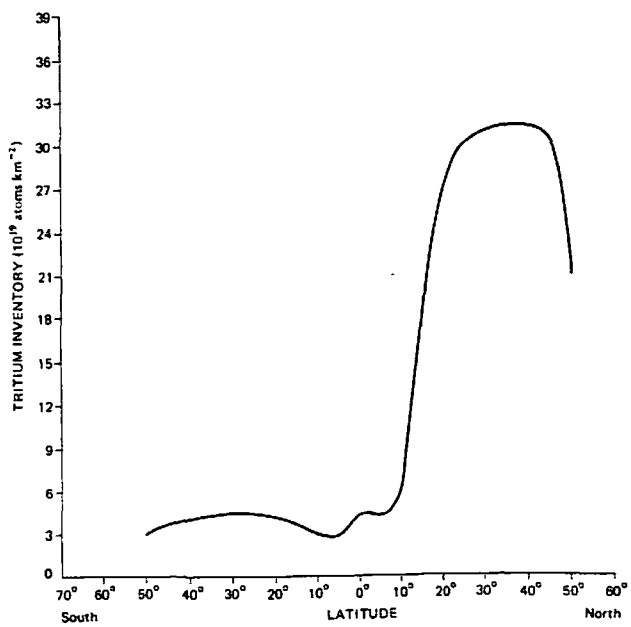


Figure I. Latitudinal distribution of the tritium inventory per unit area in the top 500 m of the Pacific Ocean, 1965-1972 (167)

2. Dose commitment from tritium

18. In the 1972 report, the dose commitments from fallout tritium were estimated in an indirect way on the basis of a comparison with the production rate of natural tritium and the measured concentrations in waters prior to the commencement of thermonuclear tests. More recent papers dealing with fallout tritium make it possible to estimate the dose commitments directly from fallout measurements. It should be realized that, due to insufficient information relating to some of the quantities involved in the calculations, estimates by both methods are uncertain.

19. Bennett (25, 37) used a three-compartment model suggested by Sanders and Reinig (219) to determine the tissue dose rate at equilibrium for a continuous intake of tritium in water. This model considers the dose rate in tissue due to tritium in tissue water as well as that which is organically bound in tissue. For a chronic intake of water with a concentration of 1 μCi l^{-1}, the tissue dose rate at equilibrium is 95 mrad y^{-1}. Of this, 84 per cent is due to tritium in water and 16 per cent to tritium combined in tissue.

20. The tritium activity concentration of surface waters in the United States of America is shown in figure II. From the tritium concentrations in 18 United States rivers and in the Ottawa river, Bennett (25, 37) estimated the whole body dose commitments to the populations of the United States and the Ottawa Valley to be 1.5 and 2.8 mrad, respectively.

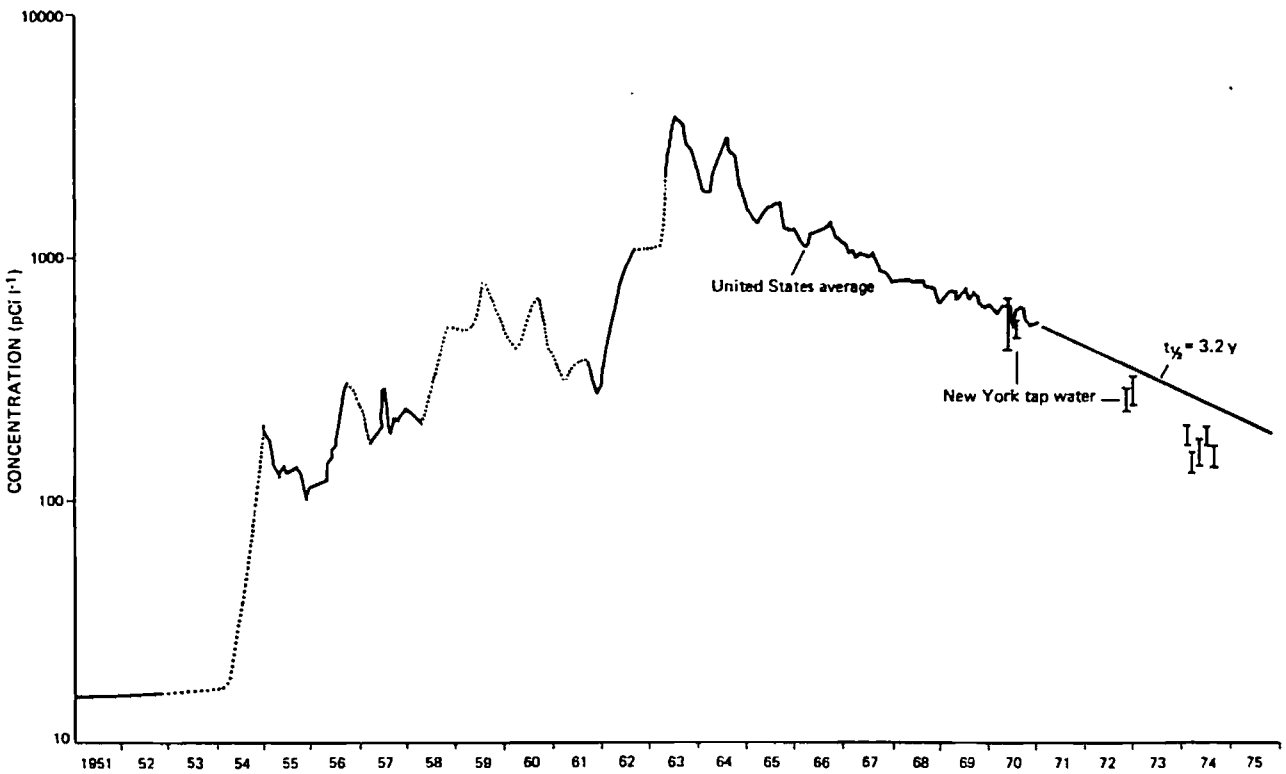


Figure II. Variation of tritium activity concentration of surface waters in the United States of America over the period 1951-1975 (25, 27)

21. Schell *et al.* (220) have evaluated the 1961 to 1967 data provided by the IAEA and WMO world survey of tritium concentration in precipitation. They observed that the latitudinal distribution of the tritium concentration in precipitation at marine stations increased exponentially from the equator to the polar regions. In the northern hemisphere, the concentration doubled about every 13° of latitude, and in the southern hemisphere, about every 16° of latitude. The concentrations observed at the continental stations were on the average higher than at the marine stations by a factor of 3.6, this effect being due partly to re-evaporation and evapotranspiration over the land mass and partly to greater injection.

22. Assuming that the dose commitment to a population living in a given latitude band is proportional to the concentration in the corresponding precipitation and that the average concentration doubles every 13° of latitude from the equator to the North Pole, a dose commitment of 2.8 mrad to the Ottawa Valley population corresponds to a dose commitment to the population of the northern hemisphere of 2.0 mrad.

23. From the extensive measurements of the tritium concentration in rainwater in both hemispheres between 1964 and 1967 carried out by IAEA (220), it appears that on the average the concentrations in the southern hemisphere were about one tenth of those in the northern hemisphere. Assuming that this ratio applies over the whole period of atmospheric tests, the dose commitment to the population of the southern hemisphere is estimated to be 0.2 mrad.

24. The dose commitment from fallout tritium can also be assessed, as in the 1972 report, using the relation $D^c = \gamma_0 W/B$, where D^c is the dose commitment, γ_0 is the tissue dose rate from natural tritium, W is the activity of tritium released by nuclear explosions, and B is the activity of natural tritium produced annually.

25. The annual dose from natural tritium is estimated to be 1.0 μrad (Annex B). Assuming a total release in the northern hemisphere of 3600 MCi of tritium from nuclear explosions, as discussed in previous paragraphs, and an annual natural production per hemisphere of about 1.9 MCi (Annex B), the dose commitment in the northern hemisphere from fallout tritium is estimated to be 1.9 mrad. In the southern hemisphere the dose commitment estimated by the same procedure is 0.47 mrad.

26. These values are in reasonable agreement with those given in paragraphs 22 and 23, namely 2 mrad and 0.2 mrad, which are taken in this report as the dose commitments from tritium in the northern and southern hemisphere, respectively. These estimates are lower than those presented in the 1972 report (4 mrad for the northern hemisphere and 1 mrad for the southern hemisphere).

27. The collective dose commitment from tritium is dominated by the contribution from the northern hemisphere, because of the higher individual doses in that hemisphere and also because of population distribution. Using the procedures outlined in Annex A and assuming a population growth of 2 per cent per year, the collective dose commitment due to tritium from nuclear explosions is estimated to be about $8\ 10^{6}$ man rad, corresponding to about $3\ 10^{-3}$ man rad per curie of released activity. It should be noted that this estimate applies to the injection of tritium by nuclear explosions carried out in the northern hemisphere.

B. CARBON-14

28. Carbon-14 is a pure beta emitter with a maximum energy of 0.156 MeV and a half-life of 5730 y. It is formed in atmospheric nuclear explosions from the capture of excess neutrons by nitrogen. After large atmospheric nuclear explosions, most of the ^{14}C is transported into the stratosphere, from where it equilibrates with the troposphere with a half-time of 1-2 y.

29. Present in the troposphere as carbon dioxide, the activity of ^{14}C reached a peak in 1965 as a result of the nuclear explosions in the late 1950s and early 1960s. Although there have been additions to the troposphere of ^{14}C from explosions since that time, these inputs have been smaller than uptake by the oceans and the biosphere, and thus the levels in the troposphere have continued to decrease.

30. Measured values of excess specific activity of ^{14}C in the troposphere and in the surface ocean are shown in figure III. In order to estimate the inventory of ^{14}C from nuclear explosions and to predict future atmospheric levels, some model to represent the exchange of ^{14}C between the atmosphere, biosphere and ocean is needed.

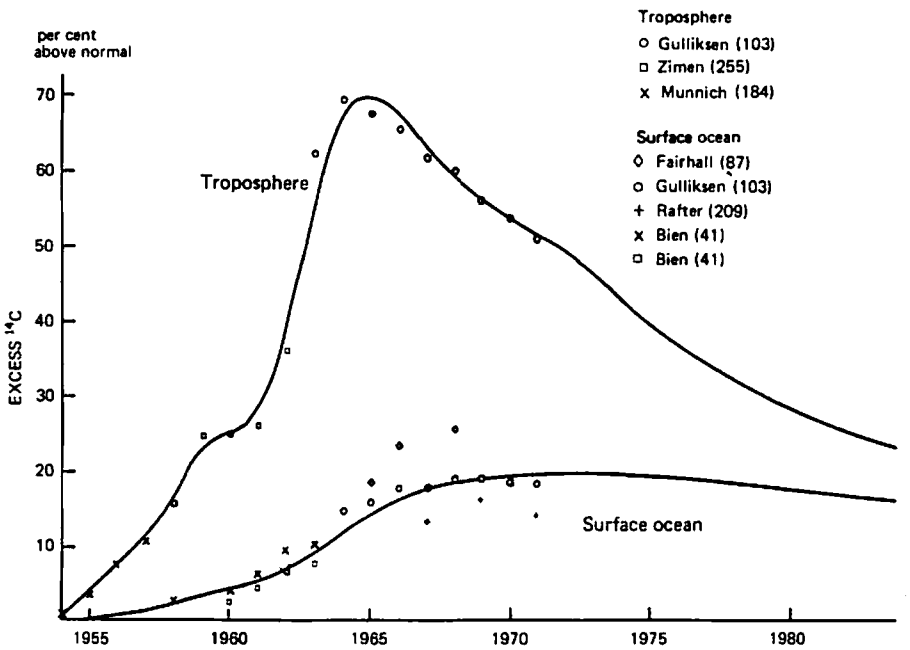


Figure III. Variation of excess ^{14}C in the troposphere and surface ocean. (The continuous line has been obtained by regression, assuming no injections after 1972)

31. Figure IV is a schematic representation of the model used in this report to predict the circulation of ^{14}C and of the excess stable carbon injected by the use of fossil fuels (196). This model is similar to previous models used by the Committee except that the thermocline region of the ocean is represented as a diffusive layer (194, 208, 242). The values of the relevant parameters are also shown in this figure. The parameters K_a, k and W_t were adjusted to fit the excess ^{14}C in the atmosphere and surface ocean. Since the transfer time between the atmosphere and the short-term biosphere (i.e., annual plants, leaves, and short-term detritus) is short, being about 2.5 y, for the purposes of these calculations the short-term biosphere

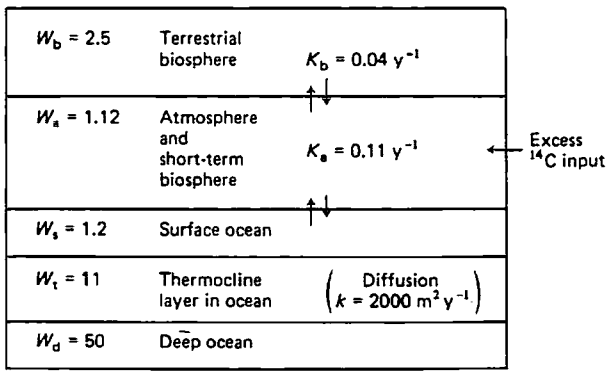


Figure IV. Model representing the exchange of excess ^{14}C between the atmosphere, the biosphere and the ocean. The factors W are the capacity of each reservoir in units of the atmospheric capacity. The parameters K_b and K_a are transfer rates and k is a diffusion coefficient.

is combined with the atmospheric compartment (13). The mean residence time of the excess ^{14}C in the atmospheric and short-term biospheric compartments, before movement to the long-term biospheric compartment or to the oceans, is $W_a/(K_a + K_b) = 7.5$ y.

32. The predicted values of the excess ^{14}C in the atmosphere and surface ocean are included in figure III. The parameters of the model, obtained by regression from the actual data on excess of ^{14}C, indicate that the input of man-made ^{14}C into the atmosphere up to 1972 was 5.8 MCi, and that the time-integrals of the man-made ^{14}Ccontent in the atmosphere up to 2000, 2020 and 2050 are equivalent to the natural content multiplied by 14.4, 17.1 and 20.5 y, respectively. Fairhall *et al.* (87), using a quite different approach, estimated the excess ^{14}C inventory up to 1971 to be 6.2 MCi.

33. Carbon-14 is taken up by plants during photosynthesis and is subsequently incorporated into the human body. Several investigators have measured excess ^{14}C levels in human tissue (81, 150). Nydal *et al.* (194), from the measurement of $^{14}C/^{12}C$ ratios in human hair and blood between 1962 and 1969, concluded that the specific activity in human tissue comes into equilibrium with that in atmospheric CO_2 with a delay time of about 1.4 y.

34. The dose commitment from man-made ^{14}C can be assessed, as shown for the case of tritium, by a comparison with natural ^{14}C. Taking the natural production rate to be 28 kCi y^{-1}, as derived from the natural ^{14}C inventory, and the tissue dose rates from natural ^{14}C (Annex B), the dose commitments shown in table 1 have been calculated.

TABLE 1. DOSE COMMITMENTS FROM THE ^{14}C PRODUCED IN NUCLEAR EXPLOSIONS

(mrad)

	Gonads	*Lung*	*Bone lining cells*	*Red bone marrow*	*Whole-body average*
Dose commitment	103	124	414	455	269
Part accumulated up to:					
2 000	7.2	8.6	29	32	19
2 020	8.6	10.3	34	38	22
2 050	10.2	12.2	41	45	27

35. The parts of the dose commitment to the world population from ^{14}C delivered up to 2000, 2020 and 2050 were estimated from the corresponding integrated atmospheric levels given in paragraph 32. They are also shown in table 1.

36. Assuming an upper limit of 10^{10} for the world population, the collective dose commitment per unit activity of ^{14}C released in the stratosphere is estimated to be about 200 man rad Ci^{-1} for soft tissues and about 700 man rad Ci^{-1} for bone lining cells and for red bone marrow.

C. MANGANESE-54

37. Manganese-54 was a significant component of fallout activity for several years after the test series in 1961-1962. It is not a fission product and was presumably produced by neutron capture reactions in the structural material used in the nuclear devices. It has a half-life of 310 d, decaying by electron capture with the emission of gamma and x rays. Little activity has been measured in air since 1966. The time-integrated activity concentration in air measured at Sterling, Virginia (United States), between 1963 and 1966 was 1.13 pCi y m^{-3} (117, 249), and is typical of the integrated values measured in temperate latitudes of the northern hemisphere. In the southern hemisphere, the values were 100 times lower. Measurements of the deposition density (the activity deposited per unit area) made at Westwood, New Jersey (United States), indicate indirectly that the integrated air concentrations in 1962 were about 10 per cent of those in 1963 (110). Using this information, the integrated activity concentration in air at Sterling, Virginia, for 1962-1974 is estimated to be 1.2 pCi y m^{-3}.

38. Voilleque and Pelletier (248) have considered the different pathways of ^{54}Mn to man and have estimated transfer factors for the pathway air → deposition on the ground → cow's milk → man. In man, the organ receiving the highest dose from ingestion is the lower large intestine. For adults, the transfer factor P_{12345} pertaining to the atmosphere-to-dose pathway via ingestion (see paragraph 2), is estimated to be $7\ 10^{-3}$ mrad per pCi y m^{-3}. For children less than one year old, the population group receiving the highest dose, these authors estimated P_{12345} to be 0.11 mrad per pCi y m^{-3}. The main dose is in the lung due to direct inhalation. Using the ICRP lung model (134, 135, 136) with the set of parameters for compounds class W, and a value of 20 per cent retention in the pulmonary region, the value of P_{145} for adults is 0.91 mrad per pCi y m^{-3}. The dose commitments from ^{54}Mn, assessed from the factors mentioned above, are $8\ 10^{-3}$ mrad to the lower large intestine (LLI) of adults, 0.16 mrad to the LLI of infants, and 1.0 mrad to the adult lung.

D. IRON-55

39. Iron-55 has a half-life of 2.7 y and decays by electron capture with the emission of x rays and bremsstrahlung with 0.23 MeV maximum energy.

Iron-55 was produced as an activation product in the nuclear tests carried out in 1961-1962 and it is estimated that a total of about 50 MCi was produced (126). The concentration of ^{55}Fe in air fell rapidly after 1962-1963 and has been essentially zero since 1970. Time-integrated concentrations in the atmosphere of the southern hemisphere were considerably below those of the northern hemisphere.

40. The uptake of ^{55}Fe by man was discussed in the 1972 report of the Committee (245), and it appears that both the terrestrial food chain and the marine food chain leading to man are important in contributing to the activity in man (137, 197). Body activities measured in a large number of people in different parts of the world in 1966 were in the range 20-30 nCi, and they dropped to 1-10 nCi in 1969 (148, 197). In Japan and in Alaska (United States) in 1966, body activities greater than 1000 nCi were observed in persons consuming large quantities of fish (197). The dose commitments in the northern hemisphere from testing in the period 1954-1962 was estimated by Persson (199), assuming a maximum body activity of 30 nCi in the temperate latitudes. The estimates are 1 mrad to the gonads and bone lining cells and 0.6 mrad to the bone marrow. A reduction by a factor of four is assumed for the southern hemisphere. The collective dose commitment per unit activity released in the northern stratosphere is estimated to be about $6\ 10^{-2}$ man rad Ci^{-1} for the gonads and bone lining cells and $4\ 10^{-2}$ man rad Ci^{-1} for the bone marrow.

E. KRYPTON-85

41. The production of ^{85}Kr by nuclear explosions can be estimated from ^{90}Sr production values, using a $^{85}Kr/^{90}Sr$ fission-yield ratio of 0.07 (164, 190). By this procedure the production of ^{85}Kr by nuclear explosions is estimated to be about 3 MCi. Krypton-85 is an inert gas and most of it remains in the atmosphere, its concentration becoming fairly uniform throughout the earth's atmosphere within a few years (88). Most of the ^{85}Kr present in the earth's atmosphere originates in releases from nuclear-fuel reprocessing plants and not from nuclear explosions (Annex D).

42. Krypton-85 has a 10.7-y half-life, is a beta emitter with a maximum energy of 670 keV, and emits a 514-keV photon in 0.4 per cent of the disintegrations. The dose to the skin, lung and gonads from a time-integrated concentration in air of 1 pCi y m^{-3} have been estimated (185) to be 1.8 μrad, $3.1\ 10^{-2}$ μrad and $1.6\ 10^{-2}$ μrad, respectively. Assuming that 3 MCi are uniformly mixed in the earth's troposphere ($5\ 10^{21}$ g air), the resulting dose commitments are estimated to be 21 μrad, 0.35 μrad and 0.2 μrad for the skin, lung and gonads, respectively. Assuming an annual increase in the world population of 2 per cent, the collective dose commitments, per curie of ^{85}Kr released in the stratosphere, are estimated to be about $4\ 10^{-3}$ man rad for skin, $7\ 10^{-4}$ man rad for lung and $4\ 10^{-4}$ man rad for gonads.

F. STRONTIUM-90

1. Inventory and deposition

43. Strontium-90, a pure beta emitter with a maximum energy of 0.54 MeV, decays with a half-life of 28 y to ^{90}Y, which has a half-life of 65 h and is a beta-emitter with a maximum energy of 2.27 MeV.

44. The total stratospheric inventory of ^{90}Sr is shown in figure V, together with that for each hemisphere for the period 1963-1975 (149). The period between 1963 and 1966 was marked by an exponential decrease of the

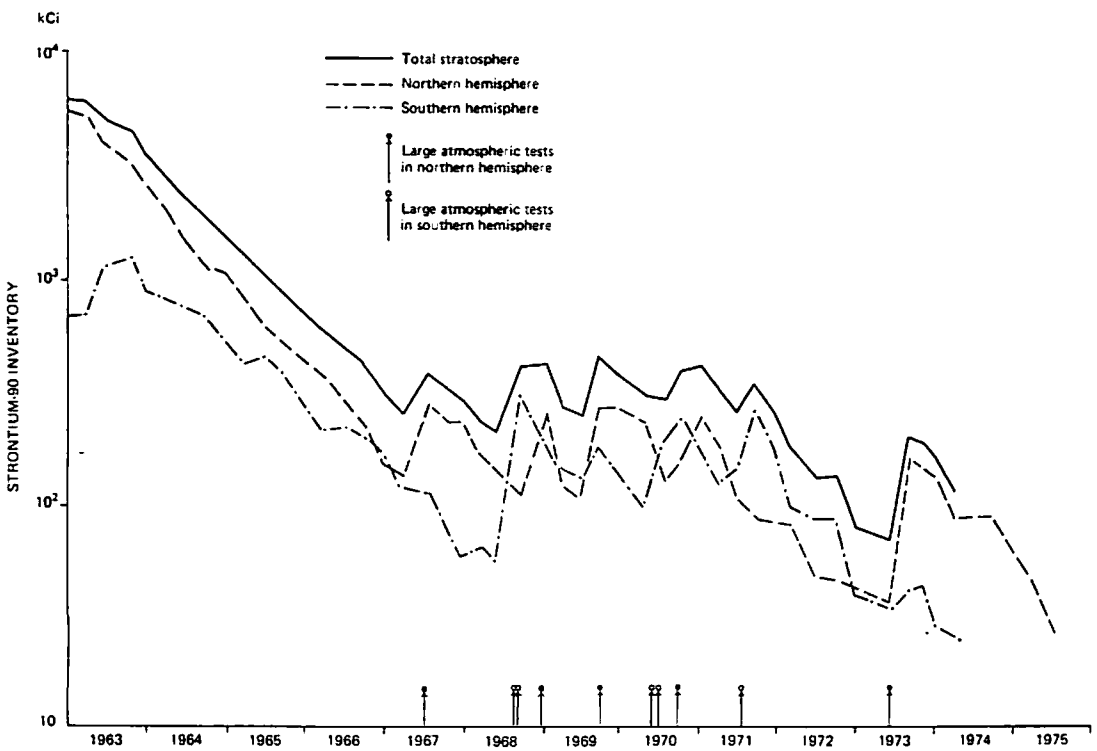


Figure V. Variation of the stratospheric inventory of ^{90}Sr over the period 1963-1975 (149)

stratospheric inventory from the peak value resulting from the atmospheric tests conducted in the early 1960s. Between 1966 and mid-1971, the inventory in each hemisphere remained fairly constant at about 20 per cent of the 1963 peak values. During this period, the northern and southern hemisphere stratospheres were replenished with ^{90}Sr from a series of tests carried out in central Asia and in the south Pacific. During 1972 and early 1973, the stratospheric inventory in each hemisphere again decreased. After mid-1973 the inventory rose after an atmospheric test in the northern hemisphere.

45. The annual deposition of ^{90}Sr in the northern and southern hemispheres is shown in table 2 for the period 1958-1975, in addition to the cumulative deposit in each hemisphere (89). (Deposition is the activity deposited on a specified area. The cumulative deposit is the activity present in a specified area at a given time; it is the result of past depositions and radioactive decay.) Between 1970 and 1973, deposition in both hemispheres fell off sharply, and the 1973 values were the smallest recorded since these measurements began. In 1974, however, there was an increase in the annual deposition in the northern hemisphere.

TABLE 2. ANNUAL DEPOSITION AND CUMULATIVE DEPOSIT OF ^{90}Sr

(MCi)

	Deposition			*Cumulative deposit*		
Year	*Northern hemisphere*	*Southern hemisphere*	*Global*	*Northern hemisphere*	*Southern hemisphere*	*Global*
Pre-1958	1.80[a]	0.65[a]	2.45[a]	1.70	0.60	2.30
1958	0.63	0.25	0.88	2.28	0.84	3.12
1959	1.05	0.18	1.23	3.26	1.00	4.26
1960	0.26	0.17	0.43	3.44	1.14	4.58
1961	0.35	0.17	0.52	3.70	1.29	4.99
1962	1.44	0.26	1.70	5.04	1.51	6.55
1963	2.62	0.31	2.93	7.51	1.78	9.29
1964	1.66	0.42	2.08	8.96	2.16	11.12
1965	0.77	0.36	1.13	9.50	2.46	11.96
1966	0.33	0.21	0.54	9.59	2.60	12.19
1967	0.17	0.11	0.28	9.52	2.65	12.17
1968	0.20	0.10	0.30	9.48	2.68	12.16
1969	0.15	0.14	0.29	9.40	2.76	12.16
1970	0.21	0.13	0.34	9.37	2.82	12.19
1971	0.19	0.15	0.34	9.33	2.90	12.23
1972	0.09	0.10	0.19	9.18	2.92	12.10
1973	0.03	0.03	0.06	8.98	2.88	11.86
1974	0.12	0.04	0.16	8.89	2.85	11.74
1975	0.06	0.03	0.09	8.73	2.81	11.54
Integrated deposition	12.13	3.81	15.94			
Stratospheric inventory	0.03	0.03[b]	0.06			
Total injection to January 1976	12.16	3.84	16.00			

Sources: References 89, 149.

[a] Estimated from the cumulative deposit, assuming a two-year decay.

[b] Assumed to be the same as for the northern hemisphere.

46. The deposition density of ^{90}Sr is measured monthly at a considerable number of monitoring stations in both hemispheres. (Deposition density is the activity deposited per unit area.) Estimates of the average integrated deposition density (the addition of all previous deposition densities in a location, without taking account of radioactive decay) of ^{90}Sr in each latitude band are shown in table 3 (89), together with the zonal populations and areas. This latitudinal distribution is useful for determining the dose commitment to the world population and in addition serves indirectly as a guide to the geographical distribution of other radionuclides released by atmospheric tests. It can be seen from table 3 that the integrated deposition density is maximum in the mid-latitude regions of each hemisphere.

47. The population-weighted deposition density is determined as follows: If N_i is the population of latitude band i and F_i is the average integrated deposition density of ^{90}Sr in that band, then the population-weighted

TABLE 3. LATITUDINAL DISTRIBUTION OF ^{90}Sr INTEGRATED DEPOSITION DENSITY

Latitude band	*Area of band (10^6 km^2)*	*Relative population of band (%)*	*Integrated deposition density of ^{90}Sr (mCi km^{-2})*
70°-80° N	11.6	0.0	19.1
60°-70° N	18.9	0.4	45.7
50°-60° N	25.6	12.2	79.2
40°-50° N	31.5	13.8	85.1
30°-40° N	36.4	18.2	62.4
20°-30° N	40.2	29.2	45.7
10°-20° N	42.8	9.8	30.0
0°-10° N	44.1	5.6	20.7
0°-10° S	44.1	5.8	18.9
10°-20° S	42.8	1.8	10.1
20°-30° S	40.2	1.6	18.0
30°-40° S	36.4	1.4	20.7
40°-50° S	31.5	0.1	24.5
50°-60° S	25.6	0.05	14.7

Sources: References 89, 155.

TABLE 4. STRONTIUM-90 AND CAESIUM-137 IN MILK

Country or area	$^{90}Sr/Ca$ quotient (pCi $(gCa)^{-1}$)										^{137}Cs concentration (pCi l^{-1})										Reference
	1966	1967	1968	1969	1970	1971	1972	1973	1974	1975	1966	1967	1968	1969	1970	1971	1972	1973	1974	1975	
Northern hemisphere																					
Austria	23	14	13	12							70	3	28	27							57, 58, 59
Belgium	13	9	8	9	6	6	5				36	17	20	15	10	13	10				72, 73
Canada	13	10	8	9	9	8	7				51	33	25	20	21	22	16				78, 79, 162, 205, 237, 253
Colombia	2	2	1		1	1	1	1													206, 207
Czechoslovakia	12																				183
Denmark	9	8	7	6	8	7	5	4	4	4	22	14	12	13	10	11	7	4	4	4	2
Egypt	13		6																		157, 158
Faroe Islands	73	51	45	37	37	34	25	23	20	19	800	586	507	463	357	352	268	251	254	198	3
Finland	13	10	9	8	7	7	6	5	5		134	92	70	54	49	44	36	30	28	25	64, 218
France (1)	19	14	12	9	8	9	8	6	6	6		21	20	19	21	22	15	8	6	8	96, 198, 222
France (2)	18	15	12	12	12	11	10	7	6	6	62	34	24	24	26	28	20	13	10	12	76
French Guiana	13	17			8	7	11	6			61	12			72	67	68				206, 207
Germany, Fed. Rep. of	16	11	9	9	8	8	7	6	6	5	61	35	27	25	31	29	25	18	20	15	52, 56
Guadeloupe		2	2	2	3	4	4	3					14		14	17	12	7			222, 253
India (Bombay)	5	3	3	2	3	2					11	6	5	5	4	4					146, 147, 170, 171
Israel	2	2																			90
Italy	13	10	8	8	7									34	25						74, 75
Jamaica	9	7	4	4	4	4	3				200	184	109	95	81	80	45				253
Japan	11	8	7	5	5	6	4	4	4	3	52	30	28	18	16	15	19	12	10	9	7, 253
Martinique		7	8	5	5	4	7	4				41	41		61	59	98	65			222, 253
Netherlands	15	9	8	7	6	5	5				43	37	28	23	17	16	10				72, 161, 168, 169
Norway	30	18	13	11	11	9	8	9	7		244	181	146	128	117	84	80	72	59	49	131
Panama	4										21	22	11	11							247
Poland	13	14	10	9	6	8	6	6	6	5	58	42	37	31	31	32	26	18	22	22	138
Puerto Rico	6	4	4	4							21	14									247
Republic of Korea	22	11	15																		143
Senegal	13	9	6		3	6	4														206
Sweden	15	10	8	7	7	7	6	5	5		63	38	30	20	23	26	18	11	11	10	106-108, 109, 228-230
Switzerland	15	9	7	7	8	9	7	5	5		29	16	15	14	15	16	12	7	11		129, 130
USSR	12	10	9	8	7	7	6	5			56	38	30	20	23	27	21	18			144, 257, 258, 261, 263, 264
United Kingdom	12	9	8	7	6	6	5	4	3	3	46	20	16	14	17	18	13	8	9	7	5, 50, 51, 178
United States	12	9									29	16									247
Alaska	12	6	6	5							34	20	13								247
Chicago	9	8	8	6									14	16	14	14	7	5			47, 125, 247
Hawaii	4	3	4	2							25	9									247
New York City	12	10	9	9	9	9	6	5	5	5											36, 112
Tampa	11	11	7	5	5	4	4				139	102	66	55	51	43	35	27			247, 253
Venezuela	4										14	9									247
Southern hemisphere																					
Argentina	5	5	4	4	3	4	4	3	2	2	24	21	19	20	20	19	17	13	12	5	21, 70, 71
Australia	7	5	4	5	6	7	5	4	4	4	28	20	15	18	19	21	18	11	7	6	9-11, 44, 91, 92, 99
Bolivia					1	1	1	1	1												76, 206
Chile	2	2	1		2	2	1	3	2						8	9					76, 69, 206, 207
Ecuador	5	2	1		1	1	1	1													76, 206, 207
Madagascar	2	2	1		2		1	1													76, 206, 207
New Caledonia	3	2	3		3	3	3	2	2		8	7	5		12	6	3	2			76, 206, 207
New Zealand	8	6	5	7	7	7	6	4			55	43	32	40	35	32	27	18	14		187-188
Peru	2	1	2																		206
Réunion		4	3	3	5	5	5	3	3			17	15	18	16	14	14	10			207, 222
Society Islands (Tahiti)	6	4	2		4	6	5	4	4		18	96	35		134	144	138	114	106		76, 206, 207

deposition density $\bar{F}$ is given by $\bar{F} = \Sigma_i F_i N_i / \Sigma_i N_i$. The population-weighted integrated deposition densities of ^{90}Sr from all tests for the northern hemisphere, for the southern hemisphere and for the whole world are 56.5, 17.6 and 52.3 mCi km^{-2}, respectively.

2. Strontium-90 in the environment

48. The deposition of ^{90}Sr occurs over land and water, but that over land is the more important pathway for human exposure. The quantitative aspects of the transfer of ^{90}Sr along terrestrial pathways are treated in detail in the following sections of this Annex.

49. Previous reports of the Committee have discussed the behaviour of ^{90}Sr in soils (244, 245). Recent measurements of the soil profile (114) have shown that ^{90}Sr is still present mostly in the upper layers, with 50 per cent in the first 4 cm and practically all in the top 30 cm. Only small amounts of ^{90}Sr are leached out of the soil and conveyed into fresh-water rivers and lakes. Concentrations in drinking waters are normally at least an order of magnitude lower than those found in other foodstuffs. Plants take up ^{90}Sr from soil through their root system. This root uptake and the time constants describing how ^{90}Sr becomes unavailable for plants are discussed in paragraphs 55 to 66.

50. Most of the ^{90}Sr fallout into the oceans is still present in the well mixed layer above the thermocline. Noshkin and Bowen (193), from measurements in the north and south Atlantic oceans, estimated that only about 1 per cent of the ^{90}Sr has reached the bottom sediments. In the open ocean, activity concentrations are about 0.2 pCi l^{-1} in the surface layer and smaller by a factor of at least 30 below the thermocline. In coastal areas and estuaries concentrations may be a factor of 5 higher.

51. Strontium-90 is taken up by marine biota, and becomes incorporated into the marine food chain. A number of determinations of the concentration factors have been performed in recent years for various marine biota by measurements of stable and radioactive strontium under laboratory and field conditions (63, 93, 191, 214, 240). Typical values are 100 for algae, 2-10 for crabs and lobster and about 1 for the muscle meat of fish. The amount in fish does not contribute greatly to the intake of ^{90}Sr by man. It is estimated that only about 3 per cent of the ^{90}Sr intake by man in Japan between 1966 and 1971 came from fish (240).

3. Levels in food

52. The annual average $^{90}Sr/Ca$ quotients in milk and in the whole diet from 1966 onwards are shown in tables 4 and 6. Values for earlier years are given in earlier reports of the Committee. Typically, levels in milk fell by about 30 per cent between 1970 and 1974. Data so far available indicate that levels in 1975 are about the same as those reported in 1974. Table 5 gives the annual average $^{90}Sr/Ca$ quotients in milk of some countries of the north temperate zone for the period 1955-1975. The numbers in the right-hand column of table 5 are the averages of the available data for each year. It can be seen that this average in 1975 is about 20 per cent of that prevailing during the peak years of 1963 and 1964.

TABLE 5. ANNUAL AVERAGE $^{90}Sr/Ca$ QUOTIENT IN MILK BY COUNTRY OR AREA
North temperate zone, 1955-1975
(pCi (gCa)$^{-1}$)

											United States				
Year	*Belgium*	*Canada*	*Denmark*	*Finland*	*France*	*Germany, Fed. Rep. of*	*Netherlands*	*Switzerland (eastern)*	*USSR (Moscow)*	*United Kingdom*	*Entire country*	*Chicago*	*New York City*	*Salt Lake City*	*Mean*
1955						3				4					3.5
1956						4				6					5.0
1957						8				6			5	4	5.3
1958						6				7		7	8	4	6.2
1959			9			8			8	10		7	11	6	8.6
1960			5	7		6			6	6		8	8	6	6.6
1961			4	6		6			4	6	7	6	7	4	5.6
1962			10	13		10	9		13	12	11	9	12	8	10.8
1963		26	24	22		27	25	27	23	26	19	17	26	19	23.3
1964		28	25	23		28	22	27	18	28	19	16	23	23	23.3
1965		19	17	18	24	21	17	23	14	19	14	12	19	17	18.2
1966	13	13	9	13	19	16	15	15	15	12	11	9	12	10	13.0
1967	9	10	8	10	14	11	9	9	8	9	9	8	10	5	9.2
1968	8	8	7	9	12	9	8	7	5	8		8	9		8.5
1969	9	9	6	8	9	9	7	7	5	7		6	9		7.8
1970	6	9	8	7	8	8	6	8	7	6			8		7.2
1971	6	8	7	7	9	8	5	9	7	6			8		7.2
1972	5	7	5	6	8	7	5	7	6	5			6		6.2
1973			4	5	6	6		5	5	4			5		5.2
1974			4	5	6	6		5		3			5		5.0
1975			4			5				3			5		4.3

TABLE 6. STRONTIUM-90 AND CAESIUM-137 IN TOTAL DIET

Country or area	$^{90}Sr/Ca$ quotient (pCi $(gCa)^{-1}$)										^{137}Cs daily intake (pCi)										Reference
	1966	1967	1968	1969	1970	1971	1972	1973	1974	1975	1966	1967	1968	1969	1970	1971	1972	1973	1974	1975	
Northern hemisphere																					
Austria	25	15	15	14							135	53	60	51							59
Denmark	14	10	8	8	7	8	8	6	7	6	79	44	39	38	32	38	31	15	18	18	2
Egypt	45		13																		157, 158
Faroe Islands	33	22	23	17	20	15	13	12	10	10	496	480	502	403	384	202	191	316	239	281	3
Finland	21										260										132
France (1)	22	19	17	15	15	14	13	10	11	9											76
France (2)			21	20	18	18	16	13	12	12			38	34	37	37	31	15	16	14	96, 198, 222
Germany, Fed. Rep. of	26	18	15	14	11	13	11	9	11	8	123	77	40	36	28	53	27	18	17	16	52, 54
Greenland	15	9	7	8	6	8	9	6	5	6	89	297	346	61	137	51	55	71	54	29	4
India	12	28	10								6				3	20					145, 172
Japan (urban)	24	18	19	21	15	12		12	9	9	20	14	13	14	9	8		7	10	7	8, 174
Netherlands	20	14	12	11	9	8	8				90	50	32	28	24	22	14				168, 169
Norway	38										420										132
Sweden	22										132	88	71	65	58	50					132, 156, 233
USSR (urban)	41	30	27	21	23	23	21	19			145	93	56	38	38	47	34	29			45, 257, 261, 262, 263
United States																					
Country average	16	12									55	30	34	28	25	24	17	11			47, 104, 125, 247
Alaska	29	26																			247
Hawaii	10	6									65	35									247
New York City	17	16	14	12	12	13	11	10	9	8											30, 36
San Francisco	6	6	4	4	4	4	4	3	3	3											30, 36
Southern hemisphere																					
Argentina	7	7	5	6	5	5	5	4	3	3		24	19	18	17	17	15	13	11	4	21, 70, 71
Australia	7	6	5	5	6	7	6	5	4	4											9, 11, 91, 92, 99, 180

53. The annual values of the ratio of the ^{90}Sr/Ca quotient in the total diet to that in milk are shown in table 7. Bennett (30, 36) has investigated the relative contributions that different foods make to the ^{90}Sr intake in New York and San Francisco. The results for New York are shown in figure VI, which presents the ^{90}Sr/Ca quotient in various components of the diet. Aarkrog and Lippert (2) have reported similar results for the Danish diet, some of which are plotted in figure VII. When expressed as ^{90}Sr/Ca quotients, the peak values recorded for fruit, vegetables and grain products are about 50 pCi $(gCa)^{-1}$, for milk products they are about 50 per cent of that, for meat, fish and eggs, only about 20 per cent. It is also notable that the ^{90}Sr/Ca quotient in milk products and meat reaches a peak during periods of high fallout rate and then decreases rapidly over the next 5-8 y, while for fruit and vegetables it remains higher for longer periods of time. It is expected, therefore, that the long-term variation of the ^{90}Sr intake with time would depend on the composition of the diet.

TABLE 7. RATIO OF THE ^{90}Sr/Ca QUOTIENT IN THE TOTAL DIET TO THAT IN MILK

Country	*1963*	*1964*	*1965*	*1966*	*1967*	*1968*	*1969*	*1970*	*1971*	*1972*	*1973*	*1974*	*1975*	*Mean for 1963-1975*
Argentina	1.8	1.5	1.3	1.4	1.4	1.3	1.5	1.3	1.3	1.3	1.3	1.5	1.3	1.4
Australia	1.1	1.0	0.9	1.0	1.2	1.3	1.0	1.0	1.1	1.1	1.1	1.1	1.1	1.1
Denmark	1.3	2.0	1.6	1.5	1.3	1.2	1.4	0.9	1.2	1.6	1.7	1.8		1.5
Finland			1.8	1.6										1.7
France				1.2	1.3	1.4	1.3	1.3	1.3	1.3	1.6	1.8	1.5	1.4
Germany, Federal Republic of	1.8	1.6	1.6	1.7	1.6	1.6	1.5	1.5	1.8	1.7	1.6	1.8	1.7	1.7
India (Bombay)[a]		1.7	2.9	2.1	6.9	2.7								3.3
Japan	2.1	2.2	2.3	2.2	2.3	2.7	4.2	3.0	3.1		3.2	2.6	3.0	2.7
Norway			1.3	1.4										1.3
Sweden			1.4	1.5										1.4
USSR	2.3	3.1	3.7	3.4	3.0	3.0	2.6	3.3						3.1
United Kingdom	0.9	0.9	1.0											0.9
United States														
Hawaii	1.6	2.2	3.5	2.5	2.0									2.4
New York City	1.1	1.3	1.2	1.4	1.6	1.6	1.3	1.5	1.6	1.8	1.9	1.9	1.6	1.5

[a] Since most of the wheat and rice is imported, the diet data do not reflect the local fallout levels.

54. Aarkrog and Lippert (2) have reported that the ^{90}Sr/Ca quotients in potatoes, cabbage and carrots grown in Denmark have not diminished greatly since 1963, whereas in milk it has fallen by a factor of five. On the other hand, Mukhin (182) has reported results on the ^{90}Sr concentrations of potatoes and cabbage grown in the Union of Soviet Socialist Republics, which have fallen by a factor of about five between 1963 and 1969. Borisov *et al.* (45) have reported that cereals have consistently been the major contributor of ^{90}Sr in the USSR diet; this would account for the fact that the ^{90}Sr/Ca quotient in total diet and also the ratio of total diet ^{90}Sr/Ca to that of milk is higher in the USSR than in other countries having high-milk diets.

4. Transfer of ^{90}Sr from fallout to diet

55. Transfers between two successive steps in the sequence linking input into the environment to the resulting dose commitment can be described by transfer factors, defined as the quotient of the infinite time-integrals of the quantities considered for each step (see Annex A). In the transfer model used by the Committee in the 1969 and 1972 reports (244, 245), which is outlined in paragraph 2 of this Annex, the transfer factor from fallout to diet is given by

$$P_{23} = \frac{\int_{-\infty}^{\infty} C(t)\,dt}{\int_{-\infty}^{\infty} f(t)\,dt} \qquad (1)$$

where $C(t)$ is the ^{90}Sr/Ca quotient in the diet at time t, and $f(t)$ is the deposition density rate of ^{90}Sr at time t.

56. If the values of $C(t)$ and $f(t)$ are assessed as averages for discrete intervals of time h, equation 1 becomes

$$P_{23} = \frac{\sum_{i=-\infty}^{\infty} hC(i)}{\sum_{i=-\infty}^{\infty} hf(i)} = \frac{\sum_{i=-\infty}^{\infty} C(i)}{\sum_{i=-\infty}^{\infty} f(i)} \qquad (2)$$

Equation 2 can be reformulated to take account of the determinations of the ^{90}Sr/Ca quotient in individual components of the diet. If the fractional contribution of component j of the diet to the total dietary calcium is W_j, and the ^{90}Sr/Ca quotient in that component is $C_j(i)$, then

$$P_{23} = \sum_j W_j \frac{\sum_{i=-\infty}^{\infty} C_j(i)}{\sum_{i=-\infty}^{\infty} f(i)} = \sum_j W_j P_{23}^j \qquad (3)$$

where P_{23}^j is the transfer factor from fallout to diet component j.

57. In the 1969 and 1972 reports of the Committee (244, 245), the ^{90}Sr/Ca quotient in a diet component was related to the past and present deposition density rate $f(\tau)$, by the expression

$$C_j(t) = \int_{-\infty}^{t} K_j(t-\tau) f(\tau)\,d\tau \qquad (4)$$

where K_j is a transfer function defined by this equation. If both $C_j(t)$ and $f(\tau)$ are given as averages over discrete

intervals of time of duration h, the time becomes $t = nh$, and equation 4 is equivalent to

$$C_j(nh) = \sum_{m=-\infty}^{n} hK_j(nh-mh)\,f(mh) = \sum_{l=0}^{\infty} hK_j(lh)\,f(nh-lh) \quad (5)$$

The transfer factor P^j_{23} can be obtained from the transfer function K_j by the relation

$$P^j_{23} = \sum_{l=0}^{\infty} hK_j(lh) \quad (6)$$

where, in practice, the time interval h is 1 y, because most of the determinations of ^{90}Sr in food have been reported on a calendar-year basis.

58. Several transfer functions between fallout and diet components have been tried in regression analyses of reported data. In the 1972 report of the Committee (245) the following function was used:

$$C_j(i) = h^j_1 f(i) + h^j_2 f(i-1) + h^j_3 \sum_{m=1}^{\infty} e^{-\mu m} f(i-m) \quad (7)$$

In this equation, $f(i)$ is the annual deposition density in the year considered, $f(i\text{-}1)$ is the annual deposition density in the previous year, and the summation is carried out over the deposition of all preceding years, each weighted by an exponential term describing the combined physical decay of ^{90}Sr and any decrease in the availability to plants of ^{90}Sr in soil. The factors b^j_1, b^j_2 and b^j_3, and the effective mean life of available ^{90}Sr, μ^{-1}, can be derived from reported data by regression analysis.

59. In the past, this transfer function was found to be adequate for predicting ^{90}Sr/Ca quotients in milk. By allowing each of the parameters b_1, b_2, b_3 and μ to vary in a regression analysis, Bennett (30, 36) has fitted equation 7 to five New York City diet components (milk products; cereals; meat, fish and eggs; fruit; and vegetables) and also to the same five components of the Danish diet (22). The results are shown in the continuous curves in figures VI and VII for New York and Denmark respectively. The factors obtained from this regression analysis are shown in tables 8 and 9 (22). The estimated transfer coefficients for each individual diet component P^j_{23} in the two sets of Danish data are in reasonably good agreement with each other, especially taking into account that the definitions of the components are not the same in the two cases. Also shown in these two tables are values of P_{23} for the total diet, estimated from a regression analysis with the total composite diet data. The 95% confidence limits on P_{23} are 4.3 and 6.4 pCi y (gCa)$^{-1}$ per mCi km^{-2}.

TABLE 8. PARAMETERS OF THE TRANSFER FUNCTION BETWEEN ^{90}Sr FALLOUT AND DIET

Obtained by regression analysis from New York City data

Parameter[a]	*Milk products*	*Grain products*	*Meat, fish, eggs*	*Vege-tables*	*Fruit*	*Total composite diet*
b_1	0.69	0.86	0.004	0.96	1.36	0.90
b_2	0.21	1.91	0.17	0.37	0.00	0.54
b_3	0.20	0.30	0.31	1.03	0.90	0.36
μ	0.14	0.13	0.28	0.07	0.03	0.10
P^j_{23}	2.23	4.92	1.13	15.45	30.46	4.87
W_j	0.582	0.179	0.111	0.089	0.039	1.0
$W_jP^j_{23}$	1.30	0.88	0.13	1.38	1.19	4.87
Total diet P_{23}			4.88			4.87

[a]The unit for parameters b_1, b_2, b_3, is pCi (gCa)$^{-1}$ per mCi km^{-2}. The unit for parameter μ is y^{-1}. The unit for the transfer factor P^j_{23} is pCi y (gCa)$^{-1}$ per mCi km^{-2}. W_j is the fractional contribution of component j to the total Ca diet.

TABLE 9. PARAMETERS OF THE TRANSFER FUNCTION BETWEEN ^{90}Sr FALLOUT AND DIET

Obtained by regression analysis from Danish data

Parameter[a]	*Milk products*	*Grain products*	*Meat, fish, eggs*	*Vege-tables*	*Fruit*	*Total composite diet*
b_1	0.98	0.98	1.90	2.37	10.04	1.07
b_2	0.46	2.49	0.45	0.00	0.50	1.22
b_3	0.23	0.02	0.28	0.90	0.45	0.19
μ	0.13	0.02	0.12	0.06	0.02	0.10
P^j_{23}	3.12	4.34	4.61	16.50	32.59	4.01
W_j	0.44	0.48	0.02	0.05	0.01	1.00
$W_jP^j_{23}$	1.37	2.08	0.09	0.83	0.33	4.01
Total diet P_{23}			4.70			4.01

[a]The unit for parameters b_1, b_2, b_3, is pCi (gCa)$^{-1}$ per mCi km^{-2}. The unit for parameter μ is y^{-1}. The unit for the transfer factor P^j_{23} is pCi y (gCa)$^{-1}$ per mCi km^{-2}. W_j is the fractional contribution of component j to the total Ca diet.

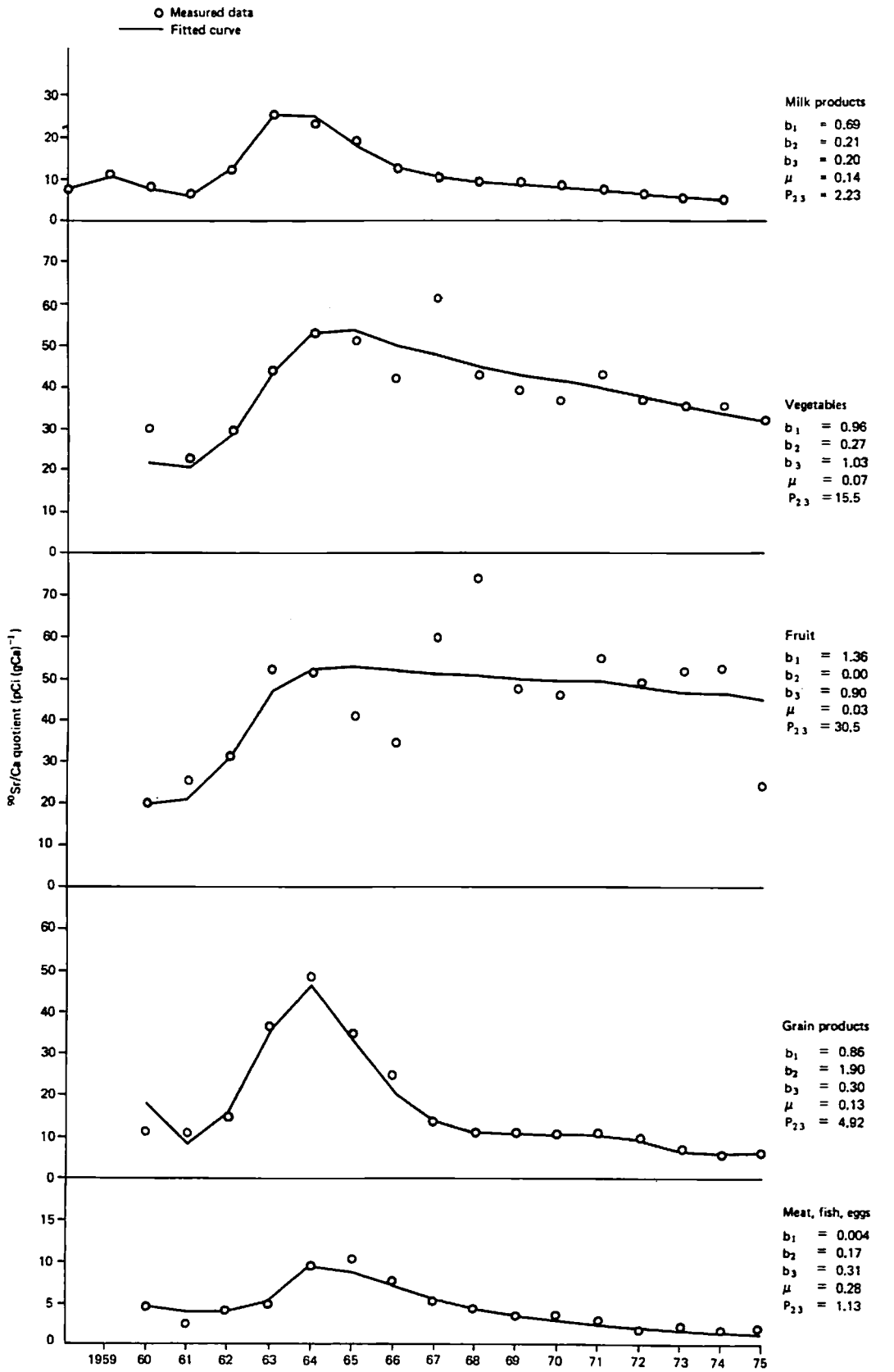


Figure VI. Variation of ^{90}Sr in various diet components in New York City, 1959-1975. The unit for the parameters b_1, b_2, b_3 is pCi $(gCa)^{-1}$ per mCi km^{-2}. The unit for parameter μ is y^{-1}. The unit for the transfer factor P_{23} is pCi y $(gCa)^{-1}$ per km^{-2}.

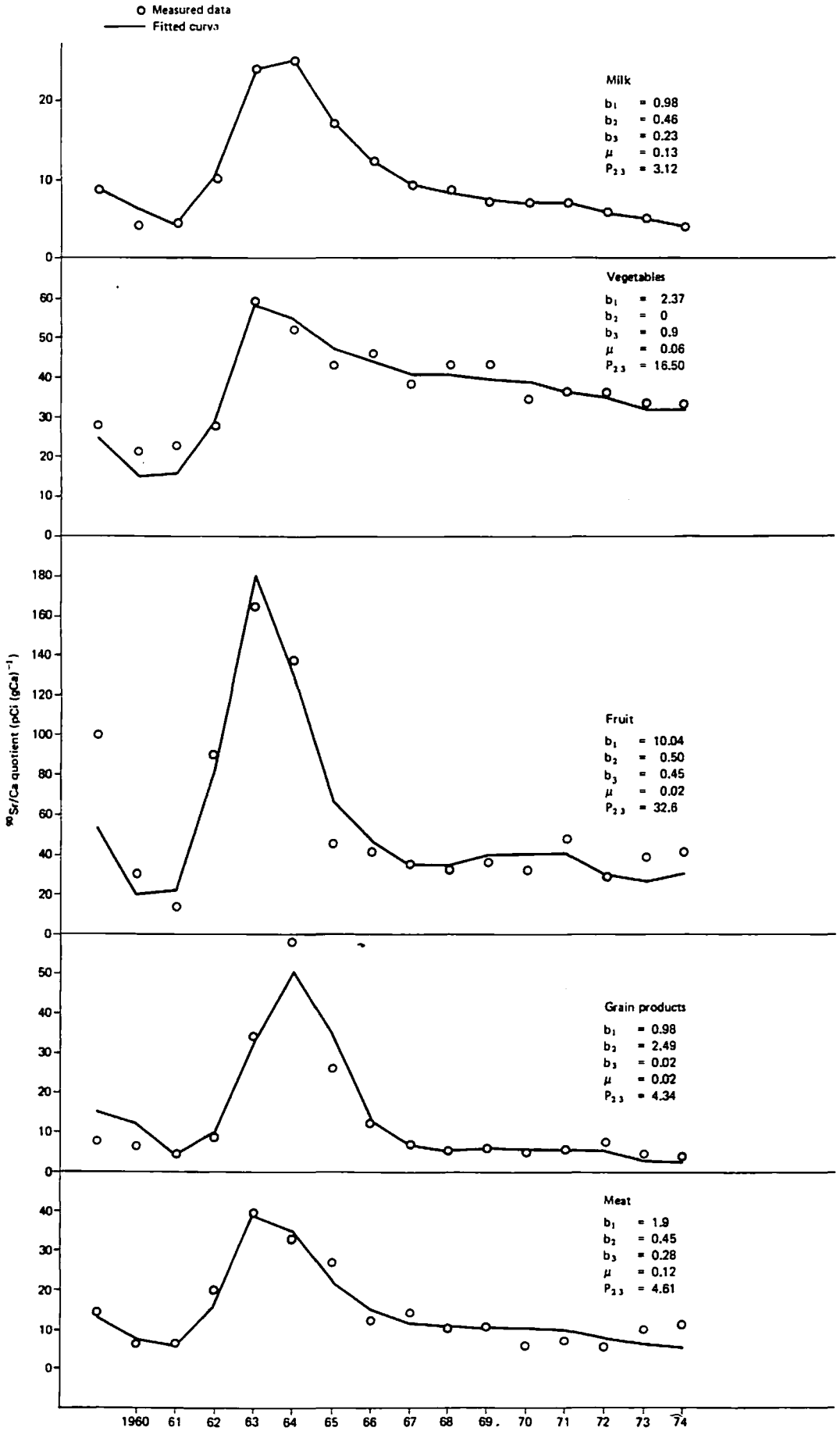


Figure VII. Variation of ^{90}Sr in various diet components in Denmark, 1960-1974. The unit for the parameters b_1, b_2, b_3 is pCi (gCa)$^{-1}$ per mCi km^{-2}. The unit for parameter μ is y^{-1}. The unit for the transfer factor P_{23} is pCi y (gCa)$^{-1}$ per mCi km^{-2}.

60. The total diet transfer coefficient P_{23} is given in terms of the transfer factor for each component in equation 3. The contribution from component j is $W_j P_{23}^j$, where W_j is the fractional contribution of component j to the total dietary calcium intake. To compare the relative contribution of different diet components to the ^{90}Sr intake, it is necessary to compare the products $W_j P_{23}^j$, which are also given in tables 8 and 9. The values of the total diet transfer factor P_{23} estimated from the different dietary components using equation 3 agree with those estimated from the composite total diet, both for New York and for Denmark. Milk products appear to contribute about 30 per cent P_{23} in both places. Meat, fish and eggs contribute only to a small extent. In Denmark grain products contribute about 45 per cent of the intake, in New York, only about 17 per cent. Fruit and vegetables contribute about 54 per cent of ^{90}Sr intake in New York, but only 24 per cent in Denmark.

61. These differences reflect not only different annual intakes for each foodstuff, but also different agricultural practices and soil conditions. In general, it may be said that ^{90}Sr in the diet comes mainly from milk products, grain products, fruit and vegetables. Most of the ^{90}Sr from grain products is received during the years of heavier fallout; in the case of milk about 40 per cent is received during the years of fallout and the rest over some 8 y afterwards. For fruit and vegetables, most of the contribution seems to be delivered over a period of 12-14 y after deposition. This pattern is consistent with observations in the Federal Republic of Germany, where lettuce, cabbage, citrus fruits and potatoes showed little change in activity concentration between 1963 and 1967 (53).

62. A similar analysis of the reported ^{90}Sr data for the individual components of the Argentine and Australian diets has been carried out (22). Since the deposition density rate of ^{90}Sr did not peak so sharply in the southern hemisphere, the estimates of parameters obtained by fitting the dietary ^{90}Sr data are probably less precise. However, differences are evident when these values are compared with the comparable ones derived from the New York and Danish data. For Argentina, the values obtained for P_{23} were (unit: pCi y (gCa)$^{-1}$ per mCi km^{-2}): 6.49 for the composite diet, 6.00 from analysis of separate dietary components. The greatest contribution came from cereals and milk products. For Australia, a value of 7.47 was obtained from the composite diet and 10.7 from an analysis of individual dietary components. The greatest contribution also came from cereals and milk products.

63. From the above analysis of diets in two countries in the southern hemisphere it appears that the transfer factors between fallout and diet are about twice as great as those for countries in the northern hemisphere with similar diets. That is consistent with the observation that concentrations of ^{90}Sr in human bone from these southern latitudes are not substantially lower than those at similar latitudes in the northern hemisphere, even though the integrated deposition density of ^{90}Sr has been only about one fourth of that in the northern hemisphere.

64. There are as yet insufficient data to predict what contribution fruit and vegetables will make to the transfer factors for diets with little or no milk products. There is also the possibility, as suggested by Borisov *et al.* (45), that the strontium and calcium present in different components of the diet are not equally available.

65. Equation 7 has been fitted by regression analysis to the milk and fallout ^{90}Sr data from several regions in the world. The resulting parameters are shown in table 10, and the fitted and measured ^{90}Sr levels in milk are shown in figure VIII for the Faroe Islands, Norway and San Francisco (22). The fallout-to-milk transfer factor, P_{23}^{milk}, for the Faroe Islands is about twice as large as in other countries.

TABLE 10. PARAMETERS OF THE TRANSFER FUNCTION FROM ^{90}Sr FALLOUT TO MILK

Obtained by regression analysis of data for various countries and areas

Parameter[a]	Argentina	Australia	Denmark	Faroe Islands	Norway	San Francisco	United Kingdom	United States	Northern hemisphere
b_1	1.36	1.69	0.98	2.72	0.70	0.61	0.89	0.87	0.87
b_2	0.85	1.18	0.46	1.28	0.44	0.61	0.47	0.23	0.45
b_3	0.22	0.43	0.23	0.90	1.02	0.19	0.15	0.31	0.23
μ	0.16	0.09	0.13	0.23	0.33	0.19	0.13	0.20	0.12
P_{23}^{milk}	3.43	7.44	3.12	7.48	3.74	2.13	2.44	2.50	3.13

[a] The unit for parameters b_1, b_2, b_3 is pCi (gCa)$^{-1}$ per mCi km^{-2}. The unit for parameter μ is y^{-1}. The unit for the transfer factor P_{23}^{milk} is pCi y (gCa)$^{-1}$ per mCi km^{-2}.

66. A representative value of P_{23} for dose commitment calculations can be derived from regression analysis of fallout and total diet data. However, only for a few localities is this combined information available for sufficiently long periods. The average of the values of P_{23} found with this procedure with the data from Argentina, Australia, Denmark and New York, is 5.7 pCi y (gCa)$^{-1}$ per mCi km^{-2}. As already discussed, P_{23} can also be assessed by estimating first the $P_2^j{}_3$ and then applying equation 3. The average of the values for Denmark and New York, estimated by this procedure, is 4.8 pCi y (gCa)$^{-1}$ per mCi km^{-2}. It should be noted that both estimated values of P_{23} apply to areas of high-milk diets.

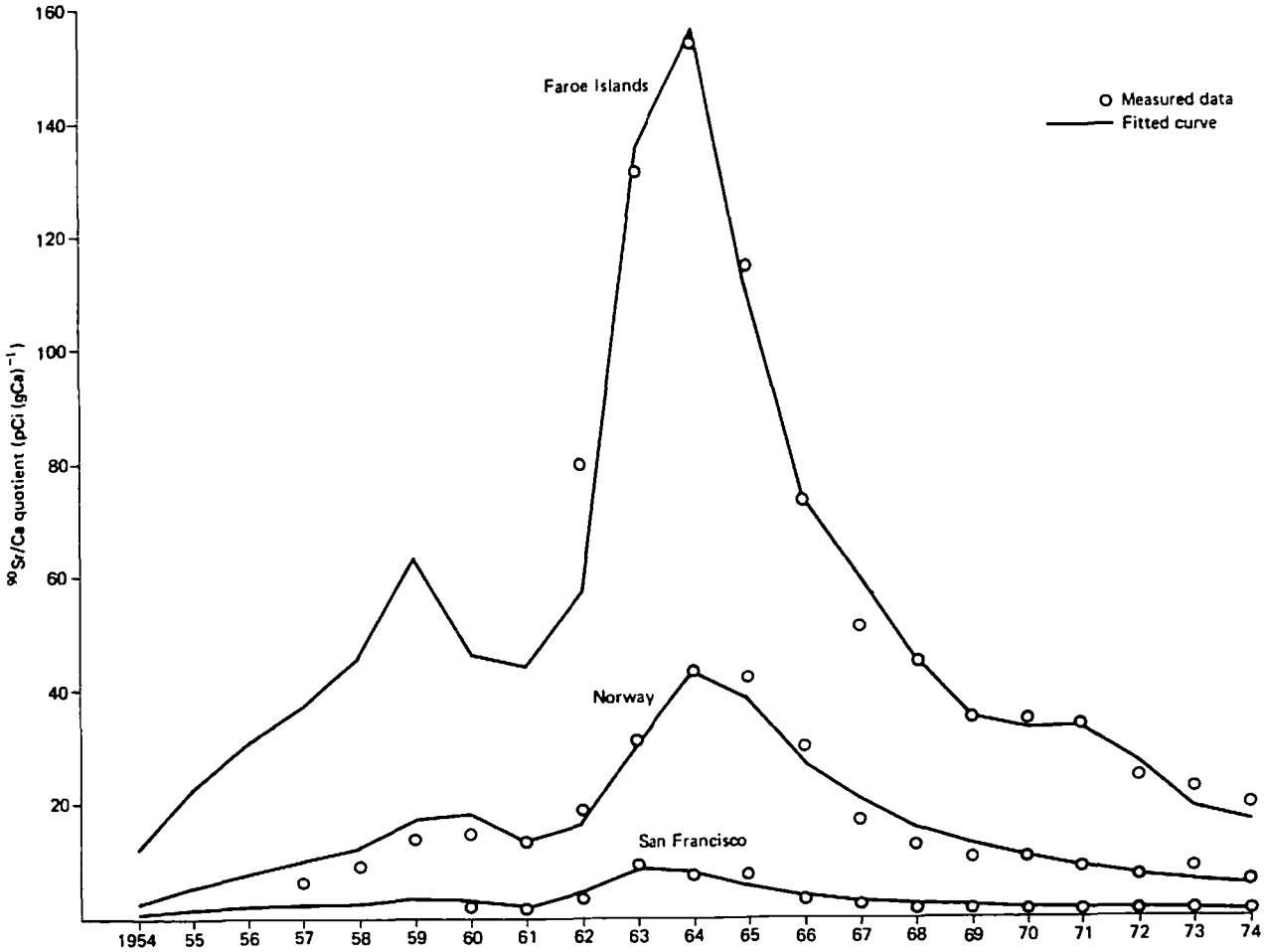


Figure VIII. Variation of ^{90}Sr in milk in the Faroe Islands, Norway and San Francisco, 1954-1974 (22)

67. A less direct procedure for estimating the value of P_{23} is to assess P_{23}^{milk} by regression analysis and then multiply this value by the ratio of the ^{90}Sr/Ca quotient in total diet to that in milk. This procedure is more uncertain because it requires the assumption that the diet-to-milk ratio would remain unchanged at the value observed in the past. On the other hand, the procedure makes it possible to estimate P_{23} for more regions, because of the availability of long series of milk measurements. The range of the values of P_{23}^{milk} given in table 10, in pCi y (gCa)$^{-1}$ per mCi km^{-2}, is 2.1-7.4, with an average of 3.3. This value, multiplied by an estimated average diet-to-milk ratio of 1.4, gives a value of 4.6 for the P_{23} factor in areas of high-milk diet.

68. Estimates of P_{23} are strongly dependent on the value of μ, the inverse of the effective mean life of available ^{90}Sr. The effect of this parameter is exemplified by calculations of P_{23} using the average values of b_1, b_2 and b_3 of table 10 and a diet-to-milk ratio of 1.4, and with μ varying over the range defined by the highest value of table 10 (0.33 y^{-1}) and the value used in the 1966 and 1969 reports of the Committee (243, 244), which most probably is an underestimate (0.05 y^{-1}). These calculations give values of P_{23} in the range of 3-10 pCi y (gCa)$^{-1}$ per mCi km^{-2}. As noted in paragraph 59, the 95% confidence limits on the estimated value of P_{23} for the New York diet are 4.3 and 6.4 pCi y (gCa)$^{-1}$ per mCi km^{-2}.

69. For the purpose of assessing dose commitments from ^{90}Sr for the world population a value for P_{23} of 5 pCi y (gCa)$^{-1}$ per mCi km^{-2} is used in this report. This value gives adequate representation of areas of high-milk diet in the northern hemisphere; but it underestimates P_{23} for at least some areas of high-milk diet in the southern hemisphere. It could also underestimate P_{23} for other diets, including those for which there are no direct assessments. From the diet-to-milk ratios of table 7, weighted by the sizes of the populations with high-milk diets and low-milk diets, it can be shown that the above value for P_{23} could lead to underestimates of the dose commitment by a factor not exceeding two for populations with low-milk diets.

5. Strontium-90 levels in bone

70. New data on the ^{90}Sr/Ca quotient in bone are shown in table 11. Only a few data are available for 1974 and 1975, but in general they are slightly less than those observed in 1971-1972. Table 12 gives the ^{90}Sr/Ca quotients in adult vertebrae for some countries in the northern hemisphere from 1962 to 1974. For the most part the differences in the results are small, the values for adult vertebrae lying between 1 and 2 pCi (gCa)$^{-1}$. The values for Nepal and Norway seem to be significantly higher than the others.

TABLE 11. STRONTIUM-90/Ca QUOTIENT IN HUMAN BONE BY COUNTRY AND AGE

(The number in parentheses is the number of samples)

(pCi (gCa)$^{-1}$)

Country	Year	Age (y)								Adult bone type[a]	Reference
		Newborn or stillborn	< 1	1	2	3	4	5-19	> 19		
					Northern hemisphere						
Canada	1968	3.2 (8)	4.1 (86)	4.8 (17)	4.3 (16)	4.4 (12)	5.8 (4)	3.8 (59)	2.7 (38)	V	
	1969	2.5 (6)	4.0 (47)	5.0 (5)	5.1 (5)	4.4 (4)	4.2 (8)	3.3 (48)	2.2 (37)	V	
Czechoslovakia	1966	2.2 (30)	3.3 (63)	3.5 (9)	3.3 (8)	3.8 (11)	3.0 (5)	2.9 (59)	1.8 (103)	V	245
	1967	1.6 (31)	2.8 (91)	4.1 (20)	3.8 (12)	2.9 (12)	2.9 (9)	2.8 (63)	1.9 (122)	V	
	1968								1.7 (54)	V	
	1969			3.2 (23)	2.3 (9)	2.8 (10)	3.0 (10)	2.4 (59)	1.8 (62)	V	
	1970	1.2 (12)	2.2 (14)	2.7 (11)	3.8 (9)	3.1 (4)	2.8 (5)	2.6 (32)	1.8 (106)	V	48
	1971	1.0 (22)	1.9 (16)	2.2 (7)		1.7 (6)	1.3 (22)	2.0 (53)	1.5 (86)	V	
	1972								1.6 (54)	V	49
	1973								1.4 (43)	V	
Denmark	1969	1.2 (19)	1.7 (33)	2.4 (3)		2.1 (1)	1.8 (3)	1.9 (36)	1.3 (27)	V	245
	1970	0.9 (18)	1.9 (26)	1.9 (4)	1.9 (4)	1.7 (4)	0.8 (1)	1.5 (31)	1.3 (49)	V	
	1971	1.1 (5)	2.7 (14)	4.5 (1)	3.3 (2)	3.3 (1)	2.0 (6)	2.2 (40)	1.7 (36)	V	
	1972	1.9 (16)	2.4 (16)	2.2 (1)		3.1 (3)	1.4 (1)	1.8 (30)	1.6 (14)	V	
	1973	1.9 (5)	2.0 (3)	0.8 (5)	1.4 (5)	3.2 (6)		1.6 (38)	1.5 (71)	V	2
	1974	1.3 (3)			1.8 (38)			1.4 (39)	1.4 (104)	V	
	1975	1.3 (1)			2.0 (13)			1.5 (32)	1.5 (85)	V	
Egypt	1968								0.4 (7)	V	245
	1969							0.1 (8)	0.2 (14)	V	
Fiji	1974								1.0 (12)	V	121
France (1)	1967	1.9 (5)	3.7 (53)	5.3 (10)	5.0 (5)		4.0 (1)	3.5 (41)	2.2 (55)	V	
	1968	1.6 (60)	3.2 (102)	4.4 (13)	3.7 (9)	3.9 (4)	3.8 (6)	2.8 (38)	2.3 (88)	V	245
	1969	1.6 (25)	3.2 (87)	3.7 (15)	3.1 (12)	3.6 (5)	3.0 (6)	2.8 (54)	2.0 (105)	V	
	1970	1.6 (37)	2.7 (73)	2.9 (15)	2.6 (11)	3.2 (6)	2.3 (15)	2.1 (42)	1.9 (132)	V	139
	1971	1.6 (54)	2.4 (67)	2.9 (16)	2.1 (9)	2.6 (3)	3.8 (3)	2.3 (32)	1.8 (153)	V	76
	1972	1.2 (29)	2.1 (33)			2.1 (11)		2.0 (31)	1.6 (93)	V	
	1973	1.08 (23)	1.7 (36)			1.8 (18)		1.6 (10)	1.5 (109)	V	
France (2)	1967								1.7 (55)	R	245
	1968								1.0 (45)	R	
	1969								1.3 (61)	R	
	1970								1.2 (18)	R	

Country	Year	Age (y)								Adult bone type[a]	Reference
		Newborn or stillborn	< 1	1	2	3	4	5-19	> 19		
Federal Republic of Germany	1968	1.2 (159)	2.4 (25)			2.8 (17)		2.5 (34)	1.8 (64)	R, S, V	245
	1969	1.1 (98)	1.9 (14)			2.3 (10)		2.0 (21)	1.7 (40)		
	1970	1.0 (94)	1.6 (112)			2.0 (12)		1.8 (21)	1.7 (36)		55
	1971	1.0 (30)	1.3 (4)			2.1 (4)		1.9 (6)	1.6 (12)		
India	1973							0.9 (1)	0.9 (10)	V	122
	1975								2.3 (12)		120
Jamaica	1970								0.9 (21)	V	245
Japan	1967		3.9 (2)	3.8 (2)	3.3 (2)	2.5 (1)	2.1 (1)	2.5 (21)	0.4 (1)	C	
	1968	1.1 (12)	2.0 (31)	3.2 (10)	2.3 (4)	2.3 (3)	1.8 (3)	2.1 (47)	0.6 (13)	C	
	1969	0.7 (30)	1.5 (15)	2.1 (5)	2.6 (7)	1.5 (7)	0.6 (1)	1.4 (26)	0.7 (12)	C	
	1970	0.7 (23)			2.5 (1)		2.0 (3)	1.7 (14)	1.2 (6)	C	
	1971	0.8 (37)			1.8 (4)			1.2 (20)	1.3 (2)	C	234
	1972	0.8 (30)	2.1 (9)	2.9 (2)		2.0 (1)	1.1 (1)	1.3 (14)	1.2 (10)	V	235
	1973	0.7 (19)	1.3 (4)	1.5 (1)				1.3 (10)	1.2 (10)	V	
	1974							1.5 (10)	1.1 (24)	V	236
	1975	0.6 (29)						1.4 (5)	1.0 (22)	V	
Nepal	1974								3.0 (12)	V	
	1975	1.9 (2)				2.8 (1)		4.0 (8)	3.5 (30)	V	121
New Guinea	1974								0.5 (12)	V	
Norway	1969	2.6 (38)	3.5 (13)			4.5 (6)		4.7 (9)	3.4 (90)	V	
	1970	2.7 (48)	3.8 (15)			4.1 (7)		4.2 (19)	3.7 (84)	V	
	1971	2.9 (43)	3.4 (26)			3.7 (7)		3.6 (20)	3.3 (46)	V	68
	1972	2.8 (44)	3.1 (15)			4.0 (7)		3.5 (20)	3.5 (77)	V	
	1973	1.6 (55)	2.9 (17)			3.7 (14)		2.5 (20)	2.7 (33)	V	
	1974	1.7 (44)	2.8 (9)			3.2 (11)		2.9 (22)	2.4 (54)	V	67
	1975	1.5 (31)	2.6 (21)			2.1 (10)		2.4 (22)	2.8 (100)	V	100
Senegal	1969								1.0 (12)	V	
	1970								1.3 (24)	V	245
Switzerland	1970								2.5 (47)	V	
	1971								2.2 (26)	V	
	1972								2.4 (45)	V	129
Thailand	1970							0.9 (1)	0.7 (6)	V	
	1971							0.7 (1)	0.5 (5)	V	245
	1973							0.7 (1)	0.5 (10)	V	122

TABLE 11 *(continued)*

Country	Year	Age (y)								Adult bone type[a]	Reference
		Newborn or stillborn	< 1	1	2	3	4	5-19	> 19		
Uganda	1970								1.1 (23)	V	245
USSR[b]	1968	1.7 (81)	2.4 (19)			3.0 (13)		2.2 (224)	1.2 (694)	N	259
	1969	1.5 (103)	2.1 (30)			3.1 (12)		2.0 (288)	1.2 (1 142)	N	260
	1970	1.4 (81)	2.4 (32)			2.9 (35)		3.1 (329)	1.4 (1 249)	N	260
	1971	1.0 (55)	2.3 (7)			2.5 (8)		2.7 (162)	1.3 (867)	N	260
United Kingdom	1968	1.3 (101)	2.9 (27)	3.2 (9)	2.7 (7)	3.4 (4)	2.7 (5)	1.9 (73)	1.6 (34)	V	245
	1969	1.2 (16)	2.6 (46)	2.2 (4)	2.0 (6)	2.3 (10)	2.5 (3)	1.8 (45)	1.5 (32)	[c]	163
	1970	1.2 (21)	2.1 (56)	2.4 (6)	2.4 (9)	2.2 (4)	1.9 (10)	1.6 (38)	1.3 (18)	V	163
United States											
New York	1969		2.6 (23)	2.7 (1)	3.2 (2)	3.6 (1)	2.8 (2)	2.5 (29)	1.7 (25)	V	245
	1970		2.5 (12)	2.8 (1)		2.4 (1)		2.1 (20)	1.6 (52)	V	245
	1971		2.2 (8)	3.3 (1)	1.7 (2)	2.7 (2)	2.0 (3)	2.1 (36)	1.4 (56)	V	24
	1972		1.6 (8)	3.4 (2)	2.9 (1)	2.7 (1)	2.6 (3)	1.8 (33)	1.4 (107)	V	26
	1973		1.6 (15)	3.3 (1)	1.4 (1)	1.9 (1)		1.5 (23)	1.3 (54)	V	31
	1974		1.7 (7)	1.6 (2)	1.6 (1)	1.2 (1)		1.7 (11)	1.2 (72)	V	33
	1975		1.4 (7)		1.6 (1)		1.7 (2)	1.4 (15)	1.1 (42)	V	37
San Francisco	1969		1.4 (80)	1.6 (5)	1.2 (5)	1.5 (4)	1.0 (2)	1.3 (21)	0.9 (80)	V	245
	1970		0.9 (74)	1.7 (5)	0.9 (1)	1.1 (3)	0.9 (1)	1.1 (14)	0.9 (46)	V	245
	1971		0.7 (70)	1.8 (3)	1.2 (1)	1.5 (3)	1.4 (3)	1.1 (11)	0.8 (132)	V	24
	1972		0.7 (83)	0.8 (1)	0.5 (1)	0.8 (2)	0.9 (1)	1.0 (9)	0.8 (119)	V	26
	1973		0.7 (50)	0.8 (1)	1.3 (1)			0.8 (1)	0.8 (69)	V	31
	1974		0.6 (40)	1.1 (1)	0.8 (1)		0.7 (1)	0.7 (8)	0.7 (55)	V	33
	1975		0.5 (36)	0.6 (2)	1.2 (1)		0.7 (6)	0.8 (50)		V	37
Venezuela	1969								0.8 (22)	V	245
	1970								0.8 (23)	V	245
		Southern hemisphere									
Argentina	1969	1.3 (19)	1.4 (29)	1.2 (9)	1.3 (6)	1.3 (9)		1.3 (75)		V	245
	1970	1.4 (9)	1.4 (21)	1.3 (12)	1.5 (10)	1.4 (11)		1.3 (69)		V	245
	1971	1.4 (10)	1.3 (20)	1.3 (15)	1.6 (17)	1.3 (12)		1.2 (75)		V	21
	1972	1.4 (8)	1.3 (21)	1.3 (12)	1.5 (15)	1.3 (13)		1.2 (71)		V	21
	1973	0.97								V	21
	1974	0.95								V	21
	1975	0.9 (8)	1.0 (12)	0.9 (7)	1.0 (4)	1.0 (6)	1.0 (7)	1.0 (12)	1.0 (18)	V	71
	1976	1.0	0.8	1.0	1.0	0.9	1.0	0.9	1.0	V	71
Australia	1968	0.8 (79)	1.5 (98)	2.0 (26)	2.0 (14)	1.9 (8)	2.2 (14)	1.4 (75)	0.9 (75)	V	245
	1969	0.9 (108)	1.4 (98)	1.6 (27)	1.5 (11)	1.6 (7)	1.4 (13)	1.2 (136)	0.9 (112)	V	245
	1970	0.7 (448)	1.4 (182)	1.6 (42)	1.5 (34)	1.2 (20)	1.2 (13)	1.1 (180)	0.9 (246)	V	10

Country	Year	Age (y)								Adult bone type[a]	Reference
		Newborn or stillborn	< 1	1	2	3	4	5-19	> 19		
Australia (continued)	1971	0.8 (413)	1.6 (192)	1.8 (32)	1.6 (27)	1.3 (21)	1.2 (11)	1.1 (162)	0.8 (231)	V	11
	1972	0.8 (398)	1.6 (143)	1.7 (45)	1.8 (19)	1.9 (18)	1.8 (13)	1.2 (128)	1.0 (143)	V	
	1973	0.7 (264)	1.1 (172)	1.5 (27)	1.7 (18)	1.4 (21)	1.3 (16)	1.0 (129)	0.8 (150)	V	13
	1974	0.6 (348)	1.0 (178)	1.3 (25)	1.5 (16)	1.0 (19)	1.2 (4)	1.0 (83)	1.0 (107)	V	
	1975	0.6 (98)	1.0 (55)	1.3 (16)	1.2 (9)	2.2 (5)	1.4 (2)	1.0 (25)	1.0 (21)	V	
Brazil	1969			1.6 (1)	1.2 (1)			1.9 (5)	1.3 (39)	V	245
Chile	1969								1.7 (20)	V	
Indonesia	1970							1.5 (2)	0.7 (4)	V	119
	1971							0.3 (1)	0.4 (3)	V	
	1973							0.4 (1)	0.4 (6)	V	122
South Africa	1966 to 1969		1.1	———	———	1.3	———	2.0	0.5	R	245

[a] V = vertebra, R = rib, S = sternum, C = composite, N = normalized to whole skeleton.
[b] The data up to age of 4 years refer to Moscow only.
[c] Mainly V.

TABLE 12. STRONTIUM-90/Ca QUOTIENT IN ADULT VERTEBRAE BY COUNTRY

Northern hemisphere, 1962-1975

(pCi (gCa)$^{-1}$)

Year	Canada	Czechoslovakia	Denmark	France	Poland	USSR (Moscow)	United Kingdom	United States (New York)	Mean
1962	1.2		0.8		1.4			1.0	1.10
1963	1.7		1.2		1.6	1.7		1.6	1.56
1964	3.1	1.8	2.4		2.5	2.4		2.0	2.37
1965	3.1	2.2	2.7	2.2	2.5	3.1	1.9	2.1	2.47
1966	2.6	1.8	2.6	2.1	2.9	2.7	2.2	2.1	2.37
1967	2.5	1.9	2.1	2.2		2.3	1.6	1.9	2.07
1968	2.7	1.7	1.9	2.3		1.7	1.6	1.9	1.97
1969	2.2	1.8	1.3	2.0		1.7	1.5	1.7	1.74
1970		1.8	1.9			1.4	1.3	1.6	1.53
1971		1.5	1.7	1.8		1.2		1.4	1.52
1972			1.6	1.6				1.4	1.55
1973			1.5	1.5				1.3	1.43
1974			1.4					1.2	1.30
1975								1.1	

6. Transfer from diet to bone

71. The transfer factor linking diet and human bone P_{34} is defined by

$$P_{34} = \frac{\int_{-\infty}^{\infty} Q(t)\,dt}{\int_{-\infty}^{\infty} C(t)\,dt} \qquad (8)$$

where $Q(t)$ is the ^{90}Sr/Ca quotient in bone at time t, averaged over the population, and $C(t)$ is the corresponding quotient in the diet at time t, also averaged over the population.

72. In the 1969 report of the Committee (244) it was shown that if the values of $Q(t)$ and $C(t)$ are evaluated for discrete intervals of time of duration h, they are interrelated by the equation

$$Q(i) = \sum_{m=0}^{\infty} hC(ih-mh)\,K(mh) \qquad (9)$$

where $K(mh)$ is the transfer function discussed in the following paragraph. It is usual for $Q(t)$ and $C(t)$ to be determined for each calendar year, so in practice h has the value of 1 y. Equation 8 can be reformulated as

$$P_{34} = \frac{\sum_{i=-\infty}^{\infty} h \sum_{m=0}^{\infty} hC(ih-mh)\,K(mh)}{\sum_{i=-\infty}^{\infty} hC(ih)} = \sum_{m=0}^{\infty} hK(mh) \qquad (10)$$

73. In the 1972 report (245) several types of transfer function were tried in regression analyses of bone and diet data. The best fits were obtained with a function consisting of a rate term plus an exponential function term, first proposed by Coulon and Madelmont (77), with h = 1 y:

$$K(m) = c\,\delta_m + g \exp(-\mu m) \qquad (11)$$

where the first term is the rate term, accounting for that strontium in bone which is in rapid exchange with the plasma, the second term is the exponential term postulated to represent the values in bone after m years following a single intake, and δ_m is a function such that $\delta_m = 1$ when $m = 0$, and $\delta_m = 0$ when $m \neq 0$.

74. The bone ^{90}Sr/Ca quotients were fitted to the corresponding diet quotients for data taken from Australia, Denmark, New York, San Francisco and also to the average northern hemisphere data, using equation 9 and the transfer function of equation 11 (22). The ^{90}Sr/Ca quotient in the diet for the northern hemisphere was estimated by multiplying the corresponding values for milk (table 7) by 1.4.

75. The values of the parameters obtained by regression analysis are given in table 13, together with estimates of P_{34} obtained by the use of equation 10. Only the parameters for the Danish data have changed substantially since the 1972 report, and they are now more in line with those for other countries. Some comparisons of measured and predicted ^{90}Sr/Ca quotients in bone are shown in figure IX. The estimates of the transfer factor P_{34} vary little from one locality to another. The range of values shown in table 13 is 0.10-0.16, the average being 0.14.

TABLE 13. PARAMETERS OF THE TRANSFER FUNCTION OF ^{90}Sr BETWEEN DIET AND BONE

Obtained by regression analysis from data for various countries and areas

Parameter	*Australia*	*Denmark*	*United Kingdom*	*New York City*	*San Francisco*	*Northern hemisphere*
c (y^{-1})	0.001	0.037	–	0.017	0.021	0.023
g (y^{-1})	0.026	0.018	0.035	0.021	0.024	0.031
μ (y^{-1})	0.22	0.20	0.28	0.28	0.20	0.25
P_{34}	0.13	0.14	0.15	0.10	0.15	0.16

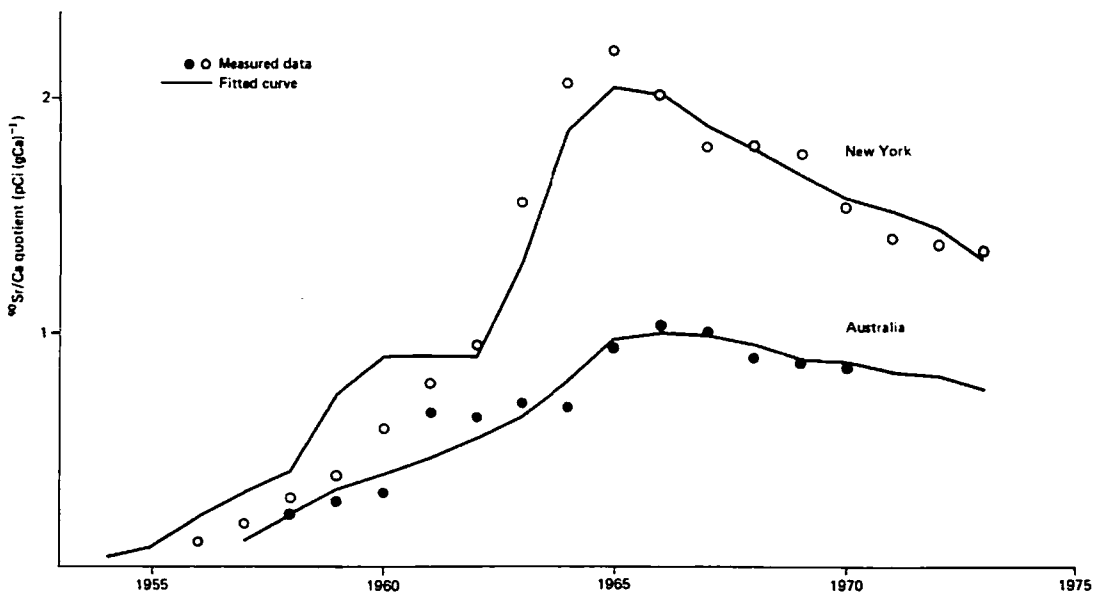


Figure IX. Variation of ^{90}Sr in bone in Australia and New York, 1955-1975

76. To account for the bone ^{90}Sr/Ca quotients in persons of all age groups, Bennett (36) has used an age-dependent transfer function. The ^{90}Sr/Ca quotient in bone at age i and year n, $Q(n, i)$, is postulated to be

$$Q(n,i) = (c_i + g_i)\,C(n,i) + \\ + [Q(n-1, i-1) - c_{i-1}\,C(n-1, i-1)]\,e^{-\lambda i} \qquad (12)$$

where $C(n, i)$ is the ^{90}Sr/Ca quotient in the diet of persons of age i in year n, and c_i and g_i are age-dependent model parameters. Bennet (36) has fitted equation 12 to the New York and San Francisco bone data for all age groups. For children under nine years of age the parameter c_i was found to be zero, consistent with a single exponential transfer model as originally proposed by Rivera (215). The best fit was obtained with a turnover rate of ^{90}Sr varying from about 100 per cent per year down to about 40 per cent per year in the pre-teenage years and then falling with age to about 20 per cent per year for adults. Beninson (18) had reported a similar variation in turnover rate with age from studies in Argentina. The fractional retention of strontium, i.e., the fraction of dietary intake incorporated into the skeleton, was also found by Bennett (37) to vary with age, being five to seven times higher for infants than for adults.

77. As shown in Annex A, the transfer factor of a sequence of steps in series in the compartment model is the product of the transfer factors of each step. The transfer factor of ^{90}Sr between fallout and bone P_{234} can therefore be calculated as $P_{234} = P_{23}\,P_{34}$. Using the

average values estimated for both factors, the P_{234} is calculated to be 0.7 pCi y $(gCa)^{-1}$ per mCi km^{-2}. This value is about 30 per cent higher than the one used in the 1972 report of the Committee, but due to the uncertainties involved in the calculations, this difference is not regarded as significant.

7. Transfer factor relating bone activity level and dose

78. In the compartment model described in paragraph 2, the transfer factor linking tissue radioactivity to tissue dose is P_{45}. The value of this factor for ^{90}Sr can be deduced from the following dosimetric considerations: The dose rate per unit beta activity in a small tissue-filled cavity in bone, $\dot{D}_0$, has been formulated by Spiers (225) as:

$$\dot{D}_0 = N_m \bar{E} (S_T/S_B)_m (K_B/K_T)$$

where $N_m = 1.17\ 10^6\ M^{-1}\ y^{-1}$ per pCi $(gCa)^{-1}$ is the number of beta particles emitted per year and unit mass of bone for each unit of the $^{90}Sr/Ca$ quotient, M being the mass of bone per unit mass of calcium ($M \simeq 5$) (160, 252); $\bar{E}$ is the effective energy of the beta rays emitted (for $^{90}Sr + ^{90}Y$, $\bar{E} = 1.13$ MeV); $(S_T/S_B)_m$ is the ratio of mass stopping powers in tissue and in bone = 1.07 (41), and K_B and K_T are the ratios of the effective range to total track length of beta particles in bone and soft tissue, respectively. They are assumed in this case to be unity (83). The dose-rate factor is therefore $\dot{D}_0 = 4.5$ mrad y^{-1} per pCi $(gCa)^{-1}$.

79. In order to obtain corresponding values for $\dot{D}_m$ and $\dot{D}_s$, the dose rate factors for bone marrow and for bone lining cells, which are the desired P_{45} transfer factors, use can be made of the $\dot{D}_m/\dot{D}_0$ and $\dot{D}_s/\dot{D}_0$ ratios estimated for cortical and trabecular bone by Spiers (226). These values are:

	$\dot{D}_m/\dot{D}_0$	$\dot{D}_s/\dot{D}_0$
Cortical contribution	0.055	0.082
Trabecular contribution	0.260	0.352
Total	0.32	0.43

The transfer factors P_{45} are therefore estimated to be:

P_{45} (marrow) = $(\dot{D}_m/\dot{D}_0)\dot{D}_0$ = 1.4 mrad per pCi y $(gCa)^{-1}$

P_{45} (bone lining cells) = $(\dot{D}_s/\dot{D}_0)\dot{D}_0$ = 1.9 mrad per pCi y $(gCa)^{-1}$.

8. Dose commitment from strontium-90

80. The dose commitment from ^{90}Sr released by nuclear explosions can be assessed using the environmental compartment model described in paragraph 2. The dominant exposure pathway is dietary intake, inhalation being completely negligible in comparison. The dose commitment D^c is related to the integrated deposition density F of ^{90}Sr by the following expression:

$$D^c = P_{234} P_{45} F$$

where P_{234} is the transfer factor linking integrated deposition density and the time-integral of the $^{90}Sr/Ca$ quotient in bone (para. 77) and P_{45} is the transfer factor linking the $^{90}Sr/Ca$ quotient in bone to the dose rate in the bone marrow or in the bone lining cells (para. 79).

81. The integrated deposition density in each hemisphere from all nuclear explosions to the end of 1975 can be calculated by applying the population weighting procedure described in paragraph 47 to the data presented in table 3. The results are (mCi km^{-2}):

	Northern hemisphere	*Southern hemisphere*
Entire hemisphere	56.5	17.6
Temperate zone	85.1	24.5

82. Table 14 presents the dose commitment from ^{90}Sr to the populations of each hemisphere and to the populations of the temperate latitudes of each hemisphere.

TABLE 14. DOSE COMMITMENTS TO BONE TISSUES FROM ^{90}Sr PRODUCED IN ALL NUCLEAR EXPLOSIONS UP TO THE END OF 1975

(mrad)

	Northern hemisphere		*Southern hemisphere*	
Tissue	*Temperate zone*	*Population-weighted average*	*Temperate zone*	*Population-weighted average*
Bone marrow	85	56	24	17
Endosteal cells	116	77	33	24

83. The dose commitments to the world population, calculated from the global mean integrated deposition density given in paragraph 47, are 52 mrad for bone marrow and 71 mrad for bone lining cells. As the total activity of ^{90}Sr released to the environment by nuclear tests is approximately 16 MCi (table 2), the collective dose commitments per unit activity of ^{90}Sr released, assessed by the procedures outlined in Annex A, are approximately 13 man rad Ci^{-1} for bone marrow and 18 man rad Ci^{-1} for bone lining cells, for the geographic pattern of past nuclear tests.

G. STRONTIUM-89

84. Strontium-89 has a half-life of 50.5 d and decays with the emission of a beta particle with maximum

energy of 1.46 MeV. It is one of the main components of fallout activity in the first few months after a nuclear test. It has been extensively measured in fallout since 1961 (111); the latitudinal distribution of the integrated deposition density is shown in table 15.

TABLE 15. LATITUDINAL DISTRIBUTION OF ^{89}Sr INTEGRATED DEPOSITION DENSITY, 1961-1963

Latitude band	*Area of band (10^6 km^2)*	*Relative population of band (%)*	*Integrated deposition density of ^{89}Sr (mCi km^{-2})*
70°-80°N	11.6	~0	34
60°-70°N	18.9	0.4	210
50°-60°N	25.6	12.2	250
40°-50°N	31.5	13.8	326
30°-40°N	36.4	18.2	288
20°-30°N	40.2	29.2	218
10°-20°N	42.8	9.8	121
0°-10°N	44.1	5.6	104
0°-10°S	44.1	5.8	88
10°-20°S	42.8	1.8	9
20°-30°S	40.2	1.6	19
30°-40°S	36.4	1.4	11
40°-50°S	31.5	0.1	11
50°-60°S	25.6	0.05	

Source: Reference 111.

85. Strontium-89 was measured in milk at some 63 cities in the United States between 1962 and 1966 (204). The time-integral of the concentration for this period was 95.5 pCi y l^{-1}. O'Brien (195) has estimated the transfer factor P_{34} linking the time-integrals of the ^{89}Sr/Ca quotient in milk and in human bone. Using the infinite time-integrals of the retention functions for cancellous bone for ^{89}Sr and ^{90}Sr presented in the ICRP alkaline earth metabolic model (160), it was estimated that the transfer factor P_{34}^{milk} for ^{89}Sr is 0.022 of the total diet P_{23} for ^{90}Sr. O'Brien (195) estimated the factor P_{45} for ^{89}Sr to be 0.71 mrad per pCi y (gCa)$^{-1}$, which, using a value of 0.14 for the P_{34} of ^{90}Sr, leads to a combined factor P_{345}^{milk} of 0.0022 mrad per pCi y (gCa)$^{-1}$. With the above time-integral of the ^{89}Sr/Ca quotient in milk, the *per caput* bone-marrow dose in the United States between 1961 and 1966 is estimated to be 0.21 mrad.

86. Relating this value to the relevant integrated deposition density of ^{89}Sr, it is estimated that the bone marrow dose commitment to the population in the temperate zone of the northern hemisphere from all tests up to 1970 is approximately 0.4 mrad.

87. As the ratio of activities $^{89}Sr/^{90}Sr$ at the time of fission is approximately 185 (62), the total atmospheric input of ^{89}Sr is estimated to have been about 2.8 10^9 Ci. The collective dose commitment to the bone marrow per unit activity release of ^{89}Sr, calculated by the procedures outlined in Annex A is approximately 4 10^{-4} man rad Ci^{-1} for the past pattern of nuclear explosions.

H. RUTHENIUM-106

88. Ruthenium-106 has a half-life of 365 days and decays to ^{106}Rh by pure beta decay with a maximum energy of 0.039 MeV. The 30-s half-life ^{106}Rh decays with a maximum beta energy of 3.45 MeV and also emits several gamma rays.

89. The time-integral of the concentration of ^{106}Ru in air can be estimated from that for ^{144}Ce given in table 20. Cerium-144 has a half-life of 285 d, so that the $^{106}Ru/^{144}Ce$ activity ratio will only change with a half-time of about 3.5 y. The ratio of the integrated deposition densities of ^{106}Ru and ^{144}Ce was 0.51 for Chilton, United Kingdom, 1967-1970 (61) and 0.53 for Pittsburgh, United States, 1961-1963 (110), and at Bombay, India, 1966-1969 (102), the ratio of the time-integrals of the activity concentrations in air was 0.38. Assuming a value of 0.50 for the ratio of the time-integrals of the activity concentrations in air of ^{106}Ru and ^{144}Ce, and using the estimates for the latter, time-integral for ^{106}Ru is estimated to be 1.5 pCi y m^{-3} in the northern hemisphere and 0.35 pCi y m^{-3} in the southern.

90. Assuming that the activity is present as an aerosol of about 0.5-μm particle size and using the ICRP lung model (135, 136) with class Y parameters, the transfer factor between activity in air and lung dose P_{145} is estimated to be 27.2 mrad per pCi y m^{-3} for the dose to the pulmonary region of the lung. The resulting dose commitments to the pulmonary region from all tests to the end of 1975 are respectively 41 and 10 mrad in the northern and southern hemispheres.

91. The total injection of ^{106}Ru, assessed from that of ^{90}Sr using the corresponding activity ratio at the time of fission, has been about 3.3 10^8 Ci. Using the procedures described in Annex A, the collective dose commitment to the lung per unit activity of ^{106}Ru released is estimated to be about 0.4 man rad Ci^{-1} for the past pattern of nuclear explosions.

I. IODINE-131

92. Iodine-131 is a beta emitter with a half-life of 8 d, and a maximum beta energy of 0.81 MeV, with the emission of gamma rays of 0.72 and 0.36 MeV and other energies. Due to its short half-life, ^{131}I is present in the long-range tropospheric fallout only shortly after atmospheric detonations. It is unlikely that the clouds of radioactive debris become well mixed during periods comparable to the mean residence time of an aerosol in the troposphere. The concentration of ^{131}I in surface air at a particular location, therefore, will depend strongly on meteorological conditions and will not necessarily be representative of a latitude band or even of a large region.

93. Fresh milk dominates as a source of ^{131}I intake in areas where it is a major diet component, because of the large areas scavenged by the grazing animal and also because of the short storage period of milk. The transfer of ^{131}I from deposition on grass to milk has been estimated from laboratory experiments (97) and from fallout field measurements (17), and varies widely, depending mainly on the density of the herbage and on cattle-feeding practices. Table 16 gives the reported time-integrated concentrations in milk over the period 1966-1974 in a number of countries, mainly in the southern hemisphere, and some 1976 data from France and Japan. The values reported for the southern hemisphere in 1974 were higher than those in 1972 and 1973 and approached the levels observed in the years 1967-1971.

TABLE 16. CONCENTRATION OF ^{131}I IN MILK AND THYROID DOSE TO INFANTS AT VARIOUS LOCATIONS, 1966-1974[a]

Location	Integrated milk concentration (nCi d l^{-1})									Calculated thyroid dose to infants (mrad)								
	1966	1967	1968	1969	1970	1971	1972	1973	1974	1966	1967	1968	1969	1970	1971	1972	1973	1974
Northern hemisphere																		
Japan[b, c]																		
Chiba	0.42	2.75					0.37	0.9		5	32					4	10	
Miyagi								1.2									14	
United Kingdom[b, c]		0.60									7							
United States																		
Sebastian City[c]	9.3									107								
Houston[c]		3.7									43							
Nashville[b, c]							0.90									10		
Southern hemisphere																		
Argentina																		
Bariloche	7.6	1.4							4.9	88	16							56
Buenos Aires	27	4.3	2.5		4.6	4.17	7.0	1.7	8.5	310	50	28		52	48	81	20	97
Salta	15	1.8							6.9	174	21							79
Australia[c]																		
Malanda (highest)[d]	11	10.4	4.5		5.8	5.4	0.17	0.05	2.47	127	120	52		67	62	2	0.6	28
Hobart-Launceston[e]	1.5	0.38	0.79		0.86	0.35	0.04	0.04	0.34	17	4	9		10	4	0.4	0.4	3.9
Country average							0.02	0.07	0.78	43	10	16		15	13	1.3	0.8	9.0
Bolivia																		
La Paz					11	2.4		5	3.0					120	30	44	60	35
Brazil																		
Guanabara					3.6									42				
Chile																		
Santiago	4.0				3.0	5.2	1.9	0.3	2.1	50	9	10		30	60	22	3	24
Colombia																		
Bogota	0.4	0.4	0.4		0.9	0.7		1.5	0.1	5	5	10		10	8		18	1
Ecuador																		
Quito	2.5		0.3						1.3	30		10						15
Fiji																		
Suva[c]	18[f]	2.9	4.4		3.7	2.9	0.4	0.4	2.4	210	33	51		43	33	5	5	28
Madagascar																		
Diego-Suarez	13	1.8	6.5			6.4				160	22	80			75			
New Caledonia																		
Noumea		0.4			3.5	2.6			16		5			40	30			184
New Zealand[c]	1.5	0.4	0.7		0.7	0.4	0.4	0.4	0.4	17	5	8		8	5	5	5	5

TABLE 16 *(continued)*

Location	Integrated milk concentration (nCi d l^{-1})									Calculated thyroid dose to infants (mrad)								
	1966	*1967*	*1968*	*1969*	*1970*	*1971*	*1972*	*1973*	*1974*	*1966*	*1967*	*1968*	*1969*	*1970*	*1971*	*1972*	*1973*	*1974*
Southern hemisphere (continued)																		
Peru																		
Arequipa			6		7.5	2.9			16			70		90	35			
Lima	6		4						2.1	70	23	50		10	13			
Tacna			10						1.2			120						
Samoa																		
Apia	15[f]	8.4	3.3		6.2	7.3	0.4	1.1	4.4	170	97	38		71	84	5	13	51
Society Islands																		
Tahiti		4.7	4.9		11	18	1.0	11	59		55	60		130	210	12	130	680
South Africa																		
Cape Town					1.5									17				
Pretoria					8.0	11.1								92	127			

[a] There are 1976 data: France (0.91, 10); Japan: Fukushuma (0.95, 11), Chiba (0.36, 4), Fukoku (0.33, 4). The first figure in the parentheses is the integrated milk concentration and the second is the thyroid dose, in the same units as in the table.

[b] The integrated concentration has been taken to be numerically equal to 10 times the highest observed concentration in nCi l^{-1}.

[c] The dose is assumed to be the time-integrated concentration multiplied by 11.5 mrad pCi^{-1} d^{-1} l.

[d] In 1973, the highest integrated milk concentration was measured at Perth (0.27 nCi d l^{-1}).

[e] Lowest.

[f] Value based on an extrapolation.

94. As ^{131}I concentrates in bovine thyroid, this organ is a suitable biological indicator of the presence of ^{131}I in the local environment. Beninson (19) measured the concentration of ^{131}I in bovine milk and thyroid in Argentina during the period 1966-1970. The ratio between the time-integral of the ^{131}I concentration in thyroid and that in milk was fairly constant for the different years and had a value of about 500. Monitoring of ^{131}I in bovine thyroid carried out in Czechoslovakia (66) confirms the very high sensitivity of this method of surveillance for ^{131}I in the environment.

95. Infants receive higher doses in their thyroids than do adults for a given intake of ^{131}I, the main reason being the smaller thyroid mass. A mass of 2 g was used for estimating doses to infant thyroids. Estimates of the dose in infant thyroids per unit activity of ^{131}I reaching the organ range from 15.5 to 18.5 mrad nCi^{-1} (179, 189), and a value of 16.5 was used in the 1972 report of the Committee. Assuming that infants consume 0.7 l of fresh milk per day and that all the ^{131}I ingested is taken up by the thyroid, the P_{345} transfer factor (relating thyroid dose in infants to the time-integrated iodine-131 concentration in milk) can be estimated to be about 11.5 mrad per nCi d l^{-1}.

96. Table 16 presents estimates of the dose in infant thyroids, as calculated with the assumptions mentioned above. They should be regarded as the highest individual doses in the areas for which the assumed consumption is realistic, and as clear overestimates in areas such as the Society Islands where fresh cow's milk is only a small fraction of the total milk consumed by infants. The dose to adults should be at least an order of magnitude lower, because the mass of their thyroids is about ten times larger, and their milk consumption is smaller.

J. CAESIUM-137

97. Caesium-137 is a beta emitter with a maximum beta energy of 1.17 MeV, which decays with the emission of gamma rays of 0.66 MeV. It has a half-life of 30 y, very close to that of ^{90}Sr, and since the measured activity ratio of $^{137}Cs/^{90}Sr$ in deposition at many sites and over a long time has been fairly constant at about 1.6 (245), it is useful to use the more complete data on ^{90}Sr to estimate the deposition of ^{137}Cs. In this way also the latitudinal distribution of ^{137}Cs integrated deposition density can be estimated from the ^{90}Sr data of table 3.

1. Caesium-137 in the environment

98. Since the half-life of ^{137}Cs is relatively long, the assessment of dose commitments requires the understanding of the behaviour of this radionuclide in the environment. A recent review of the literature on this subject has been published by Moiseev *et al.* (262). The deposition of ^{137}Cs occurs over land and over the oceans. As in the case of ^{90}Sr, it has been found that fallout over land is the more important pathway as far as dose commitments to man are concerned.

99. After deposition over land, caesium-137 enters the dietary pathway, being taken up by plants either through the root system or by direct uptake by the leaves. Caesium-137 seems to become more strongly fixed in the soil than ^{90}Sr does (14, 114, 159, 267), but its availability to plants depends markedly on the soil type and has been found to decrease in time (256). In a sandy soil in Massachussetts (United States), Hardy (114) found that 84 per cent of the fallout ^{137}Cs was in the top 4 cm of soil, and 97 per cent was in the top 31 cm. Marei *et al.* (159) have identified regions in the USSR where the soil is wet, peaty and podzolic, from which the transfer of ^{137}Cs into the food chain is 10 times higher than for other regions. Other regions of the world where there are soils giving rise to high ^{137}Cs transfer into diet have also been identified, for example, in the Faroe Islands (3), New Zealand (188) and Sweden (151). The mechanism of such enhanced transfer has also been studied (94). Much smaller amounts of ^{137}Cs than of ^{90}Sr are leached out of the soil to enter rivers and lakes.

100. Regarding deposition of ^{137}Cs on the oceans, measurements made on sediments of the Atlantic Ocean indicate that only about 3 per cent of the fallout ^{137}Cs has reached the bottom (193). Activity concentrations in surface waters of the open ocean are about 0.2 pCi l^{-1} (46), and in the deep ocean they are lower by a factor of about 30. Hodge *et al.* (127), from measurements of ^{137}Cs concentrations in Pacific tuna, estimated the half residence-time of ^{137}Cs in surface waters to be about 17 y.

101. Marine food chains seem to be of secondary importance in relation to human intakes. The reported concentration factors between sea water and mose biota are about 50 (93, 191, 214, 240). It has been estimated that in Japan, between 1966 and 1971, only about 8 per cent of the dietary intake of ^{137}Cs came from the consumption of fish products (240).

2. Levels in diet

102. Since ^{137}Cs is an alkali metal like potassium, and since the concentration of potassium in lean body mass is constant (225), it is convenient to express the ^{137}Cs activity in food and in the human body as the $^{137}Cs/K$ quotient, usually in picocuries per gram. Data on the ^{137}Cs concentration in milk and on its daily intake from the total diet are shown in tables 4 and 6. Data available for 1973 and 1974 indicate that, generally speaking, levels are still falling. The transfer of ^{137}Cs from deposition to diet is normally high during the first year after deposition and relatively small subsequently. Concentrations in milk are strongly dependent on deposition in the same year. That explains why in the northern hemisphere the milk concentrations on the average decreased from 1966 to 1969, were relatively stable from 1969 to 1971, and decreased again from 1971 to 1973.

103. The transfer of ^{137}Cs from deposition to diet can be studied quantitatively using an approach similar to that for ^{90}Sr (paras. 55-69). The measured $^{137}Cs/K$ quotients in the various components of the Danish diet are plotted against time in figure X (2). Evans and

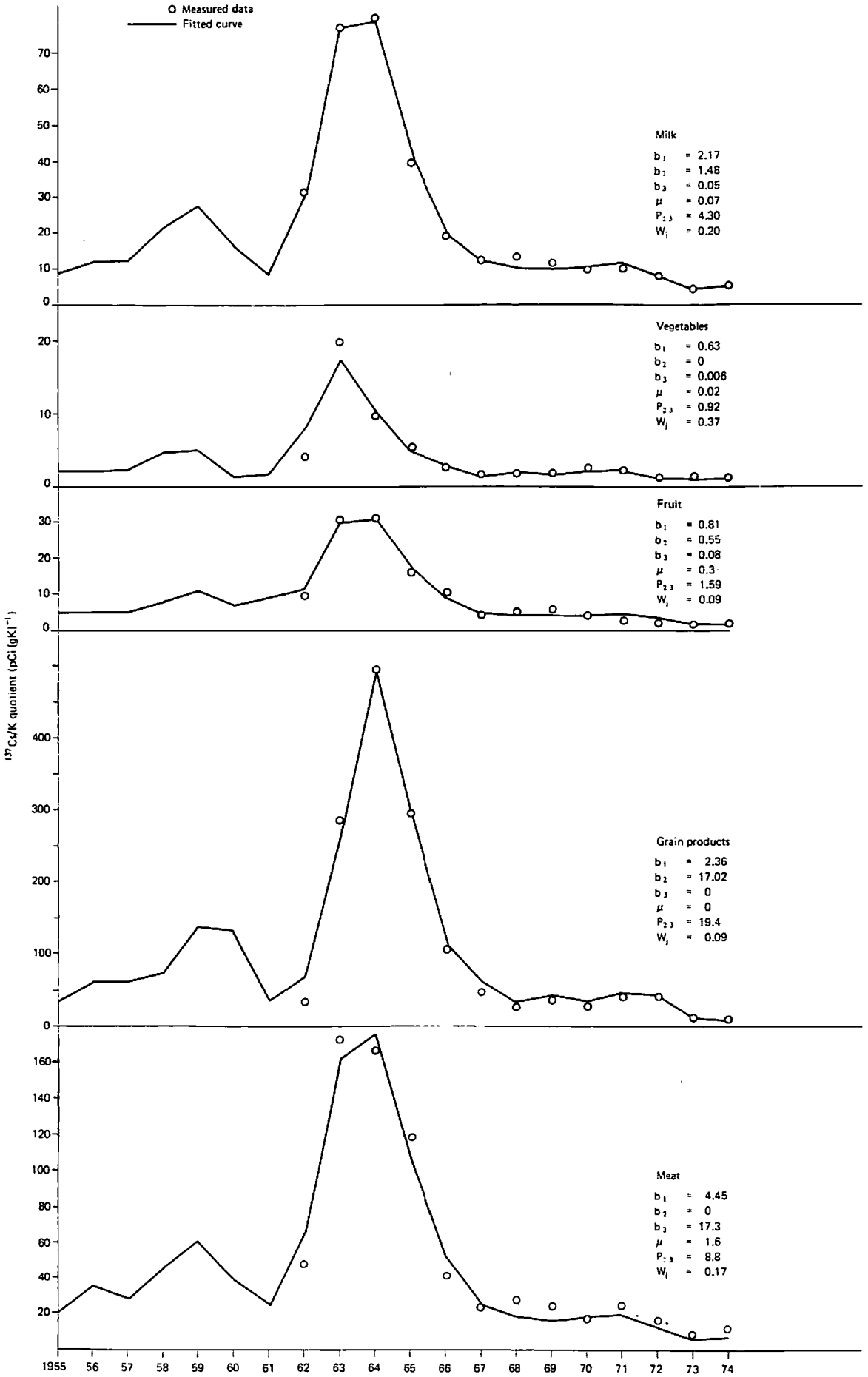


Figure X. Variation of ^{137}Cs in various diet components in Denmark, 1955-1974. The unit for parameters b_1, b_2, b_3 is pCi $(gK)^{-1}$ per mCi km^{-2}. The unit for parameter μ is y^{-1}. The unit for the transfer factor P_{23} is pCi y $(gK)^{-1}$ per mCi km^{-2}.

TABLE 17. PARAMETERS OF THE TRANSFER FUNCTION BETWEEN ^{137}Cs FALLOUT AND DIET

Obtained by regression analysis from Danish data

Parameter[a]	Milk products	Grain products	Meat, fish, eggs	Vege-tables	Fruit	Total composite diet
b_1	2.17	2.36	4.45	0.63	0.81	1.56
b_2	1.48	17.02	0.0	0.0	0.55	2.21
b_3	0.05	0.02	17.24	0.006	0.08	0.04
μ	0.07	0.0	1.60	0.02	0.30	0.12
P_{23}^j	4.32	19.38	8.80	0.92	1.59	4.08
W_j	0.20	0.09	0.17	0.37	0.09	1.00
$W_j P_{23}^j$	0.86	1.74	1.50	0.34	0.14	4.08
Total diet P_{23}			4.58			4.08

[a]The unit for parameters b_1, b_2, b_3 is pCi (gK)$^{-1}$ per mCi km^{-2}. The unit for parameter μ is y^{-1}. The unit for the transfer factor $P_2 I_3$ is pCi y (gK)$^{-1}$ per mCi km^{-2}. W_j is the fractional contribution of component j to the total K diet.

Bennett (86) have carried out a regression analysis using these data and the annual deposition data, with a transfer function of the same form as that shown in paragraph 58 for ^{90}Sr. The figure also shows the curves fitted to the data with the parameters given in table 17. In Denmark the main contribution to the intake of ^{137}Cs has been from meat and grain products, with a sizeable contribution from milk. Fruit and vegetables contribute much smaller amounts. The same is true of Chicago (United States). In Japan, however, the main contribution has been from cereals (240). For all foods the transfer seems to be rapid, being essentially completed within the first two years after deposition.

104. The same transfer function was also fitted to the ^{137}Cs/K quotients in fresh milk in several countries, and the resulting parameters are shown in table 18. The transfer factors P_{23}^{milk} linking deposition density and the time-integrated ^{137}Cs/K quotient in milk for Argentina, Australia, Faroe Islands, New Zealand, Norway and USSR are significantly greater than those for Denmark and the United States. The value reported for Finland, 15.8 pCi y (gK)$^{-1}$ per mCi km^{-2} (65), is also in this higher range. It should be noted that parameters relating to Denmark in table 18 are for fresh milk, while those in the first column table 17 refer to milk products.

105. The results of the regression analysis for the estimation of P_{23}, or its components such as P_{23}^{milk}, are consistent with the assessments carried out by the Committee for its 1969 and 1972 reports (244, 245). A value of 4.1 pCi y (gK)$^{-1}$ per mCi km^{-2} was estimated in these reports for the factor P_{23}, identical with that shown in table 17, which was derived by regression analysis. The same value, rounded to 4 pCi (gK)$^{-1}$ per mCi km^{-2}, will be used in this report for the purpose of assessing dose commitments from ^{137}Cs for the world population. This value of the transfer factor adequately represents some areas in the northern hemisphere, but on the available evidence discussed above, it would appear to underestimate P_{23} for other areas, especially in the southern hemisphere.

106. The latitudinal distribution of ^{137}Cs deposition density in 1972 (assessed from the ^{90}Sr data assuming a constant ^{137}Cs/^{90}Sr activity ratio) is shown as the curve in figure XI. Also shown in figure XI are the ^{137}Cs concentrations in milk in 1972 at various localities. The ^{137}Cs milk concentrations for a number of them depart markedly from a general correlation with the deposition data. Since data on ^{137}Cs concentration in foods are not available for many areas of the world, particularly in the tropical regions, it is not possible to assess what the importance of this effect might be on the global scale.

TABLE 18. PARAMETERS OF THE TRANSFER FUNCTION FROM ^{137}Cs FALLOUT TO MILK

Obtained by regression analysis of data for various countries and areas

Parameter[a]	Argentina	Australia	Denmark	Faroe Islands	New Zealand	Norway	USSR	United Kingdom	United States
b_1	2.21	7.24	2.37	6.80	6.79	3.52	4.43	1.75	2.28
b_2	0.00	4.78	0.69	5.44	0.68	2.26	0.22	1.61	1.34
b_3	1.80	0.30	0.06	2.83	3.62	2.63	0.31	0.03	0.00
μ	0.27	0.18	0.30	0.17	0.51	0.24	0.18	0.023	0.05
P_{23}^{milk}	8.02	13.59	3.23	27.51	12.91	15.48	6.22	4.75	3.63

[a]The unit for parameters b_1, b_2, b_3, is pCi (gK)$^{-1}$ per mCi km^{-2}. The unit for parameter μ is y^{-1}. The unit for the transfer factor P_{23}^{milk} is pCi y (gK)$^{-1}$ per mCi km^{-2}.

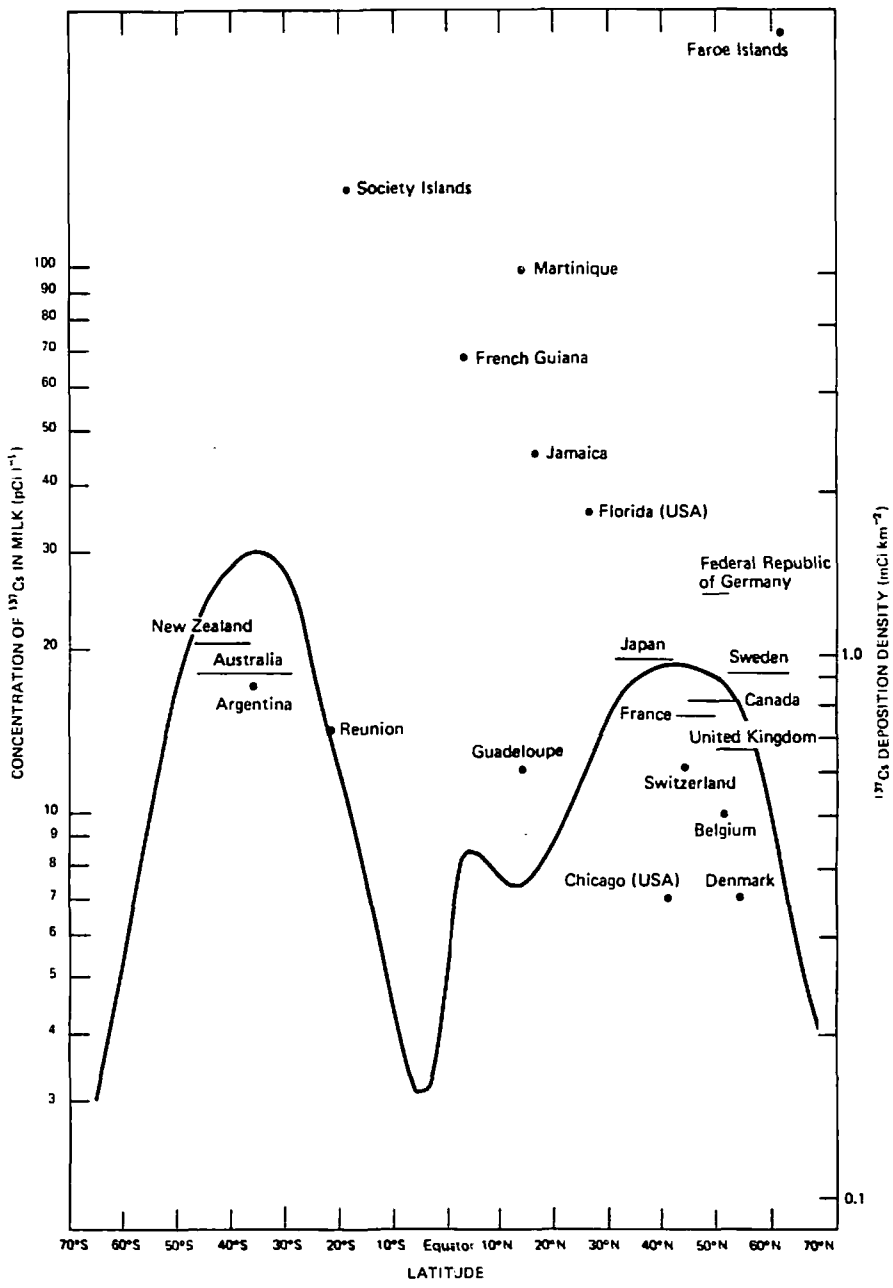


Figure XI. Latitudinal distribution of ^{137}Cs deposition density (curve) and the concentration of ^{137}Cs in milk at various locations (dots and segments), 1972

3. Caesium-137 in the human body

107. Caesium-137 ingested by man is distributed in the body, with about 80 per cent being deposited in muscle and 8 per cent in bone (225). About 10 per cent of the activity taken in is eliminated rapidly, with a biological half-life of about 1 d, while the remaining 90 per cent is excreted at a lower rate (225). The biological half-life of this main fraction varies between less than 50 d to more than 200 d in adults (43, 124, 245) and is shorter in children than in adults (124). Owing to this relatively short biological half-life, the activity of ^{137}Cs in the body tends to follow the fluctuations of the concentration of ^{137}Cs in the diet.

108. Table 19 summarizes the information on ^{137}Cs/K quotients in the human body in the period 1964-1974. For all localities, the values have continued to decrease since the 1972 report of the Committee. The ^{137}Cs/K quotients in subarctic populations are between two and three orders of magnitude higher than those in the middle latitudes, as shown by data from Finland, Norway and Sweden and from the northern USSR and United States (Alaska) (123, 200, 210, 238, 250). These high values are due to the lichen-reindeer (or caribou) food chain (245).

109. The short biological half-life of caesium in the body makes it possible to assess the transfer factor between diet and body P_{34} from the ^{137}Cs/k quotients integrated over a few years. Using this procedure, an average value of 3 is derived from the data of tables 6 and 19 converted into ^{137}Cs/K quotients, which is practically identical to the value used in the 1969 and 1972 reports, namely 2.9.

TABLE 19. CAESIUM-137/POTASSIUM QUOTIENT IN THE HUMAN BODY
(pCi (gK)$^{-1}$)

Location	*Approximate latitude (degrees N or S)*	*Sex*	*1964*	*1965*	*1966*	*1967*	*1968*	*1969*	*1970*	*1971*	*1972*	*1973*	*1974*	*1975*	*Reference*
						Northern hemisphere									
Belgium	50	M, F	158	135	87	50	29								244
Canada (Ottawa)	45	M, F		170											175
Denmark	55-60	M, F	185	168	106	65	46	40	23	13	16	11	10	11	2
Egypt	30	M, F				23	14		12						181
Finland	60	M, F		182	150	107	72	53	44	34	38	37	28	29	231, 232
France	50	M, F	227	194	93	64	36	32	26	28	28	21	18	17	198
Germany, Fed. Rep. of															
Karlsruhe	49	M, F	151	111	81	49	27	16	15	15	17	11	9	12	
Düsseldorf	51	M	243	186	128	76	41	32	31	22	30	23	19	15	52
Israel	35	M					48								
Japan	30-45	M	93	77	54	33	20	14	13	16	12	10	9	8	186, 239
Norway	60	M, F		430	290										132
Poland	50-55	M, F	164	185		71									152
Sweden (Stockholm)	60	M, F	205	187	139	107	74	54	47	46	38	31	22		233
Switzerland (Geneva)	45	M	206	179	103	54	30	24	21	23	19				
		F	139	121	66	41	26	19	18	22	19				129
USSR															
Moscow	55	M	258			50	34	29	38						266
		F				42	27	22	36						265
Leningrad	60	M, F	174	142	92	68	70								
United Kingdom															
London area	50	M		148	89	45									101
		F	149	109	60	33									
West Cumberland	55	M	257	190	110	52	30								
United States															
Country average	25-50	M, F	141	109	60	35	17								104
Florida	25-30	M, F		149	132	120									216
West Berlin	52	M, F				68	49	47	36	29	25	19	10	11	52
						Subarctic region									
Canada															
Eastern (Eskimos)	60-70	M			5 800										42
Central (Eskimos)	60-70	M				11 000									
Finland															123
Inari (reindeer herders)	70	M	7 800	9 000	7 800	5 500	5 200	3 400	3 100	4 100					
		F	8 800	11 200	7 900	3 800	4 200	3 600	2 800	3 300					
USSR															
Murmansk	65-70	M	14 000	18 000	25 500	17 500	16 500	15 500	12 500	11 500	9 000				238
United States															
Alaska	65-70	M	9 100	6 600	4 900	4 300	2 400								210
						Southern hemisphere									
Argentina	35-40				31	20	16	13	15	14	12	10	9	4	21, 71
Australia	30-40			65	42	37	18		16	30	25	17			11

110. An alternative approach for the derivation of P_{34} is the assessment by regression analysis of the parameters of a postulated transfer function relating diet to body. Applying this procedure to the data from Denmark and the United States, and assuming a single exponential transfer function, the estimated values of P_{34} are 2.6 for Denmark and 3.0 for the United States (86), in good agreement with the value of 3 mentioned in paragraph 109.

4. Dose commitment from caesium-137

111. The combined transfer factor P_{234}, linking deposition to the ^{137}Cs/K quotient in the body, is the product of P_{23} and P_{34}. From the estimated average values for these two factors (paras. 105 and 109), a value of 12 pCi y $(gK)^{-1}$ per mCi km^{-2} is calculated for the combined factor P_{234}.

112. An alternative procedure for the assessment of P_{234} is the direct use of the time-integrated ^{137}Cs/K quotient in the body $\int Qdt$ and the integrated deposition density F, both over the same period of several years, the factor being $P_{234} = \int Qdt / F$. This procedure, applied to data from Argentina in the period 1966-1974 (16, 21), estimates the factor P_{234} to be 11 pCi $(gK)^{-1}$ per mCi km^{-2}. For Stockholm the time-integrated ^{137}Cs/K quotient in the body in the period 1962-1972, is 1053 pCi y $(gK)^{-1}$ (244, 245), while for the same period the integrated deposition density of ^{137}Cs in the region (at Tumba, near Stockholm) is 58 mCi km^{-2}. This gives a value of P_{234} of 18 pCi y $(gK)^{-1}$ per mCi km^{-2}, about 50 per cent higher than the average estimate given above. Aarkrog estimated P_{234} in Denmark by regression analysis from the body ^{137}Cs/K quotients and the annual deposition densities, obtaining a value of about 11 pCi y $(gK)^{-1}$ per mCi km^{-2} (2).

113. The transfer factor P_{234} could vary mainly as a result of variations of P_{23} with the local conditions, particularly soil characteristics (para. 99) and the nature of the diet. In the 1972 report (245), the Committee assessed the possible range of P_{23} values, based on USSR data and the conservative assumption that available ^{137}Cs decreased only by radioactive decay. This range, multiplied by the value of P_{34} given in paragraph 109, implies that P_{234} would be smaller than 22 pCi y $(gK)^{-1}$ per mCi km^{-2}. The use of a value of 12 pCi $(gK)^{-1}$ per mCi km^{-2} for P_{234} (para. 112), for the purpose of assessing dose commitments, could therefore not underestimate these commitments by a factor of more than two.

114. As was shown in the 1969 report of the Committee (244), the transfer factor P_{45}, linking tissue activity and tissue dose, is approximately independent of age if expressed as dose per unit of the time-integrated ^{137}Cs/K quotient. The value of $P_{45} = 1.8\ 10^{-2}$ mrad per pCi y $(gK)^{-1}$, combined with the estimate of P_{234} = 12 pCi y $(gK)^{-1}$ per mCi km^{-2}, gives a value for the overall transfer factor P_{2345} of about 0.2 mrad per mCi km^{-2}.

115. The integrated deposition density of ^{137}Cs can be assessed from that of ^{90}Sr (paras. 47 and 81), using an activity ratio of 1.6 (para. 97). The values are (mCi km^{-2}): temperate latitudes of the northern hemisphere, 136; temperate latitudes of the southern hemisphere, 39; global value weighted by the population distribution, 84. The resulting dose commitments are respectively 27 and 8 mrad for the populations in the temperate latitudes of the northern and southern hemisphere and 17 mrad for the world population.

116. It is to be noted that the above dose commitments are based upon information obtained in areas where ^{137}Cs in the soil becomes unavailable to plants fairly rapidly. For populations consuming food from other types of soil, the dose commitments could be higher (para. 113), and for people in the subarctic regions eating reindeer and caribou meat, the dose commitments are indeed much larger. Assuming, however, that the contribution of such different situations to the total collective dose is not large, it can be estimated that the collective dose commitment from internal exposure, per unit activity of ^{137}Cs released, is of the order of 3 man rad Ci^{-1} for the past pattern of nuclear explosions.

K. CAESIUM-136

117. Caesium-136 is a beta emitter with a half-life of 13.5 d. The maximum beta energy is 0.66 MeV, and several gamma rays with energies up to 1.25 Mev are emitted. Since it must be produced directly by fission and not by beta decay, because ^{136}Xe is stable, the activity produced in nuclear tests is fairly small. By using the ^{136}Cs/^{140}Ba fission yield ratio and the deposition-to-milk transfer factors of ^{137}Cs and ^{140}Ba, O'Brien (195) has estimated the integrated deposition density of ^{136}Cs and the time-integrated concentration in milk in the United States between 1961 and 1965. These calculated values agree roughly with the few measurements which have been made of ^{136}Cs (177). The time-integrated concentration in milk in the United States between 1961 and 1965 was estimated to be 4.2 pCi y l^{-1}. Using data on trasfer factors for ^{137}Cs and ^{140}Ba as a guide, O'Brien estimated P_{345} (milk-to-dose) for ^{136}Cs to be $1.3\ 10^{-3}$ mrad per pCi y l^{-1}. The estimated dose commitment for the population of the temperate regions of the northern hemisphere from all tests to 1970 is 0.01 mrad.

L. BARIUM-140

118. Barium-140 is a beta emitter with a half-life of 12.8 d and a maximum beta energy of 1.02 MeV. It emits several gamma rays. Its daughter product, the 40.2-h half-life ^{140}La, decays with a 2.18-MeV maximum-energy beta emission and several gamma rays, with energies up to 1.6 MeV. Barium-140 is measurable in fallout only for a few weeks after a nuclear explosion. This radionuclide was measured in the pasteurized milk supply networks of the United States by the Public Health Service between 1961 and 1966 (204). The time-integrated concentration in milk was 16.2 pCi y l^{-1} for this period. O'Brien (195) estimated the factor P_{45} for ^{140}Ba to be about 3.0 mrad per pCi y $(gCa)^{-1}$ in bone. In addition, using the P_{34} value for ^{90}Sr together with the ICRP model for alkaline-earth metabolism (160), the factor P_{34}^{milk} for ^{140}Ba was estimated to be

$5.5\ 10^{-5}$. With these values, in the United States the mean dose to bone marrow for the period 1961-1965 is estimated to be $2.6\ 10^{-3}$ mrad. The dose commitment in the temperate zone of the northern hemisphere is estimated to be $6\ 10^{-3}$ mrad, assuming an average consumption of 0.6 l of milk per day.

M. CERIUM-144

119. Cerium-144 has been widely measured in air and in fallout (61, 249). It has a half-life of 285 d and together with its daughter decay product, the 1.7-min ^{144}Pr, emits beta particles of 2.99-MeV maximum energy and several gamma rays. Table 20 shows, for a number of sites in each hemisphere, the ratio of the integrated deposition density of ^{144}Ce to that of ^{90}Sr, together with similar ratios of the time-integrated activity concentrations in air (obtained by the sum of the average monthly activity concentrations over the specified period of time). These ratios are indicated in the table as $\Sigma^{144}Ce/\Sigma^{90}Sr$. Using a value of 15 as representative for the ratio for all tests up to 1974, the mean integrated deposition density of ^{144}Ce is estimated to be (mCi km^{-2}): northern temperate zone, 1257; southern temperate zone, 360; world (population-weighted), 765, based on data of table 2 and paragraph 47.

TABLE 20. RATIO OF THE INTEGRATED DEPOSITION DENSITIES OR OF THE TIME-INTEGRATED AIR CONCENTRATIONS OF ^{144}Ce and ^{90}Sr AT VARIOUS LOCATIONS

Location	*Period*	*Type of ratio*	$\Sigma^{144}Ce/\Sigma^{90}Sr$
Buenos Aires, Argentina	1966-1974	Deposition density	18.9
Moosonee, Canada	1963-1974	Air concentration	13.5
Antofagasta, Chile	1963-1974	Air concentration	12.8
Santiago, Chile	1963-1974	Air concentration	15.0
Puerto Mont, Chile	1963-1974	Air concentration	12.3
Lower Hutt, New Zealand	1968-1972	Deposition density	16.0
Chilton, United Kingdom	1961-1965	Deposition density	20.2
Chilton, United Kingdom	1967-1970	Deposition density	14.7
Sterling, United States	1963-1974	Air concentration	13.5
Miami, United States	1963-1974	Air concentration	14.2

120. The inhalation of ^{144}Ce gives rise to lung irradiation. At Moosonee (Canada) and Sterling and Miami (United States), the time-integrated concentrations of ^{144}Ce in air from 1963 to 1974 were 1.33, 1.78 and 1.66 pCi y m^{-3}, respectively, giving a mean of 1.6 pCi y m^{-3} (117). The time-integrated activity concentrations in air at Antofagasta and Santiago (Chile) for the same period were 0.36 and 0.39 pCi y m^{-3}, respectively, giving a mean of 0.38 pCi y m^{-3}. Assuming that these two means are representative of the northern and southern hemisphere, and using the ^{90}Sr integrated deposition data of table 2 to extrapolate the integrated air concentrations to cover the period 1954-1974, the resulting estimates for that period are respectively 3.0 and 0.7 pCi y m^{-3} for the northern and southern hemispheres.

121. Using the ICRP lung model (135, 136) with parameters of class Y, and assuming a mean particle size of 0.5 μm, which results in a 20-per-cent deposition in the pulmonary region of the lung, the transfer factor P_{15} (time-integrated air concentration-to-dose) is estimated to be 22 mrad per pCi y m^{-3}.

122. Applying this value of P_{15} to the time-integrated air concentrations given in paragraph 120 results in dose commitments to the lung of 65 and 15 mrad for the populations of the northern and southern temperate regions, respectively. The lung dose commitment to the world population is estimated to be about 38 mrad. Assuming a ^{144}Ce/^{90}Sr activity ratio of 48 at the time of fission, it can be estimated that the collective dose commitment to the lung per unit activity released is of the order of 0.3 man rad Ci^{-1}, for the past pattern of nuclear testing.

N. PLUTONIUM

1. Plutonium in the environment

123. Several isotopes of plutonium have been released into the environment by nuclear tests carried out in the atmosphere between 1945 and 1976. The most important, with half-lives shown in parentheses, are ^{239}Pu (24 000 y), ^{240}Pu (6600 y), ^{238}Pu (87 y) and ^{241}Pu (14 y). The last radionuclide is mainly a beta emitter and decays to the alpha emitter ^{241}Am (430 y). Since ^{239}Pu and ^{240}Pu are not usually distinguished in environmental activity measurements, reported ^{239}Pu activities should be assumed to apply to a mixture of ^{239}Pu and ^{240}Pu (116). Measurements have indicated that this mixture contains approximately 60 per cent of ^{239}Pu on an activity basis.

124. Plutonium released to the atmosphere during atmospheric tests is subsequently deposited on land and on the oceans as insoluble aerosol particles of the oxide. Profile measurements in sandy soil have shown that about 70 per cent is in the first 4-cm layer and virtually all in the top 30 cm (114). The profile depends on local climate and the physico-chemical properties of the soil. Other measurements (38) indicate that about 40 per cent of the plutonium is in the top 5 cm of soil.

125. The uptake of plutonium from soil by plants can be expressed as a concentration factor, usually defined as the ratio of the activity concentration in fresh plants to that in dry soil. Reported values for the plutonium concentration factor vary widely over the range $4\ 10^{-8}$ to $3\ 10^{-2}$, but representative values are on the average

of the order of 10^{-4} (38). From measurements of the ^{239}Pu intake and of the activity in the bone, muscle and liver of cows that had grazed on a contaminated range of the Nevada test site, a gastro-intestinal uptake factor of $3.4\ 10^{-5}$ was obtained (224). In similar study on the uptake of plutonium by reindeer that had fed on lichen, the uptake factor was found to be about $2.4\ 10^{-5}$ (128).

126. In the ocean, plutonium has moved to greater depths than has ^{90}Sr and ^{137}Cs. Noshkin *et al.* (193) found that 2-36 per cent of oceanic plutonium in the Atlantic Ocean was in the sediments. In the water, they found that about 50 per cent of the activity was below the thermocline. In 1964 the activity concentration of plutonium in the Pacific Ocean was about 10^{-4} pCi l^{-1} (202). Plutonium is taken up by marine biota, and the concentration factors for algae, plankton, crustacea are 1000-3000; for fish (muscle), 1-10 (192).

2. Levels in the environment

127. Most of the plutonium now dispersed around the world came from tests carried out prior to 1963; subsequent tests have contributed an additional 10 per cent to the global inventory (118). The deposition density rate and the integrated deposition density of ^{239}Pu-^{240}Pu can be inferred from the corresponding values for ^{90}Sr, as it has been observed that the Pu/^{90}Sr activity ratio in stratospheric- and surface-air samples has remained fairly constant in time with a value of about 0.017 (28, 116). A comparison of the cumulative deposit of Pu in soil with that of ^{90}Sr can also be used to estimate the global deposition of plutonium. From such measurements the global deposition of ^{239}Pu-^{240}Pu up to the end of 1973 is estimated to be 320 kCi, of which 250 kCi were in the northern hemisphere and 70 kCi in the southern hemisphere (116). This global deposition amounts to about 3 t of the ^{239}Pu isotope. In 1975 the stratospheric inventory in the northern hemisphere was less than 1 kCi (149).

128. Nuclear tests have contributed 9 kCi of ^{238}Pu to global fallout (116), while the re-entry of a satelite into the earth's atmosphere in 1964 contributed some 17 kCi, 70 per cent of which has deposited in the southern hemisphere, as discussed in the 1972 report of the Committee (245).

129. Although ^{239}Pu-^{240}Pu concentrations in ground-level air have been measured on a wide scale only since 1965, previous ^{239}Pu-^{240}Pu activity concentrations in air can be estimated from ^{90}Sr concentrations in air, assuming that the ^{239}Pu-^{240}Pu/^{90}Sr ratio has remained constant and that both nuclides have the same deposition velocity (149). Using this approach, Bennett found that the air activity concentration in New York reached a peak of about 1.7 fCi m^{-3} in 1963 and by 1972 had decreased to 0.031 fCi m^{-3} (22). The average deposition density rate of ^{239}Pu-^{240}Pu in New York for 1972-74 was 0.017 mCi km^{-2} y^{-1}, while the cumulative deposit density in 1974 was 2.68 mCi km^{-2} (38).

130. Bennett (32, 35) has reported results from a complete-diet sampling programme conducted in New York during 1972 and 1974, which showed an average annual dietary intake of 1.6 pCi of ^{239}Pu-^{240}Pu. Of the food groups analysed, grain products, and fruit and vegetables had the highest activity concentrations, both being about $5\ 10^{3}$ pCi kg^{-1}. It was also apparent from this study that external contamination of food is an important contributor to intake.

3. Pathways to man and dose commitments

131. Plutonium uptake and deposition in human tissues can follow the inhalation of airborne plutonium or the ingestion of contaminated food. The available data indicate that for plutonium released by atmospheric tests, the most important pathway to man is the inhalation of contaminated air. Dose commitments have been estimated for each pathway.

132. Bennett (28) has estimated that the cumulative intake by inhalation in New York from 1954 through 1975 was 43 pCi. As a single intake, this would have given rise to a body activity of 8.5 pCi, assuming a 20-per-cent retention factor as is indicated in the ICRP lung model (135, 136). But since the intake occurred over several years, allowing for loss of activity from the lung, the activity in the body was about 4 pCi at maximum in 1964, and for 1974 it was estimated to be 2.4 pCi (38).

133. The ^{239}Pu contents of various human organs measured at several areas of the United States in 1972 and 1973 in occupationally unexposed persons have recently been reported (12, 213). In this study, particular care was exercised in separating the lymph-node tissue, so that as little as possible of non-lymphatic tissue was included. These results are shown in table 21, together with the estimated values of

TABLE 21. CONCENTRATION OF PLUTONIUM IN BODY TISSUES OF NON-OCCUPATIONALLY EXPOSED PERSONS IN THE UNITED STATES, 1972-1973

(The number in parentheses is the number of samples)

(pCi kg^{-1})

	Lung	*Liver*	*Lymph node*	*Kidney*	*Vertebrae*
Los Alamos	0.36 (8)	0.72 (5)	16.0 (4)	0.09 (5)	0.72 (5)
Non-residents of Los Alamos	0.18 (17)	0.31 (10)	9.0 (15)	0.54 (10)	0.19 (16)
Colorado	0.31 (29)	0.81 (25)	6.8 (22)	1.4 (25)	0.50 (25)
Savannah River	0.18 (20)	0.54 (14)	18.0 (6)	1.0 (11)	0.31 (12)
Mean	0.27 (74)	0.68 (54)	11.0 (47)	0.68 (51)	0.31 (58)
Computed from fallout plutonium (1972)[a]	0.19	0.52	32.0	0.07	0.19

[a] Assuming organ weights for the lung, liver, lymph node and bone of 1.0, 1.7, 0.015 and 5.0 kg, respectively.

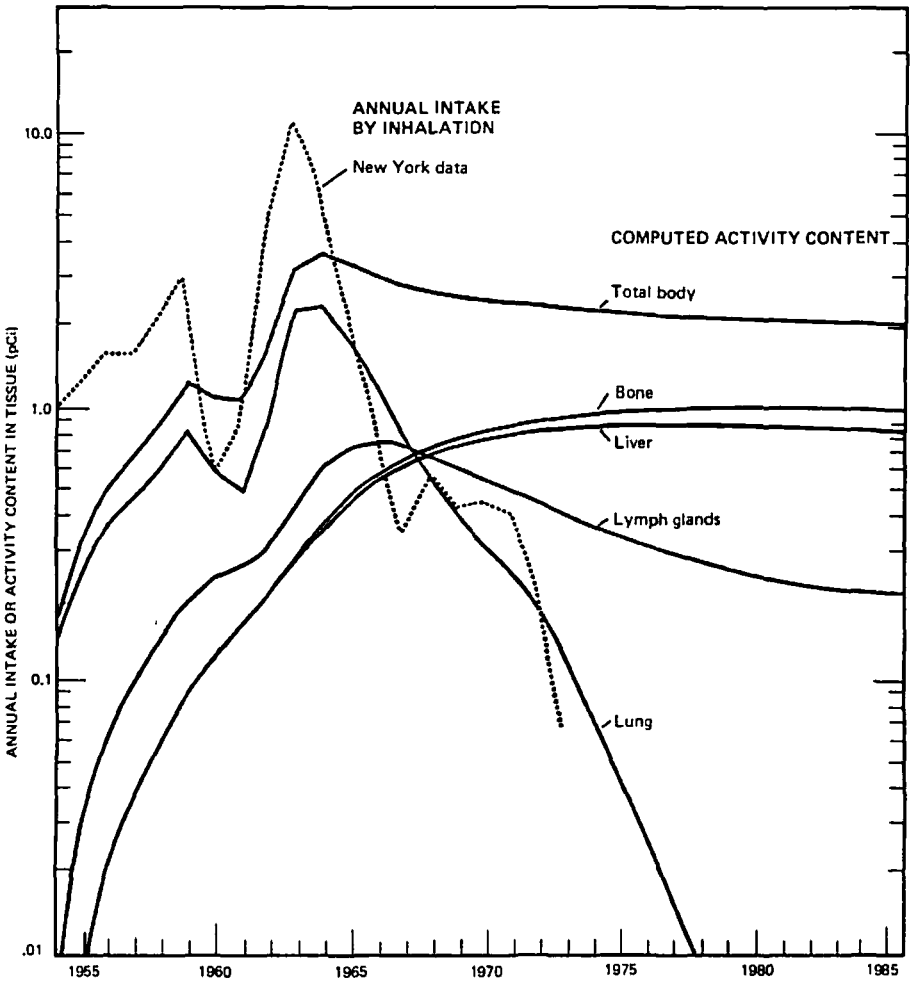


Figure XII. Annual ^{239}Pu inhalation intake (dotted curve) and computed activity content in human body tissues (solid curves)

Bennett based upon the New York data (28). The agreement is quite reasonable, considering the difficulties involved. It should be noted that, to get these results, Bennett used the ICRP lung model with class Y parameters (appropriate for insoluble aerosol particles), while the results with other classes of parameters were at variance with the measured values (28).

134. Inhalation of radioactivity resuspended from the soil surface by winds could add to the long-term intake due to airborne plutonium. Bennett (32), on the basis of natural ^{238}U concentrations in air and soil, considered that 10^{-9} m^{-1} would be a realistic estimate for the resuspension factor, applicable to activity in the top 1 cm of soil. This is in agreement with that estimated from normal dust loading of the atmosphere (6). This estimate is also in agreement with values determined using an artificial tracer in a lightly vegetated area (221). Using such a factor, resuspension would only contribute 0.5 per cent to the total integral activity of ^{239}Pu-^{240}Pu in air between 1954 and 2000 (29, 34). Since plutonium penetrates into the soil and thus becomes unavailable for resuspension, this effect is not expected therefore to contribute significantly to the dose commitment from plutonium.

135. By using estimates for the ^{239}Pu concentration in New York air between 1954 and 1972, assessed from ^{90}Sr deposition density data together with ^{90}Sr and ^{239}Pu concentration in air measured between 1965 and 1972, and utilizing the ICRP lung model (135, 136), Bennett has estimated the dose to man from inhalation of fallout ^{239}Pu through 2000 (28). The estimated ^{239}Pu annual intake and activity content in body tissues are shown in figure XII. The cumulative doses to 2000 are (mrad): lungs, 1.6; liver, 1.7; bone lining cells, 1.5. As the atmospheric inventory of ^{239}Pu decreases rapidly, the contribution from inhalation after 2000 is very small, and these cumulative doses are therefore good approximations of the dose commitments. The present estimate for the dose commitment to bone differs significantly from that given by the Committee in its 1972 report, which was based upon concentrations in surface air at Ispra, Italy, and on earlier values of parameters for the ICRP lung model (135, 136). It is also to be noted that the lung doses have been calculated on the basis of a uniform distribution of ^{239}Pu over the whole organ (28, 245). As plutonium particles are assumed to be insoluble, the actual distribution of doses in the lung is probably non-homogeneous, but the calculated value can be taken to represent the mean dose to the lung.

136. Assuming that the ^{239}Pu concentrations in New York air are representative of the whole 40°-50° latitude band, that the global distribution of ^{239}Pu deposition is the same as that for ^{90}Sr, and that the latitudinal distribution of the population remains unchanged, the

population-weighted dose through 2000 to the bone lining cells would be 1.0 mrad in the northern hemisphere and 0.3 mrad in the southern hemisphere.

137. For the purpose of estimating dose commitments from the ingestion of the plutonium mixture, two extreme cases will be considered, assuming in the first that the amount of plutonium transferred to food depends on the deposition density rate and in the second, that it depends on the cumulative deposit density.

138. Under the first assumption, P_{23} is estimated from the quotient 1.6 pCi y^{-1}/0.017 mCi km^{-2} y^{-1} to be 94 pCi per mCi km^{-2}. The total individual intake from plutonium deposited from all tests up to 1974 would be 94 pCi per mCi km^{-2} X 2.68 mCi km^{-2} = 252 pCi. Under the second assumption, on the other hand, the lifetime intake is estimated to be 1.6 pCi y^{-1} X 70 y = 112 pCi.

139. Of the ingested plutonium it is assumed that a fraction 3 10^{-5} is absorbed through the GI tract and that 45 per cent of this goes to the bone (136). For the two assumed cases of intake of 252 pCi and 112 pCi, the activity deposited in bone is 3.4 10^{-3} and 1.5 10^{-3} pCi, respectively.

140. The dose rate in bone per unit activity of plutonium is 0.098 mrad y^{-1} pCi^{-1} (28). Under the first assumed case, the activity in bone is 3.4 10^{-3} pCi, and the average exposure period in the population is 35 y. The dose commitment is therefore assessed to be 1.2 10^{-2} mrad.

141. Under the second assumed case the bone activity increases linearly with age with an average in the population of 1.5 10^{-3} pCi X 0.5 = 0.75 10^{-3} pCi. The factor of 0.5 takes account of the fact that the *per caput* bone activity is approximately 0.5 times that at death. The annual dose, averaged over all ages, is therefore 7.5 X 10^{-5} mrad. If it is assumed that the ^{239}Pu in the soil becomes unavailable only by decay, the dose commitment is estimated to be 2.6 mrad.

142. Taking into account population distribution and using the procedures outlined in Annex A, the collective dose commitments to the lung and to bone lining cells, per unit activity released by past nuclear explosions, are of the order of 10 man rad Ci^{-1}.

III. EXTERNAL IRRADIATION

143. Many radionuclides present in fallout emit gamma rays and contribute to the dose from external irradiation. The most important from this point of view are a number of short-lived radionuclides, the most significant of which are ^{95}Zr and its daughter ^{95}Nb, and the long-lived ^{137}Cs.

144. In principle, it is possible to calculate the external doses from the integrated deposition density of each radionuclide. Table 22 shows the conversion factors for estimating absorbed dose in air, 1 m above ground, that were used in the 1972 report and which are based largely on the work of Beck *et al.* (15). For short-lived radionuclides, a plane source on the surface of the ground is postulated, but for ^{137}Cs an exponential profile is assumed with a mean depth of 3 cm.

TABLE 22. CONVERSION FACTORS FOR THE ASSESSMENT OF ABSORBED DOSES IN AIR 1 m ABOVE GROUND

	^{95}Zr	^{103}Ru	^{106}Ru	^{137}Cs	^{140}Ba	^{141}Ce	^{144}Ce
Dose-rate conversion factor (mrad y^{-1} per mCi km^{-2})	0.341[a]	0.072	0.042[a]	0.033	0.316[a]	0.011	0.004[a]
Mean life (y)	0.257	0.157	1.44	43.7	0.051	0.129	1.13
Dose conversion factor (mrad per mCi km^{-2})	0.087	0.011	0.060	1.44	0.016	0.0014	0.0045

Note: A plane source on the ground surface is assumed except for ^{137}Cs, for which the source is assumed to be exponentially distributed with a mean depth of 3 cm.

[a] Including contributions from the daughter radionuclides, assumed in transient equilibrium.

145. The assessment of organ doses from absorbed doses in air is discussed in Annex A. A combined factor of 0.8 is used in this report to account for the change of material (air to tissue) and for back-scatter and shielding afforded by other tissues of the body. The estimation of the organ doses from external radiation due to fallout require the use of a further factor representing the shielding effect of buildings. This shielding is taken to reduce the absorbed dose rate in air in the building, on average, to 20 per cent of its outdoor value. Assuming that on the average 80 per cent of the time is spent indoors, the effective shielding factor of the building is 0.4 (241, 245).

146. The overall factor used in this report to convert air absorbed doses to organ doses is therefore 0.8 X 0.4 = 0.32. Transfer factors P_{25} relating integrated depositions of selected gamma-emitting nuclides to the resulting doses in the tissues of interest to the Committee can be calculated by multiplying the conversion factors shown in table 22 by 0.32.

A. SHORT-LIVED RADIONUCLIDES

147. Although the deposition of short-lived radionuclides has not been measured over the whole period during which nuclear tests were conducted, there are sufficient data available to estimate approximately the mean integrated deposition density. This estimation is based on the use of ratios of the time-integrated air concentrations and of integrated deposition densities of the relevant nuclides, assessed from measurements at a

number of sites, and the known latitudinal distribution of the integrated deposition densities of some nuclides, such as ^{90}Sr.

148. The integrated deposition density of ^{144}Ce has been estimated by this procedure in previous sections of this Annex and is shown in table 20. In paragraph 89 it was noted that the $^{106}Ru/^{144}Ce$ activity ratio changes slowly with time and was estimated to be 0.5 during the period of deposition.

149. From the estimated values of the integrated deposition density of ^{144}Ce and ^{106}Ru and the conversion factors of table 22 multiplied by 0.32 (para. 146) it is possible to assess the dose commitment from these nuclides (see table 25).

150. The activity of a number of fission products in air has been monitored at sites varying in latitude in the vicinity of the meridian 80°W since 1963 (117). The ratio of the time-integrated air activity of ^{95}Zr to that of ^{90}Sr for the period 1966-1974 is plotted as a function of latitude in figure XIII. By 1966 there was probably very little ^{95}Zr activity left from tests prior to 1963. The deposition density of ^{95}Zr in each latitude band in the period 1966-1973 was estimated from the corresponding data for ^{90}Sr for the same period, using ratios taken from figure XIII. The results are shown in table 23 (117).

TABLE 23. LATITUDINAL DISTRIBUTION OF ^{95}Zr INTEGRATED DEPOSITION DENSITY, 1966-1973

Latitude band	*Area of band (10^6 km^2)*	*Relative population of band (%)*	*Integrated deposition density of ^{95}Zr (mCi km^{-2})*
70°-80°N	11.6	0.0	8
60°-70°N	18.9	0.4	28
50°-60°N	25.6	12.2	61
40°-50°N	31.5	13.8	64
30°-40°N	36.4	18.2	59
20°-30°N	40.2	29.2	49
10°-20°N	42.8	9.8	27
0°-10°N	44.1	5.6	32
0°-10°S	44.1	5.8	98
10°-20°S	42.8	1.8	137
20°-30°S	40.2	1.6	195
30°-40°S	36.4	1.4	147
40°-50°S	31.5	0.1	105
50°-60°S	25.6	0.05	23

Source: Reference 155.

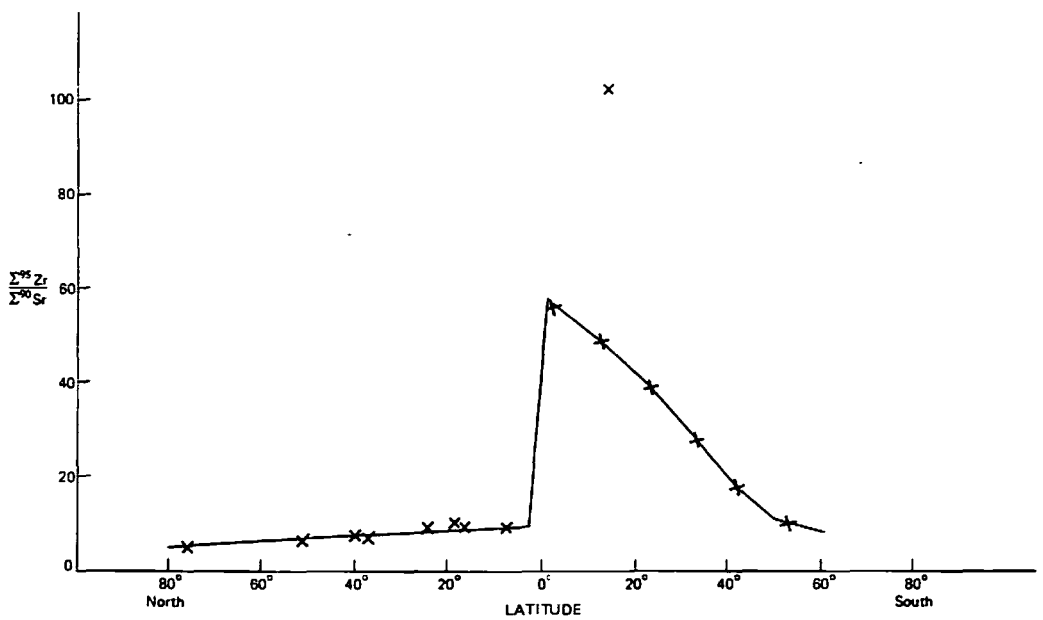


Figure XIII. Latitudinal variation of the ratio of time-integrated air concentrations of ^{95}Zr and ^{90}Sr for the period 1966-1974

151. There are few data on the global deposition of ^{95}Zr prior to 1963, and it is probably in this period that the greatest deposition occurred in the northern hemisphere. It is possible to estimate the ^{95}Zr integrated deposition density from that of ^{89}Sr if some reliable estimate for their ratio could be made. The $^{95}Zr/^{89}Sr$ ratio only changes with a half-time of about 200 d owing to radioactive decay. The ratio of the time-integrated air concentrations $\Sigma^{95}Zr/\Sigma^{89}Sr$ in 1963 at Thule (Greenland), Moosonee (Canada), Sterling and Miami (United States) were 2.3, 2.7, 2.9 and 3.0, respectively, with a mean of 2.7 (117). The mean ratio at seven northern hemisphere sites in 1962 was 1.5 (60, 115, 242). The northern hemisphere deposition of ^{89}Sr in 1962 and 1963 of 27 and 15 MCi respectively, reported by Hardy (111), leads to a weighted mean of 1.93 for the integrated concentration ratio $\Sigma^{95}Zr/\Sigma^{89}Sr$.

152. Between 1961 and 1969 the deposition density of ^{89}Sr in the 40°-50°N latitude band was 346 mCi km^{-2} (111). Using the ^{90}Sr deposition data given in table 2 as a guide, the ^{89}Sr deposition density in this zone up to 1966 is estimated to be 477 mCi km^{-2} in the northern hemisphere and 57 mCi km^{-2} for the same zone in the southern hemisphere. The ^{95}Zr deposition densities in the northern and southern 40°-50° zones up to 1966 are estimated as 920 and 110 mCi km^{-2} respectively, using the $\Sigma^{95}Zr/\Sigma^{89}Sr$ ratio of 1.93 given in paragraph 151. Adding to these numbers the corresponding values for the period 1966-1974 from table 3, the estimated ^{95}Zr deposition densities up to the end of 1973 are 984 and 214 mCi km^{-2} for the northern and southern 40°-50° zones, respectively. The population-weighted global average ^{95}Zr deposition density is estimated, using the ^{90}Sr data as a guide, to be 650 mCi km^{-2}.

TABLE 24. RATIO OF THE INTEGRATED DEPOSITION DENSITIES OR OF THE TIME-INTEGRATED AIR CONCENTRATIONS OF ^{103}Ru, ^{141}Ce, ^{140}Ba and ^{95}Zr AT VARIOUS LOCATIONS AND TIMES

Location	*Period*	*Type of ratio*	$\frac{\Sigma^{103}Ru}{\Sigma^{95}Zr}$	$\frac{\Sigma^{141}Ce}{\Sigma^{95}Zr}$	$\frac{\Sigma^{140}Ba}{\Sigma^{95}Zr}$
Buenos Aires, Argentina	1966-1974	Deposition density	0.72	–	0.92
Pretoria, South Africa	1966-1973	Air concentration	0.88	–	0.89
Stockholm, Sweden	1969-1972	Air concentration	–	0.19	0.52
Chilton, United Kingdom	1961-1964	Deposition density	–	–	0.63
Chilton, United Kingdom	1967-1970	Deposition density	0.66	0.53	0.46
Pittsburg, United States	1961-1963	Deposition density	–	0.93	0.26
		Average	0.75	0.55	0.62

153. It is possible to estimate the dose commitment from ^{103}Ru, ^{141}Ce and ^{140}Ba from the calculated ^{95}Zr integrated deposition density. Table 24 gives the ratios of the integrated air concentrations or integrated depositions of these radionuclides to that for ^{95}Zr for several sites and periods of time. If F_j is the integrated deposition density of radionuclide j and K_j is the conversion factor of table 22 multiplied by 0.32 (para. 146), the total external dose commitment can be expressed as

$$D^c = \sum_j K_j F_j = K_a F_a + F_a \sum_{j \neq a} K_j \frac{F_j}{F_a} \qquad (13)$$

and therefore

$$D = K_a^* F_a \qquad (14)$$

where K_a^*, the effective P_{25} factor for nuclide a, is defined by

$$K_a^* = K_a + \sum_{j \neq a} K_j \frac{F_j}{F_a} \qquad (15)$$

154. In this way the dose commitment from a group of radionuclides can be estimated from the integrated deposition density of a given radionuclide a. The effective P_{25} factor for computing the dose commitment due to ^{95}Zr, ^{103}Ru, ^{141}Ce and ^{140}Ba from the ^{95}Zr deposition density was determined using equation 15 together with the integrated activity ratios of table 24 and the conversion factors of table 22 multiplied by 0.32 (para. 146). The estimated value of this effective conversion factor is 0.034 mrad per mCi km^{-2}, with upper and lower limits of 0.04 and 0.03 mrad per mCi km^{-2}, respectively, obtained by using the largest and smallest ratios shown in table 24.

155. The combined dose commitments from ^{95}Zr, ^{103}Ru, ^{141}Ce and ^{140}Ba, calculated using this effective P_{25} factor and the estimated ^{95}Zr integrated deposition density given in paragraph 152, is shown in table 25, which also shows the total dose commitment from short-lived radionuclides.

TABLE 25. DOSE COMMITMENT DUE TO EXTERNAL RADIATION FROM SHORT-LIVED RADIONUCLIDES

(mrad)

Radionuclide	*Northern temperate zone*	*Southern temperate zone*	*Global (population-weighted)*
^{144}Ce	1.8	0.5	1.0
^{106}Ru	12	3.5	7.3
$^{95}Zr + {}^{103}Ru + {}^{141}Ce + {}^{140}Ba$	34	7.4	22
Total	48	11	30

Note: These estimates include a factor of 0.32 to allow for body screening and average shielding from buildings.

156. It is interesting to compare the estimated values of table 25 with actual determinations of the external dose in both hemispheres. At Chilton in the United Kingdom the total gamma absorbed dose in air from fallout has been determined by a combined procedure including direct measurements and computation from measured depositions (61). The estimate, for the period 1951 to 1973, is 137.7 mrad; the contribution from ^{137}Cs is estimated as 33.3 mrad, so that the contribution from short-lived radionuclides is 104.4 mrad. The corresponding tissue dose (applying the factor 0.32) is 33 mrad. In the southern hemisphere, for Buenos Aires up to 1975, a tissue dose of 15 mrad has been estimated (19, 20, 166, 167), based upon direct calculation from measured deposition densities of individual short-lived fission products.

B. CAESIUM-137

157. The integrated deposition density of ^{137}Cs from all tests was given in paragraph 115. Using this information and the conversion factor for caesium from table 22, multiplied by 0.32 (para. 146), the dose commitment to body tissue is estimated to be (mrad): northern temperate zone, 62; southern temperate zone, 18; world population, 38.

C. TOTAL DOSE COMMITMENT FROM EXTERNAL IRRADIATION

158. The global dose commitment from external irradiation is estimated to be 68 mrad, the combined short-lived nuclides and ^{137}Cs contributing each about half of this value. As ^{137}Cs released in nuclear detonations is accompanied by a given proportion of short-lived products, it is possible to assess the collective dose commitment from external exposure normalized to unit activity of ^{137}Cs released. The value calculated by the procedures indicated in Annex A is of the order of 10 man rad Ci^{-1}.

IV. SUMMARY OF DOSES AND DOSE COMMITMENTS FROM NUCLEAR EXPLOSIONS

159. It is difficult to summarize the doses for the whole world population from nuclear test explosions because they arise from a variety of radionuclides which differ widely in their behaviour in the environment and in their dosimetric characteristics. To state current annual doses would reveal only a small part of an exposure situation,

which is known to vary not only with time, but also with geographical location, living conditions and age. For a given group of individuals, for whom these factors are known, the annual doses from external and internal exposures may be presented as a function of age for some selected organs and tissues of interest; that would give a full picture of the annual doses for the particular groups. For some long-lived radionuclides that are globally distributed, such as ^{137}Cs, this information may be derived for the whole world population as *per caput* annual doses which would be representative of individuals irrespective of age and location. For other radionuclides, however, the individual annual doses will vary substantially with location and age. That is the case with short-lived radionuclides, such as ^{131}I, ^{131}I, as regards location, and with bone-seeking radionuclides, such as ^{90}Sr, as regards age. Even for these radionuclides, however, once the population group of interest has been identified, it is possible to describe the current and expected exposure situations for the individuals involved, drawing on the information given in the various sections of this Annex.

160. If the variation of individual organ dose rates with time were known for all locations, living conditions and ages, a world population *per caput* dose rate could be calculated. Its integral over infinite time would be the global dose commitment from the nuclear explosions to date. Using the methods described in this Annex, however, this integral can be evaluated even though the *per caput* dose rate as a function of time is not known or is difficult to derive. Because the global dose commitment, as described in Annex A, can be used as a relative measure of the detriment, the Committee, as in previous reports, has found this quantity to be a useful single measure of the irradiation consequences for the whole world population. It is therefore summarized in table 26.

TABLE 26. SUMMARY OF DOSE COMMITMENT FROM RADIONUCLIDES PRODUCED IN ALL NUCLEAR TESTS CARRIED OUT BEFORE 1976

(mrad)

	Northern temperate zone				*Southern temperate zone*				*World population*			
Source of radiation	*Gonads*	*Bone marrow*	*Bone lining cells*	*Lung*	*Gonads*	*Bone marrow*	*Bone lining cells*	*Lung*	*Gonads*	*Bone marrow*	*Bone lining cells*	*Lung*
External												
Short-lived nuclides	48	48	48	48	11	11	11	11	30	30	30	30
^{137}Cs	62	62	62	62	18	18	18	18	38	38	38	38
Internal												
^{3}H	2	2	2	2	0.2	0.2	0.2	0.2	2	2	2	2
^{14}C[a]	7	32	29	9	7	32	29	9	7	32	29	9
^{54}Mn				1								1
^{55}Fe	1	0.6	1	1	0.3	0.2	0.3	0.3	0.7	0.4	0.7	0.7
^{90}Sr		84	120			24	33			52	71	
^{89}Sr		0.4								0.3		
^{106}Ru				41				10				24
^{137}Cs	27	27	27	27	8	8	8	8	17	17	17	17
^{144}Ce				65				15				38
^{239}Pu[b]			1	1			0.3	0.3			0.9	0.9
Total[c]	150	260	290	260	45	93	100	72	94	170	190	160

Notes: 1. The dose commitments for ^{85}Kr, ^{136}Cs and ^{140}Ba, although discussed in the text, are not shown in this table because they are negligible compared with the values included.

2. For internal irradiation, where body activities have been measured, uncertainties are probably within a factor of 2. For external irradiation and for lung-dose estimates, where the models used were not checked by direct measurement, the uncertainties are probably within a factor of 5.

[a] Dose accumulated up to the year 2000. The total dose commitment to gonads and lung is about 120 mrad, to bone lining cells 414 mrad and to bone marrow 455 mrad, delivered over some 8300 y.

[b] These dose commitments appear to be the same in different organs because of rounding. Only inhalation contributions are shown; for discussion on the ingestion pathway see chapter II, section N.

[c] Rounded to two significant figures.

161. The values shown in table 26, taken from the relevant paragraphs in the preceding sections, have been rounded off. For this reason, when the differences between the estimated organ dose commitments are small, the table gives the appearance of a uniform dose over several organs. In the case of doses from external gamma radiation, or from internal emitters that are homogeneously distributed in the body, such as ^{3}H and ^{137}Cs, the dose commitment is essentially the same for all the relevant organs of the body.

162. The methods for calculating the values of the dose commitments given in table 26 have been reassessed since the 1972 report of the Committee. In some cases, particularly for short-lived nuclides and ^{90}Sr, this reassessment has produced dose commitment estimates that differ significantly from those given in the 1972 report.

163. For the radionuclides listed in table 26, the irradiation to which the world population was committed by nuclear tests up to 1975 is already largely completed for all except ^{137}Cs (external and internal), ^{3}H, ^{14}C, ^{90}Sr and ^{239}Pu. Therefore, in terms of current annual doses, only these five nuclides need to be considered. Caesium-137 makes major contributions for

all body tissues which are essentially independent of age; whereas the further substantial contribution from ^{90}Sr in bone marrow and bone lining cells is strongly dependent on age. In comparison, the contributions of ^{3}H, ^{14}C and ^{239}Pu to current annual doses are very small.

164. Although ^{137}Cs and ^{90}Sr are the only substantial contributors to current annual doses to the body organs and tissues included in table 26, it is not possible to summarize this annual dose situation in a simple description for the whole world population. It may be helpful, however, to indicate the magnitude of the annual doses in 1975 using ^{137}Cs as an illustrative example. Whole-body contents of ^{137}Cs in 1975 (table 19) ranged from 8 to 29 pCi $(gK)^{-1}$, which would have caused annual doses to body tissues in the range 0.1-0.5 mrad. The external exposure from ^{137}Cs deposition in soil would have added less than 0.2 mrad to these doses. Because of the long half-life of ^{137}Cs, the world population is committed to continued exposure from this radionuclide for many years. This accounts for the substantial contribution of ^{137}Cs to the dose commitment.

165. For nuclear tests carried out in the atmosphere in the northern and southern hemispheres since the Committee's 1972 report, ^{131}I in milk supplies has led to irradiation of the thyroid glands of exposed populations in the periods immediately following the tests. Doses due to ^{131}I in infant thyroids–the most highly exposed organ–ranged up to 15 mrad in the northern hemisphere in 1974 and 1976, whereas, in the southern hemisphere, doses to infant thyroid ranged up to about 100 mrad in 1973 and up to some hundreds of mrad in 1974.

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ANNEX D

Radioactive contamination due to nuclear power production

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Introduction

1. The use of nuclear reactors to generate electricity has continued to increase since the Committee's first attempt to assess the radioactive releases from the nuclear fuel cycle and the resulting dose commitment (140). The total installed nuclear electric generating capacity in the world in 1976 was 79.8 GW from 188 reactors operating in 19 countries (66). The predicted capacity for 2000 is 2000 GW, about half the value predicted in the 1972 report of the Committee.

2. The nuclear fuel cycle consists of the process of mining and milling of uranium, conversion to fuel material, usually including enrichment in the isotope ^{235}U, fabrication of fuel elements, utilization of the fuel in nuclear reactors, reprocessing of spent fuel and recycled utilization of recovered fissile materials, transportation of material between fuel-cycle installations, and disposal of radioactive wastes.

3. Almost all the radioactivity associated with the fuel cycle is present in stored, spent fuel elements and in well contained fractions separated from the fuel during the reprocessing operations. However, at each step of the fuel cycle, releases of small quantities of radioactive material into the environment may occur. Most of the radionuclides released into the environment are only of local or regional concern, because their half-lives are short compared to the time required for dispersion to greater distances. Some radionuclides, on the other hand, having longer half-lives or being more rapidly dispersed, can become globally distributed.

4. The Committee is interested in assessing the dose commitments due to releases of radioactive material from all fuel-cycle operations. As the scale of these operations is related to the nuclear installed capacity they serve, it seems reasonable to express such assessments in terms of the dose commitment (or collective dose commitment) per unit of electrical energy generated (MW(e) y).

5. The total collective dose commitment to the world population may be assessed by estimating the contribution from four components: the occupationally exposed group, the local population, the regional or intermediate population, and the world population. This Annex deals only with the collective doses incurred through exposure of the public, while the occupational contributions are analysed in Annex E. The local and regional contributions to the collective dose commitment are discussed separately for each component of the fuel cycle; the global contributions made by nuclides of world-wide distribution are discussed for the cycle as a whole. The handling of solid wastes generated in the nuclear fuel cycle is considered in chapter V of this Annex.

6. Doses and collective dose commitments to local and regional populations can be estimated satisfactorily given adequate knowledge of the effluents, the transfer factors in the routes by which man is exposed and the results of properly designed environmental monitoring programmes. However, the data based on measurements available to the Committee are insufficient for the purpose of assessing all collective dose commitments, especially global collective dose commitments, from all fuel cycle operations, and some generalizations concerning effluent release rates and environmental transfer factors have had to be made. Monitoring programmes are usually confined to local areas and are frequently planned to verify compliance with applicable regulations. More detailed measurements are seldom carried out and in many situations are not even feasible. In some cases, however, monitoring can contribute to improvements in the assessment of model parameters, monitoring and modelling being in these cases complementary procedures.

7. The Committee has reviewed information relating to both approaches. Since the 1972 report, a number of national and international symposia have dealt with various aspects of environmental dispersion mechanisms and of population exposures (46, 63, 67, 69, 149, 150). A wide range of other publications have contributed to increased knowledge of environmental transport and improved estimates of radiation doses. In addition, environmental and safety studies for specific fuel-cycle installations and a few comprehensive reviews of the entire fuel cycle have been prepared (148, 151, 153, 156, 157, 158, 162).

8. The discussion of the effluents of nuclear power installations and the collective dose estimates are, as far as possible, based on operating experience. Included are data on releases in all periods of operation, including those associated with abnormal operation or with periods in which there is no electricity generated or fuel reprocessed. The averages, therefore, do not represent typical release rates during normal operation, but instead reflect the overall nuclear power experience, normalized to the total amount of generated electricity. Where operating experience is insufficiently documented, some generalizations regarding effluent release rates and the environmental transfer parameters are made in order to make a complete assessment of the collective doses from nuclear fuel-cycle operations. It must be stressed that such generalizations will always lead to less accurate estimates of the dose commitments than assessments based directly on studies of particular releases and the particular environment into which the releases are made. Moreover, in the future, improved practices may give results that are considerably different from those derived from current and past experience. Therefore, any application of the assessments given here to more specific situations or any extrapolation to the future must recognize these inherent limitations.

9. In addition to the small releases of radioactive material during normal operation the possibility exists that additional amounts of radioactive materials may be accidentally discharged. A number of studies have considered the potential composition and amounts of accidental releases (61). The assessment of population exposure due to long-term nuclear power programmes requires the estimation of the expected contribution of such events. Recent evaluations of their probability make it possible to assess the expectation of collective dose from the release of radioactive material due to accidents in reactors, as discussed in the appendix.

I. MINING AND MILLING

10. Uranium is obtained from ore mined in several countries throughout the world. The countries with the largest production during 1975 were Canada, France, South Africa and the United States of America. Reserves of varying quantity and grades, and mining operations of varying scale are reported in several other countries (110).

11. Uranium ore has been obtained mainly from underground mines, although large amounts are now coming from open-pit mines. In the United States, 70 per cent of the ore production in 1973 came from 33 open-pit mines and the remainder from 122 underground mines (14). In South Africa, uranium is extracted from gold-mine tailings (117).

12. Since the ore normally contains less than 0.2 per cent uranium, processing mills are usually located in the mining areas to avoid transportation of large quantities of what is ultimately waste material. In some cases, however, ore is treated locally by heap-leaching, and precipitated pre-concentrates are then transported to the mills. In the mills, the ore is blended and crushed, then wet ground and transferred as a slurry to leaching tanks. According to the ore characteristics, either a sulphuric acid or a sodium carbonate alkaline leach process is utilized. The soluble uranium is recovered by solvent extraction, or, in the case of the alkaline leach process, by precipitation. The uranium concentrate is calcined and pulverized, forming the final product of the mill, the semi-refined compound called yellowcake.

A. EFFLUENTS

13. Mine wastes include liquids, solids, and exhaust ventilation gases. The liquids are mostly water from mine drainage and water used in drilling; it is discharged to ponds and allowed to evaporate. Leaching of mine tailings may be an additional source of liquid waste. Solid waste is primarily waste rock and low-grade ore. Ventilation of mines results in the discharge of large volumes of air containing radon and radon daughters.

14. The radionuclides contained in the ore include uranium, primarily ^{238}U, and the uranium daughter products, such as ^{230}Th and ^{226}Ra. In most cases little, if any, natural thorium (^{232}Th) is contained in the mill feeds. One tonne of ore containing 2 kg U_3O_8 has an activity of 566 μCi from each member of the ^{238}U decay chain, or a total of about 7900 μCi (126). About 14 per cent of the total activity contained in the ore fed to the mills is recovered in the uranium concentrate (14), while the average recovery of uranium is 91 per cent. In addition, the uranium concentrate contains about 5 per cent of the total thorium and 0.2 per cent of the radium contained in the ore (126). With little of the parent remaining, the short-lived daughters ^{234}Th (24.1 d), ^{234m}Pa (1.17 min) and ^{231}Th (25.5 h) are lost by decay from the mill wastes. The remaining 70 per cent of the activity originally present in the ore is largely undissolved and is discharged in the solid mill tailings.

15. Most of the radium in the ore is insoluble and remains in the tailing solids; a small portion, about 1 per cent or less, is dissolved. Radium in mill liquid effluents may vary from 250 to 500 pCi l^{-1} (14). Up to 50 per cent of the ^{230}Th in the ore may be dissolved in acid solutions and be contained in liquid effluents until the solution has been neutralized and the thorium precipitated. The radionuclides ^{223}R, ^{227}Th, ^{227}Ac, ^{210}Pb and ^{210}Po may also be present in the liquid effluents, but relatively little information is available on those nuclides because the ^{226}Ra level has been the most restrictive, making ^{226}Ra the most relevant nuclide of concern. At most mills, tailing ponds are of sufficient size for waste liquids to evaporate or seep into the ground. When space is not available, some liquid effluents are released into rivers, usually after treatment to reduce the radium content.

16. Releases of radioactive particles and radon gas into the air during milling operations may originate from the ore piles, the crushing, grinding and leaching operations, and the tailings piles. The release of radon activity from a dry tailings pile containing 560 pCi ^{226}Ra per gram is estimated to be 500 pCi m^{-2} s^{-1} (156). The release rate at any one location may vary, however, by an order of magnitude owing to the effects of such weather variables as wind speed, barometric pressure, atmospheric stability, rainfall, and snow cover (133). A pile saturated with water, as it may well be at an operating mill, may have its radon release rate reduced by a factor of 25 (156).

17. From a recent survey of milling practices at active uranium mills in the United States (126), the annual airborne radioactive releases from operating mills at two representative locations have been estimated. Table 1 gives the average and normalized (per MW(e) y) releases of various radionuclides from a mill processing 664 000 t of ore per year (151). The ore is assumed to be dusty and to contain 6 per cent moisture. Dust from ore crushing contains all radionuclides in equilibrium. However, yellowcake dust contributes to the uranium release and accounts for the lack of equilibrium in the total release. The sources of the airborne radioactivity in this estimate, in addition to the mill itself, include radon from the tailings pond and radon and particulates from the dry beach area. Since in this particular survey the maximum value of dry beach area was assumed for an active mill, namely the value that applies near the end of the assumed 20-y life of the mill, the releases from the dry beach area have been reduced by a factor of 2 to reflect more nearly average values for an operating mill. This correction mainly affects the amounts of radon released.

TABLE 1. ESTIMATED RADIOACTIVE AIRBORNE EFFLUENTS FROM MILLING OPERATIONS

Radionuclide	*Annual activity release from mill and active tailings area*[a] *(Ci)*	*Normalized release*[b] *(mCi per MW(e) y)*
^{238}U	0.09	0.01
^{234}U	0.09	0.01
^{234}Th	0.01	0.001
^{230}Th	0.01	0.001
^{226}Ra	0.009	0.001
^{210}Pb	0.009	0.001
^{210}Bi	0.009	0.001
^{210}Po	0.009	0.001
^{222}Rn	1 400	170

Source: Reference 126.

[a] Assuming an ore processing rate of 664 000 t y^{-1}.

[b] Assuming a uranium content of 0.2 per cent and an annual requirement of 160 t of uranium for a 1 GW(e) light-water reactor.

18. The tailings area remaining after the mill has ceased operation becomes a long-term source of environmental radioactive contamination due to wind or water erosion and to radon emanation. Stabilization programmes are generally conducted or planned so that erosion from tailing areas is alleviated (126). Radon-222 arises from decay of ^{226}Ra in secular equilibrium with long-lived ^{230}Th (80 000 y). A few per cent of uranium isotopes in the ore may also remain in the tailings material, constituting through the decay chain an even more long-lived source of ^{222}Rn emanation.

19. Emanation from the tailings arises primarily from radon produced in the surface layer. Of the total radon produced, up to about 20 per cent diffuses out of the crystallized structure of the mineral (28). The relatively short half-life of ^{222}Rn (3.8 d) results in the decay of much of the radon during gaseous diffusion towards the surface of the tailings pile. About 90 per cent of the radon released to the air originates in the top 1-2 m (124, 156), and the release rate is not changed by increasing the tailings depth much beyond about 3 m.

20. Covering the tailings pile with soil reduces the radon emanation rate by a factor of two for each metre of cover. Accordingly, about 6 m of earth cover is required to reduce the emanation to values observed naturally for soils (124).

B. LOCAL AND REGIONAL COLLECTIVE DOSE COMMITMENTS

21. Kristan *et al.* (78) have reported ^{226}Ra to be the most significant nuclide in water releases from mining and milling operations. When, as a result of releases, there is some increased radium concentration in fish, consumption of fish could be the dominant exposure pathway to individuals in the local population. Another possible pathway is via drinking water.

22. An inactive mill at Durango, Colorado (United States), has been studied extensively (137, 138). Before 1959, this mill discharged untreated effluents into the Animas River. Estimated ^{226}Ra release rates to the river were 0.2 mCi d^{-1} in dissolved form and 30 mCi d^{-1} in suspended solids (36). The radium concentration in the river was 12.6 pCi l^{-1} below the mill and 2.9 pCi l^{-1} 100 km downstream, compared to 0.3-0.6 pCi l^{-1} upstream. Concentration factors of 500-1000 for algae and aquatic insects, 3-4 for fish flesh and 100 for fish bone were reported (137). Because of the environmental contamination, waste treatment was introduced, which reduced the concentration of ^{226}Ra in the river to essentially the natural level (137). More recent surveys of uranium milling areas in the United States have not shown measurable water contamination beyond the plant sites (129, 130, 131).

23. Under the assumption that adequate waste treatment prevents seepage of process liquid effluents directly into rivers, the local collective dose commitments from milling operations are expected to depend on the airborne releases (table 1), which contribute to external exposure from deposited material and to internal exposure via the inhalation and ingestion pathways. The mills in the United States are typically located in areas not particularly suited for farming. The raising of beef cattle in the vicinity of the mills and the consumption of the beef may represent the only significant contribution to the intake by ingestion. Population in the milling areas is generally sparse and little growth can be expected. Based on a survey of five mills in the United States, Sears *et al.* (126) found that a population of about 5 10^{4} within a radius of 80 km is representative. This corresponds to an average population density of less than 3 km^{-2}, with lower and non-uniform population densities very close to the mill. For areas at a greater distance, a population density of 25 km^{-2} would be representative. Variations in these figures, particularly the local population density, would be expected for specific mills in various other countries.

24. The collective dose from direct inhalation of radioactive materials released during operation can be assessed by considering the dispersion of the airborne particulates and radon with distance from the mill or tailings area. Annual average dispersion factors of about 10^{-6} s m^{-3} at 1 km have been found appropriate for the meteorology of typical mill locations (126), while for large area sources the value is smaller by a factor of about 4 (156). In this Annex, a value of 5 10^{-7} s m^{-3} at 1 km is assumed to apply for both the mill and the tailings area.

25. Over a limited range, the decrease of the concentration of activity in air with distance from the source appears to be approximately inversely proportional to the 1.5 power of the distance (126), but this behaviour cannot be easily verified by measurements since concentrations barely exceed natural levels at a few kilometres. Shearer and Sill reported measurements of radon concentrations 5, 1.5 and 0.15 times background at 0.8, 1.7 and 8.3 km respectively from inactive mill tailing areas (127). This corresponds to concentrations inversely proportional to the 1.5 power of the distance. Similar results were obtained by Breslin, who analysed various measurements of radon and particulate concentrations with distance from seven tailings areas (20). The relationship at much greater distances must be assumed to be only approximate, but it should serve to give indications of average dispersion over longer release periods.

26. Deposition of the airborne particulates reduces the area over which the integration of collective doses is carried out. For ground-level releases of particulate material, less than 30 per cent of the released material remains in the plume at 100 km and less than 20 per cent at 200 km (164). Integrating the collective doses to 500 km, therefore, will include virtually all the collective dose from airborne particulates released by the mill. Estimates of the collective doses from direct inhalation of particulates, calculated assuming the population distribution given in paragraph 23, are summarized in table 2.

27. The collective dose commitment from radon released during operations from the mill and the tailings area can be estimated by the same procedure used for the case of inhalation of particulates. For a radon release of 0.17 Ci per MW(e) y (table 1), and using a dispersion

TABLE 2. ESTIMATED COLLECTIVE DOSE COMMITMENT FOR AIRBORNE PARTICULATE RELEASES FROM MILLING OPERATIONS

Radionuclide	Normalized activity released (Ci per MW(e) y)	Collective dose commitment per unit activity released (man rad Ci^{-1})							Normalized incomplete collective dose commitment (man rad per MW(e) y)		
		Ingestion[a]			Inhalation			External			
		Lung (whole)	Bone marrow	Bone lining cells	Lung (whole)	Bone marrow	Bone lining cells	Whole body	Lung (whole)	Bone marrow	Bone lining cells
^{238}U	$1\ 10^{-5}$	0.06	0.1	0.4	1.2	0.06	0.3		$1\ 10^{-5}$	$2\ 10^{-6}$	$7\ 10^{-6}$
^{230}Th	$1\ 10^{-6}$	0.06	0.03	0.4	19.0	12.0	180.0		$2\ 10^{-5}$	$1\ 10^{-5}$	$2\ 10^{-4}$
^{226}Ra	$1\ 10^{-6}$	0.04	0.1	1.0	3.6	0.09	0.6	10.0	$1\ 10^{-5}$	$1\ 10^{-5}$	$1\ 10^{-5}$
^{210}Pb[b]	$1\ 10^{-6}$	0.09	0.3	1.0	1.7	0.7	2.5		$2\ 10^{-6}$	$1\ 10^{-6}$	$4\ 10^{-6}$

[a] The values are the incomplete collective dose commitments due to deposition on the ground, incurred mainly through the ingestion pathway but also including a contribution from inhalation of resuspended materials. External exposure from deposited activity (^{226}Ra including its daughters) is considered separately.

[b] Including the contribution to dose from ^{210}Po daughter.

factor of $5\ 10^{-7}$ s m^{-3}, the normalized time-integrated concentration in air at 1 km is 0.024 pCi h l^{-1} per MW(e) y. Using a dose factor of 45 μrad per pCi h l^{-1} for radon in equilibrium with its daughters and an equilibrium factor $F = 0.6$ (see Annex B), the normalized dose commitment at 1 km is estimated to be $6\ 10^{-4}$ mrad per MW(e) y. At a few kilometres the equilibrium factor outdoors is probably smaller than 0.6 but would increase indoors because of the delay of the air circulated indoors. Therefore, not much error is introduced by assuming that the same value (0.6) applies over tens of kilometres. The local collective dose commitment within 100 km from the mill can be estimated to be

$$S^c = \int_1^{100} D_1 \left(\frac{\rho}{\rho_1}\right)^{-1.5} N_\delta\ 2\pi\rho\ d\rho = 2\ 10^{-4} \text{ man rad per MW(e) y}$$

where D_1 is the dose commitment per unit electricity generated at the reference distance ρ_1 = 1 km, N_δ is the population density (3 km^{-2}), and ρ is the distance from the mill.

28. The regional collective dose commitment from 100 to 1500 km, obtained from similar integrations, but adjusted to account for radioactive decay and assuming a population density of 25 km^{-2} (para. 23), is $4.4.\ 10^{-3}$ man rad per MW(e) y. The sum of the local and regional components of the collective dose commitment is $5\ 10^{-3}$ man rad per MW(e) y. This value refers to the basal cells of segmented bronchioles; the corresponding collective dose commitments in the whole lung, gonads, bone marrow, and bone lining cells are listed in table 3.

29. An approximate estimate of the incomplete collective dose commitment due to the deposition of the released particulates by external exposure and the ingestion pathway, including inhalation of resuspended materials, may be obtained by assuming that the released nuclides, once deposited on the ground, behave similarly to their naturally occurring counterparts. Assuming that the deposited nuclides are distributed over a depth of 20 cm of soil and that the dose from all relevant exposure pathways is proportional to the activity concentration in that layer of soil, the incomplete collective dose commitment is given by

$$S^{\tau}_{i,j} = \frac{D^*_{i,j}}{A^*_j} Q_j N_\delta \tau$$

where $S^T_{i,j}$ is the incomplete collective dose commitment in tissue i due to nuclide j, $\dot{D}^*_{i,j}$ is the dose rate in tissue i from the natural levels of nuclide j, A^*_j is the activity per unit surface area in the top 20-cm layer of the naturally occurring nuclide j, Q_j is the activity released of nuclide j (assumed to be equal to the deposited activity), N_δ is the population density, and τ is the assumed duration of the practice. It is assumed in this model that only decay removes the deposited nuclides from the soil.

30. Representative values for $\dot{D}^*_{i,j}$ and A^*_j can be found in Annex B. As most of the released particulate activity is deposited within a distance of 80 km (126), a value of 3 man km^{-2} is used for N_δ. Little is known about the effective residence time of these nuclides in soil. However, a conservative assessment of the incomplete collective dose commitment can be obtained by assuming that the availability of the nuclide decreases only by radioactive decay.

TABLE 3. COLLECTIVE DOSE COMMITMENTS FROM RADON RELEASED DURING ACTIVE MILL OPERATION[a]

(man rad per MW(e) y)

Geographic region	Tissue		
	Segmental bronchioles	Lung (whole)	Gonads, bone marrow, bone lining cells
Local (1-100 km)	$2\ 10^{-4}$	$4\ 10^{-5}$	$3\ 10^{-7}$
Regional (100-1 500 km)	$4\ 10^{-3}$	$9\ 10^{-4}$	$7\ 10^{-6}$

[a] Assuming a normalized release of 0.17 Ci per MW(e) y.

31. Table 2 presents the calculated incomplete collective dose commitments per unit activity released, the estimated amounts and the incomplete collective dose commitments per unit electrical energy generated. The incomplete commitments are integrated over the period of operation of the mills, and give some indication of the maximum future annual *per caput* doses to be expected from that operation, assuming the duration of the milling practice is 100 y. Reasonably assured reserves of uranium ore correspond to approximately 10^6 t of uranium (110), a value equivalent to some 6000 light-water reactor-years. At the presently installed capacity, the mining and milling practice could proceed for less than 100 y, unless further ore reserves become available.

32. The external exposure due to deposited ^{226}Ra will give an absorbed dose rate in air of the order of 30 rad h^{-1} per Ci m^{-2} for a plane source and 5 rad h^{-1} per Ci m^{-2} when the material is evenly distributed in the upper 20 cm of the soil, provided the activity per unit mass is considerably higher than in the soil material. Assuming a shielding factor of 0.32, the incomplete dose commitment will be in the range 4-25 man rad Ci^{-1} or (4-25) 10^{-6} man rad per MW(e) y. The average values are of the order of 10 man rad Ci^{-1} and 10^{-5} man rad per MW(e) y.

33. Estimating of the contribution to the collective dose commitment per MW(e) y made by radon release from the tailings pile remaining after the active life of the mill entails some sophisticated guesswork. Radon emanation could continue for millions of years because of the long half-life of the remaining ^{238}U precursor, but the continued presence of the pile on the surface for such a long period is unlikely. This Annex considers only the simpler but still uncertain case of an uncovered tailings pile undisturbed for times of the order of the half-life of ^{230}Th (80 000 y).

34. The uranium requirement of light-water reactors, 160 t per GW(e) y, is equivalent to 80 000 t of 0.2-per-cent ore, resulting in just slightly less than 80 000 t of solid tailings material. In the United States, more than 80 10^6 t of tailings (equivalent to 10^6 MW(e) y) occupied, 8 10^6 m^2 in 1970 (156), corresponding to 8 m^2 per MW(e) y.

35. For a radon emanation rate from the tailings piles of 500 pCi m^{-2} s^{-1} (156), and a dispersion factor of 5 10^{-7} s m^{-3}, the normalized concentration in air at 1 km is 2 10^{-6} pCi l^{-1} per MW(e) y, assuming that 1 MW(e) y corresponds to 8 m^2 of the tailings pile, as discussed in the previous paragraph. Over the mean life of ^{230}Th (1.44 X 80 000 y), the time-integrated radon concentration is 0.23 pCi y l^{-1} per MW(e) y. Using the dose factors and the dispersion assumptions discussed in previous paragraphs for the case of radon releases during operation of the mill, the collective dose commitments for radon release from the inactive tailings area can be assessed. The dose commitment to segmented bronchioles at 1 km is 50 mrad per MW(e) y. The local (1-100 km) collective dose commitment is estimated to be 20 man rad per MW(e) y, the regional (100-1500 km) value being about 400 man rad per MW(e) y. Both these values correspond to irradiation of the basal cells of segmental bronchioles.

36. An alternative estimate of the collective dose commitment due to radon release from the tailings of an inactive mill can be obtained by comparison with natural radon emanation from soil and the corresponding radon concentration in air. With the assumptions used above and assuming the natural radon exhalation rate to be 0.42 pCi m^{-2} s^{-1} and the corresponding radon concentration in air to be 0.1 pCi l^{-1} (see Annex B), the collective dose commitment is calculated to be

$$S^c = (500\ \text{pCi m}^{-2}\text{s}^{-1}) \left(\frac{0.1\ \text{pCi l}^{-1}}{0.42\ \text{pCi m}^{-2}\text{s}^{-1}} \right) \times$$
$$\times (8\ \text{m}^2\ \text{MW(e)}^{-1}\ \text{y}^{-1})(10^{-6}\ \text{km}^2\ \text{m}^{-2}) \times$$
$$\times (25\ \text{man km}^{-2})(1.44)(80\ 10^3\ \text{y})(0.6) \times$$
$$\times (4.5\ 10^{-5}\ \text{rad pCi}^{-1}\text{h}^{-1}\text{l})(8760\ \text{h y}^{-1})$$
$$\approx 650\ \text{man rad per MW(e) y}$$

in reasonable agreement with the value assessed in the previous paragraph. The corresponding collective dose commitment would be 100 man rad per MW(e) y to the whole lung and 0.8 man rad per MW(e) y to the gonads, bone marrow and bone lining cells. The incomplete collective dose commitments (see Annex A), estimated for an assumed duration of the mining and milling practice of 100 y, are smaller than the above values by a factor of 10^3.

37. Table 4 summarizes the estimated values of the collective dose commitments due to radon release from the tailings area of inactive mills. These estimates are quite uncertain, and the true values will depend strongly on future practice. For example, if the fuel is reprocessed and if uranium is used in breeder reactors, the corresponding equivalent area of the tailings pile (8 m^2 per MW(e) y) will be much smaller and, therefore, the contribution to the collective dose commitment per MW(e) y made by milling will also be reduced.

TABLE 4. COLLECTIVE DOSE COMMITMENT TO TISSUES FROM RADON RELEASED FROM INACTIVE MILL TAILINGS

(man rad per MW(e) y)

Type of commitment	*Segmental bronchioles*	*Lung (whole)*	*Gonads, bone marrow, bone lining cells*
Complete	500	100	0.8
Incomplete	0.5	0.1	0.0008

Note: The commitment is for the local plus regional areas (radius 1-1500 km), assuming no soil cover. The values should be halved if a soil cover of 1 m is assumed.

II. URANIUM FUEL FABRICATION

38. The uranium ore concentrates produced at the mills are further processed and purified and usually enriched in the isotope ^{235}U before being converted to uranium dioxide or metal and fabricated into fuel elements. Natural uranium, which contains 0.7 per cent ^{235}U, can be utilized in heavy-water or graphite-moderated reactors. Light-water reactors require fuel enriched to 2-4 per cent ^{235}U.

39. Gaseous diffusion is the usual procedure for enrichment, but other methods can also be used. The U_3O_8 concentrate extracted from the ore must first be converted to the volatile compound, uranium hexafluoride (UF_6). The hydrofluor process consists of reduction, hydrofluorination and fluorination of the ore concentrates to produce crude UF_6, followed by fractional distillation to obtain the pure product. At the gaseous-diffusion installation, the UF_6 is pumped through a series of porous barriers which discriminate against the passage of the heavier isotope of uranium by a factor of 1.0043 at each stage. About 1700 barrier stages are required to produce an enrichment to 4 per cent (151).

40. In the final fuel fabrication step, UF_6 is converted again to an oxide or to the metal for use in fuel elements. For use as fuel in light-water reactors, the dioxide powder is pelletized, sintered and loaded into stainless steel or zircaloy tubing which is then capped and welded. Uranium-metal fuel for use in some gas-cooled reactors is clad in magnesium alloy (magnox). The fuel rods are assembled in arrays as fuel assemblies for installation in the reactor core.

A. EFFLUENTS

41. The radioactive materials discharged to the environment from fuel fabrication, conversion and enrichment installations are limited. Most of the uranium compounds are solid, and conventional air-cleaning equipment is used to remove particulates from airborne wastes. Liquid wastes are collected in settling tanks or ponds. Estimates of release amounts from typical installations, based on limited monitoring information, have been published in the United States (151). A summary of these estimates is given in table 5.

TABLE 5. ESTIMATED RADIOACTIVE RELEASES FROM FUEL FABRICATION OPERATIONS IN THE UNITED STATES

	Installation release rate (Ci y^{-1})		*Equivalent installation size (GW(e))*	*Normalized release (10^{-6} Ci per MW(e) y)*		
	Airborne	*Liquid*		*Airborne*	*Liquid*	*Operation*
U	0.04	1.2	27.5	1.5	44.0	Conversion
	0.18	1.8	90.0	2.0	20.0	Enrichment
	0.005	0.5	26.0	0.2	20.0	Fabrication
^{226}Ra		0.09	27.5		3.4	Conversion
^{230}Th		0.04	27.5		1.5	Conversion
^{234}Th		0.26	26.0		10.0	Fabrication
^{234}Pa		0.26	26.0		10.0	Fabrication

Source: Reference 151.

42. Residual amounts of ^{226}Ra and ^{230}Th are removed from the uranium material in the conversion operation. Small amounts of these isotopes may be included in the liquid effluents from the conversion installations. The thorium daughters of uranium are separated at the mill, but ^{234}Th, with a half-life of 24 d, grows back to over 99 per cent secular equilibrium in 170 d; small amounts of ^{234}Th and its short-lived daughter ^{234}Pa are thus assumed present with uranium in liquid effluents from the fuel fabrication plant.

43. Estimates of the release of radioactive materials into the environment from enrichment and fuel fabrication installations in the United Kingdom are also available (106). The release of uranium to the atmosphere from the Capenhurst enrichment plant in the period 1972-1975 averaged 5 kg y^{-1}. Assuming 280 μCi of ^{238}U and of ^{234}U per kilogram of U_3O_8, the annual release is equivalent to 0.0028 Ci.

44. The alpha activity released annually in liquid effluents from the Capenhurst plant for the same period is estimated to be 0.09 Ci (106). The Springfields fuel fabrication plant in the United Kingdom of Great Britain and Northern Ireland discharged small amounts of liquid radioactive waste into the tidal river Ribble. Average alpha activity released annually in liquid effluents during 1972-1975 was 34 Ci (106).

B. LOCAL COLLECTIVE DOSE COMMITMENT

45. The liquid discharges from the Springfields fuel fabrication plant result in external exposure of individuals who frequent the river bank near the outfall. The annual collective dose due to the local population is estimated to be less than 0.1 man rad (100).

46. Estimates of collective dose commitments from airborne releases can be obtained in a manner similar to that used for releases from milling operations. The combined airborne release of uranium from all fuel fabrication operations, on the assumption that the values given in table 5 are representative, is about 4 10^{-6} Ci per MW(e) y. A population density of 25 km^{-2} has been assumed to apply at all relevant distances from the fuel fabrication installations. The estimated collective dose commitment assumes that the released uranium, once deposited on the ground, will remain available to enter the ingestion or the resuspension-inhalation pathway to man for the entire mean-life of ^{238}U. This assumption obviously leads to a considerable overestimation of the complete collective dose commitments. The values for the incomplete collective dose commitments (see Annex A) given in table 6 assume that fuel fabrication operations to serve reactors will be continued for a limited time, which for purposes of calculation is taken to be 500 y.

TABLE 6. ESTIMATED INCOMPLETE COLLECTIVE DOSE COMMITMENTS FOR URANIUM IN AIRBORNE EFFLUENTS FROM FUEL FABRICATION OPERATIONS[a]

Per unit activity released (man rad per Ci)						*Per unit electrical energy generated (man rad per MW(e) y)*		
Ingestion[b]			*Inhalation*			*Total*		
Lung	*Bone marrow*	*Bone lining cells*	*Lung*	*Bone marrow*	*Bone lining cells*	*Lung*	*Bone marrow*	*Bone lining cells*
0.5	0.8	4.0	2	0.09	0.4	$1\ 10^{-5}$	$4\ 10^{-6}$	$2\ 10^{-5}$

[a]Including conversion, enrichment and fabrication and assuming a normalized ^{238}U release of $4\ 10^{-6}$ Ci per MW(e) y.

[b]The values are collective doses due to deposition on the ground. They are mainly incurred through the ingestion pathway, but include also the contribution from inhalation of resuspended materials.

III. REACTOR OPERATION

47. The common reactor types include the pressurized-water moderated and cooled reactor (PWR), the boiling-water moderated and cooled reactor (BWR), the gas-cooled, graphite-moderated reactor (GCR), the water-cooled, graphite-moderated reactor (LWGR), the heavy-water moderated reactor (HWR), which may be cooled by heavy water, light water or gas, and the fast breeder reactor (FBR).

48. Table 7 gives the number of operational reactors of each type and the electric generating capacity for each country at midyear in 1976 (74). The total installed nuclear generating capacity in the world in 1976 was 79.8 GW(e) from 188 reactors in 19 countries.

A. EFFLUENTS

49. During the operation of a nuclear reactor, radioactive fission and activation products are produced. These radioactive materials are for the most part retained within the fuel elements. Most of the radionuclides which diffuse into or are formed within the coolant are removed by the gaseous and liquid waste processing systems. Low-level releases, which occur during normal operation, are controlled and monitored.

50. The type and quantity of radioactive materials released from reactors depends on the reactor type and on the specific waste processing systems utilized. Radionuclides may reach the environment through either the gaseous or liquid effluent streams. In the airborne effluents are found fission noble gases (krypton and xenon isotopes), activation gases (^{41}Ar, ^{14}C, ^{16}N, ^{35}S), tritium, radioactive halogens and particulates. In the liquid effluents are tritium, fission products and activated corrosion products.

1. Fission noble gases

51. Several isotopes of the noble gases krypton and xenon occur by fission in the nuclear fuel. The total volume of xenon and krypton generated is about 25 cm^3 NTP per thermal megawatt-day. The fraction that escapes from the fuel pellets during normal operation generates gas pressure in the fuel can. The appearance of noble gas activity in effluent streams results mainly from fuel-cladding failure. Only insignificant amounts are formed in the coolant by fission of trace uranium on external fuel-element surfaces.

52. In PWRs the primary coolant is maintained in a sealed loop, which is opened only infrequently. Therefore, much of the short-lived noble gas activity decays before venting. Short-lived noble gases originate mainly from water that has leaked from the primary coolant system.

53. A side stream of the primary coolant in PWRs is continually diverted into a subsystem (primary coolant letdown) for control of chemical content and for coolant purification. The gaseous waste effluents from this system are compressed into tanks and held for a period of 30-120 d for decay of short-lived isotopes. Other gaseous effluent streams in PWRs originate from the main condenser exhaust, secondary coolant blowdown, reactor building ventilation including containment purges (~4 times a year), and turbine and auxiliary building ventilation (166).

54. In table 8, which lists the reported noble gas releases from PWRs, it can be seen that the normalized release amounts span a considerable range. Leakage is an important and variable source term. The total activity released divided by the net electrical energy generated for all PWRs for which effluent data are available varied from 10 to 20 Ci per MW(e) y during 1970-1974. The composition of the release from PWRs is primarily longer-lived ^{133}Xe (5.3 d), but some shorter-lived noble gas isotopes are also present. Krypton-85 (10.7 y) may provide a few per cent to the PWR release activity composition. The activity of specific noble gas isotopes in the releases reported for PWRs in the Federal Republic of Germany and in the United States during 1974 are given in table 9.

55. In BWRs, continuous removal of non-condensable gases in the steam flow occurs via the main condenser air-ejector system. The noble gases enter the gaseous waste stream primarily at this point. Secondary

TABLE 7. WORLD NUCLEAR ELECTRIC GENERATING CAPACITY IN 1976

Net values in MW(e) and number of reactors in parentheses

Country	Reactor type						Total
	PWR	BWR	GCR	HWR	LWGR	FBR	
United States	24 398 (34)	15 208 (23)	330 (1)				39 936 (58)
United Kingdom			6 660 (31)	92 (1)		244 (2)	6 996 (34)
Japan	2 879 (5)	3 264 (7)	154 (1)				6 297 (13)
Germany, Federal Republic of	4 033 (5)	1 148 (4)	14 (1)	52 (1)			5 247 (11)
Union of Soviet Socialist Republics	2 094 (6)	94 (5)			2 882 (11)	146 (2)	5 216 (24)
Sweden	822 (1)	2 362 (4)					3 184 (5)
France	270 (1)		2 133 (7)	70 (1)		250 (1)	2 723 (10)
Canada				2 540 (7)			2 540 (7)
Belgium	1 663 (4)						1 663 (4)
Spain	153 (1)	440 (1)	480 (1)				1 073 (3)
Switzerland	700 (2)	306 (1)					1 006 (3)
German Democratic Republic	879 (3)						879 (3)
Bulgaria	837 (2)						837 (2)
India		396 (2)		207 (1)			603 (3)
Italy	242 (1)	150 (1)	150 (1)				542 (3)
Netherlands	447 (1)	52 (1)					499 (2)
Argentina				319 (1)			319 (1)
Pakistan				125 (1)			125 (1)
Czechoslovakia				110 (1)			110 (1)
Total	39 416 (66)	23 420 (49)	9 921 (43)	3 423 (13)	2 882 (11)	640 (5)	79 794 (188)

Source: Reference 66.

pathways include the turbine gland-seal system, the condenser mechanical vacuum pump, and any leakage of process fluids to ventilated building spaces (165).

56. Table 8 also lists the reported noble gas released activities from BWRs. The normalized releases vary from less than 100 to more than 10 000 Ci per MW(e) y. The value representing the overall operating experience has declined from about 1500 Ci per MW(e) y in 1970 to 1000 Ci per MW(e) y in 1974. The release composition of noble gas isotopes from BWRs varies somewhat, dependent on the specific hold-up time. The hold-up times range from 20 to 30 min for older BWRs to 2 h or more for more recently designed hold-up systems. The reported release compositions for BWRs in the Federal Republic of Germany and in the United Sates during 1974 are given in table 9. Important components of the releases are ^{135}Xe (9.2 h), ^{133}Xe (5.3 d), ^{138}Xe (17 m), ^{88}Kr (2.8 h), ^{87}Kr (76 m) and ^{85m}Kr (4.4 h). The specific release activities are not necessarily typical for any one reactor, but the total normalized release is similar to the overall average from table 8.

57. In GCRs, fission noble gas release is insignificant. Gas-cooled reactors include the Magnox type, the advanced gas-cooled reactor (AGR) and the high-temperature gas-cooled reactor (HTGR). The Magnox type utilizes metallic uranium fuel and CO_2 coolant. Because of the magnesium-alloy cladding fuel temperatures must be kept at less than 650°C, at which temperature release of noble gases from the fuel material is negligible.

TABLE 8. NOBLE GASES DISCHARGED IN AIRBORNE EFFLUENTS FROM REACTORS IN VARIOUS COUNTRIES, 1970-1974

Reactor	Start-up year	Net electrical power (MW(e))	Release (hCi)					Normalized release (Ci per MW(e) y)				
			1970	1971	1972	1973	1974	1970	1971	1972	1973	1974
P W R												
Belgium												
BR-3, Mol	1962	10			0.25					190		
France												
SENA, Chooz	1967	270	0.003	4.5	31.3	19.9		0.02	20	130	82	
Germany, Fed. Rep. of												
Obrigheim	1968	328	7.7	1.46	3.20	2.93	13.5	27	5.7	12		
Stade	1972	630			2.45	2.61	0.89			6.5		
Biblis	1974	1 147					0.06					
Italy												
Trino, Vercellese	1964	247	0.019	0.59	1.03			0.13	3.8	4.5		
Japan												
Mihama 1	1970	340	0.9	1.4	0.62	0.51	0.07	11	5.6	4.9	5.4	2.8
Mihama 2	1972	500			0.26	0.34	0.34			1.1	1.2	1.1
Takahama 1	1974	826					0.07					0.27
Netherlands												
Borssele	1973	447				0.31	5.83				4.0	18
United States												
Yankee Rowe	1961	175	0.017	0.013	0.018	0.035	0.040	0.12	0.08	0.25	0.29	0.38
Indian Pt. 1	1962	265	1.7	0.36	0.54	0.12	0.61	39	4.1	3.8	–	4.5
San Onofre	1968	430	4.2	7.67	19.1	11.0	1.78	12	21	59	42	5.0
Connecticut Yankee	1968	575	0.7	3.25	0.65	0.032	0.0074	1.7	6.8	1.3	0.12	0.015
R. E. Ginna	1970	420	10.0	31.8	11.8	0.58	0.76	38	100	43	1.5	3.2
Point Beach, 1,2	1970/72	2 X 497		0.84	2.81	5.75	9.74		2.1	7.9	9.9	13
H. B. Robinson	1971	700		0.018	0.26	3.1	2.31		0.061	0.51	7.2	4.2
Palisades	1971	700			0.51	0.45	0.00003			2.3	1.7	0.0038
Maine Yankee	1972	790			0.002	0.16	6.36			0.04	0.41	16
Surry, 1,2	1972/73	2 X 788			0.00001	0.87	55.0			0.0003	1.0	82
Turkey Pt. 3,4	1972/73	2 X 693				0.53	4.66				0.99	5.2
Indian Pt. 2	1973	873				0.015	5.58				0.38	15
Ft. Calhoun	1973	457				0.066	0.30				0.96	1.1
Prairie Island, 1,2	1973/74	2 X 530				0.008	0.36				3.6	2.2
Oconee 1,2,3	1973/74	3 X 886				9.3	19.4				35	31
Zion 1,2	1973	2 X 1 050				0.004	2.99				0.052	5.6
Arkansas 1	1974	820					0.20					3.0
Kewaunee	1974	520					3.35					18
Three Mile Island	1974	810					0.92					3.8
		Total	25.2	51.9	74.8	58.6	135.1					
Electrical energy generated (MW(e) y)			1 906	3 124	3 960	6 083	9 045					
Overall normalized release (Ci per MW(e) y)			13.2	16.6	18.9	9.6	14.9					
B W R												
Germany, Fed. Rep. of												
Kahl	1961											

Overall normalized release (Ci per MW(e) y)			13.2	10.0								
BWR												
Germany, Fed. Rep. of												
Kahl	1961	15	2.90	2.10	–	0.48	0.99	220	160	–	37	95
Gundremmingen	1966	237	7.35	6.50	11.0	23.7	4.15	35	29	53	120	19
Lingen	1968	174	110	8.70	5.1	2.6	9.5	960	75	84	18	180
Würgassen	1972	640			0.59	0.56	0.05			9	2.4	0.9
Italy												
Garigliano	1964	152	275	640	290			3 300	4 800	6 000		
Japan												
Tsuruga	1969	331	130	42	4.9	5.2	5.6	470	170	19	18	33
Fukushima 1,2	1970/74	460/784	1.2	70	97	4.9	14	160	230	330	22	29
Netherlands												
Dodewaard	1968	52	2.41	2.76	8.32	6.70	4.16	57	60	220	160	130
United States												
Dresden 1	1960	200	900	753	877	840	98.4	5 700	9 500	7 000	13 000	2 500
Big Rock Pt.	1962	70	280	284	338	230	188	6 100	7 200	5 900	4 800	4 900
Humboldt Bay	1963	69	540	514	430	350	572	11 000	14 000	10 000	7 300	13 000
Lacrosse	1969	53	0.95	0.53	30.6	91	49.0	64	21	1 100	4 000	1 300
Oyster Creek	1969	640	110	516	866	810	279	270	1 200	1 700	2 000	660
Nine Mile Pt.	1969	625	9.5	253	517	872	558	44	770	1 400	2 200	1 500
Dresden 2,3	1970/71	2 X 800	250	580	429	880	627	1 800	1 300	460	890	830
Millstone Pt. 1	1970	652		276	726	79	912		650	2 000	370	2 200
Monticello	1971	545		75.8	751	870	1 490		450	1 900	2 300	4 500
Quad Cities, 1,2	1972	2 X 800			132	900	950			300	780	1 000
Pilgrim 1	1972	655			18.1	230	546			200	490	2 400
Vermont Yankee	1972	514			55.2	180	63.9			1 100	880	220
Peach Bottom 2,3	1973/74	2 X 1 000				0.004	0.2					0.4
Browns Ferry	1973	1 050					64					150
Cooper Station	1974	760					1.6					7.6
		Total	2 619	4 024	5 587	6 376	6 438					
Electrical energy generated (MW(e) y)			1 790	3 121	4 369	5 552	6 166					
Overall normalized release (Ci per MW(e) y)			1 460	1 290	1 280	1 150	1 040					
GCR												
France	1963/	70										
EDF 1,2,3 Chinon	1965/	200	8.09	4.23	11.52	2.8		19.6	10.9	23.2	8.7	
	1966	480										
	1969/	480										
SL 1,2 St. Laurent	1970	505	0.31	3.43	3.86	5.0		19.3	9.5	5.9	7.0	
Bugey	1972	540			0.84	3.1				6.5	10.6	
Germany, Fed. Rep. of												
AVR-Jülich	1968	13	0.031	0.027	0.028	0.021	0.010	3	2.4	2.7		
Italy												
Latina	1963	153	2.50	2.47	3.66			18.4	11.7	26.6		
Japan												
Tokai	1965	166	4.9	4.8	5.9	6.0	6.3	46.7	42.1	52.7	52.6	55.8
		Total	15.8	14.9	25.8	16.9	6.3					
Electrical energy generated (MW(e) y)			880	1 085	1 546	1 444	113					
Overall normalized release (Ci per MW(e) y)			18.0	13.7	16.7	11.7	55.8					

TABLE 8 *(continued)*

Reactor	Start-up year	Net electrical power (MW(e))	Release (hCi)					Normalized release (Ci per MW(e) y)				
			1970	1971	1972	1973	1974	1970	1971	1972	1973	1974
H W R												
Argentina												
Atucha	1974	320					1.8					17
Canada												
Douglas Pt.	1966	220	161					1 500				
Pickering 1,2,3,4	1971/72/73	4 X 508		58.1	40.0	31.0	3.1		170	57	19	2
France												
EL-4-Monts d'Arrée	1967	70	0.072	53.8	144.5	130			2 700	2 500	2 500	
Germany, Fed. Rep. of												
MZFR-Karlsruhe	1965	51		0.53	0.96	0.22	0.95		14	19	19	23
		Total	161	112	186	161	5.9					
Electrical energy generated (MW(e) y)			107	402	808	1 694	1 770					
Overall normalized release (Ci per MW(e) y)			1 500	280	230	95	3					

Sources: References 1, 26, 27, 43, 44, 97-99, 120, 141, 143, 144, 161, 163.

TABLE 9. COMPOSITION OF NOBLE GASES DISCHARGED IN AIRBORNE EFFLUENTS FROM REACTORS

Reactor	Electrical energy generated in 1974 (MW(e) y)	Amount released (Ci)												
		^{133}Xe	^{135}Xe	^{138}Xe	^{85}Kr	^{131m}Xe	^{88}Kr	^{135m}Xe	^{85m}Kr	^{133m}Xe	^{87}Kr	^{41}Ar	^{37}Ar	Total
P W R														
Germany, Fed. Rep. of														
Obrigheim	293.4	12 100	1 320									35		
Stade	608.2	711	156		23									
United States														
Yankee Rowe	103.9	16.4	1.2	0.0005	1.5	0.02	0.03	0.0006	0.06	0.02	0.02	0.9	0.5	
San Onofre	353.9	1 420	9.7		63.9	105			0.9	177				
Connecticut Yankee	502.3	2.3	0.4		4.0		0.3	0.3			0.2			
R. E. Ginna	239.7	630	110		8.9				7.1			1.1		
Pt. Beach 1,2	764.8	6 040	1 300	321	23.1	394	542	322	374	133	251	32.0		
H. B. Robinson	547.9	2 110	43.1			0.8			2.8			3.2		
Palisades	8.9	0.02	0.01			0.008			0.0002	0.00003				
Maine Yankee	411.0	5 460	23.7		532	88.6				3.3				
Surry 1,2	673.5	54 600	223		8.1		19.3		19.8	2.6	14.9	15.0		
Turkey Pt. 3,4	901.8	3 980	172	15.8	291	38.0	14.5	51.1	17.5	22.2	4.7	52.1		
Ft. Calhoun	274.0	0.03	1.2		0.5									

Prairie Island	160.0	357	0.1		0.0005		0.03	0.03	0.001	0.2		1.1		
Oconee 1,2,3	632.4	18 600	527		0.7	16.2	37.5		74.5	37.2	1.6	87.4		
Zion 1,2	536.5	2 980	6.3											
Arkansas 1	65.1	0.02			0.06	0.02			0.03	2.5	0.0001	0.0001		
Kawaunee	182.6	2 690	128					0.00001	2.2	11.1		2.7		
Three Mile Island	239.7	891	12.6			0.7	0.003	0.0002	0.5	6.7		5.8		
	Total	112 600	4 035	336.8	956.8	643.3	613.7	373.4	499.4	395.8	272.4	236.3	0.5	
Corresponding electrical energy (MW(e) y)		7 500	7 435	1 771	5 690	4 029	3 978	2 855	4 874	4 498	3 644	4 804	104	
Normalized release (Ci per MW(e) y)		15.0	0.54	0.19	0.17	0.16	0.15	0.13	0.10	0.09	0.07	0.05	< 0.01	17
Proportion of total (%)		90	3.2	1.1	1.0	1.0	0.9	0.8	0.6	0.5	0.4	0.03	< 0.1	100

		Amount released (kCi)											
		^{135}Xe	^{88}Kr	^{133}Xe	^{138}Xe	^{87}Kr	^{83m}Kr	^{85m}Kr	^{135m}Xe	^{85}Kr	^{137}Xe	^{133m}Xe	*Other*
B W R													
Germany, Fed. Rep. of													
Kahl	10.4	0.6	0.06		0.02	0.04		0.2				0.02	0.04
Gundremmingen	219.2	0.2	0.3	1.9	0.4	0.1	0.04	0.5	0.1	0.04	0.3		0.3
Lingen	52.9	1.7	1.4	0.6	0.7	1.0	0.2	0.4	0.6	0.04	1.0	0.03	0.7
Würgassen	55.7	0.02	0.004	0.001	0.002	0.007		0.005	0.001				0.02
United States													
Dresden 1	40.0	10	5.7	2.1	48	11		1.6	20				
Big Rock Pt.	38.8		17.5		54.8	30.2		10.2	8.2	0.4	3.8	0.7	3.7
Humboldt Bay	43.4	107	76.4	36.2	169	75	14.4	21.9	65.6		4.7	1.2	0.8
Lacrosse	37.7	6.6	3.8	1.7	18.2	4.8		1.5	8.9	0.005	3.3	2.9	0.2
Oyster Creek	422.4	73.4	50.7	22.6	55.1	47.3		16.1	13.9		0.03	0.2	0.006
Nine Mile Pt.	376.7	182	133	59.3	61.5	78.7		43					
Dresden 2,3	753.4	185	95.1	83.8	67.6	111		38.3	46.5				
Millstone Pt.	411.0	257	142	255	66.5	89.9		51.6					
Monticello	331.1	533	200	216	223	210		98.4		9.8			
Quad Cities 1,2	924.7	270	175	193	61	127	125	61	25.2	6.6			
Pilgrim 1	228.3	153	90.8	81.4	63	71.2		36.3					
Vermont Yankee	285.4	34.8	0.8	22.2	3.2	1.2		1.7					
Browns Ferry	593.6	0.5	0.8	4.5	5.8	1.4		0.4	6.3	45.6			1.5
Cooper Station	205.5	0.1	0.001	0.01		0.2	0.02	0.04	0.2		0.05		
	Total	1 814.9	993.4	980.3	897.8	860.0	139.6	383.1	195.5	62.5	13.2	5.0	6.4
Corresponding electrical energy (MW(e) y)		4 991	5 030	4 981	4 825	5 030	1 446	5 030	3 388	2 403	1 020	606	1 474	
Normalized release (Ci per MW(e) y)		360	200	200	190	170	100	80	60	30	10	8	4	1 400
Proportion of total (%)		26	14	14	13	12	7	5	4	2	0.9	0.6	0.3	100

Sources: References 55, 163.

58. The AGR utilizes slightly enriched UO_2 as fuel and CO_2 as coolant. The cladding is stainless steel. Somewhat higher operating temperatures are reached, about 1300°C, but noble gas release is still expected to be quite low. Commercial AGRs have come into operation only recently.

59. The helium-cooled HTGR utilizes graphite-coated, highly enriched UO_2 or UC_2 as fuel. The prototype HTGRs thus far constructed, AVR (Federal Republic of Germany), Dragon (United Kingdom) and Peach Bottom (United States), have utilized charcoal filters to retain the noble gases which reach the primary coolant for long periods. The release composition is thus primarily ^{133}Xe and ^{85}Kr. Noble gas release reported from Peach Bottom averaged about 5 Ci per MW(e) y for 1968-1973 (141, 161). For the AVR reactor, the noble gas release has been 2-3 Ci per MW(e) y for 1969-1972 (27). Larger HTGRs are expected to release noble gases at the rate of 1-3 Ci per MW(e) y (49).

60. Table 8 also gives a limited amount of data on the total activity of noble gases released from GCRs and HWRs. In some cases, measurements at GCRs did not distinguish fission noble gases from ^{41}Ar. Therefore, in reports of release data from these reactors, the amounts of fission noble gases are upper limits.

2. Activation gases

61. In contrast to the noble gas fission products released in BWR and PWR operation, several activation gases are formed in GCR operation. Direct activation of the CO_2 coolant gives rise to ^{16}N by the (n, p) reaction with ^{16}O. Argon-41 arises from the (n, γ) reaction with ^{40}Ar in the coolant and also in shield-cooling air, where this is used.

62. The amounts of ^{41}Ar released depend on the reactor characteristics. Release rates of ^{41}Ar from GCRs in the United Kingdom are not measured routinely, but for a Magnox reactor, the rate has been estimated to be approximately 20 Ci h^{-1} from shield cooling and an additional 10 Ci d^{-1} from CO_2 leakage (38). A number of recent measurements at three reactors in the United Kingdom indicate ^{41}Ar releases on the order of 100-300 Ci per MW(e) y (115). Estimated discharges for an AGR due to a coolant leakage of 1 per cent per day are about 3 Ci per MW(e) y for ^{41}Ar and 2 Ci per MW(e) y for ^{16}N (113).

63. Another airborne effluent from GCRs is ^{35}S, arising from (n, γ) reactions with ^{34}S and (n, p) reactions with ^{35}Cl. The impurity levels of sulphur and chlorine in moderator graphite are approximately 50 and 2 ppm, respectively (113). Release of ^{35}S from the Oldbury and Wylfa (Magnox) reactors in the United Kingdom averaged 0.002 Ci per MW(e) y during 1972-1974 (106).

64. Nitrogen-16 (7.3 s) is also formed in the coolant in light-water reactor cores. In BWRs a portion of the ^{16}N is transported with the steam before decay to the less-shielded turbines. The photons (6.1 and 7.1 MeV) from ^{16}N decay in the turbines are a potentially significant component of the gamma radiation field near the turbine building (86, 87).

3. Tritium

65. Tritium occurs by ternary fission in nuclear fuel and also by neutron activation reactions with lithium and boron isotopes dissolved in, or in contact with, the primary coolant and with naturally occurring deuterium in the primary coolant. Erdman (31) has estimated the normalized tritium generation rate in LWRs from ternary fission to be about 15 Ci per MW(e) y, based on a recent measurement of $0.85\ 10^{-4}$ tritons per thermal fission in ^{235}U (34), and assuming $2\ 10^{-4}$ tritons per thermal fission in ^{239}Pu and ^{238}U (31). The estimate assumes 55 per cent fissions in ^{235}U, 41 per cent in ^{239}Pu and 4 per cent in ^{238}U. Other estimates indicate about 23 Ci per MW(e) y (107). An average assumed for use in this Annex is 20 Ci per MW(e) y. The generation rate estimate for a fast breeder reactor is also 20 Ci per MW(e) y (31).

66. Estimated generation rates and appearance of tritium in effluent streams of reactors are summarized in table 10. Assessments of tritium activity in the coolant have generally assumed that 1 per cent of the tritium generated in the fuel is transferred to the coolant through pinhole defects in the fuel element cladding. In earlier PWRs, which utilized stainless steel cladding, as much as

TABLE 10. ESTIMATED RATES OF GENERATION OF TRITIUM AND OF ITS APPEARANCE IN EFFLUENT STREAMS OF DIFFERENT TYPES OF REACTORS

(Ci per MW(e) y)

	BWR		*PWR*		*GCR*		*HWR*	
Source	*Generation*	*Effluent stream*	*Generation*	*Effluent stream*	*Generation*	*Effluent stream*	*Generation*	*Effluent stream*
Fission	20	0.2	20	0.2	20	0.2	20	0.2
Soluble boron shim			0.5	0.5				
Deuterium activation	0.01	0.01	0.001	0.001			600	20[a]
Lithium activation			0.02	0.02	0.5	0.1		
Boron activation (control rods)	9							
Total	29	0.2	21	1	21	0.3	620	20

Sources: References 39, 76, 128, 136.

[a] Depending on the irradiation time and on the net leakage of heavy water.

80 per cent of the fission-produced tritium could permeate the cladding. With the zircaloy cladding in current usage, 1 per cent or less of the fission-produced tritium is expected to appear in the effluent streams (85). Although tritium is formed within the control rods in BWRs, it has not been shown to diffuse through the B_4C matrix of the control rods (136).

67. Reports on PWR operation (tables 11 and 12) show the average normalized release of tritium to be about 2 Ci per MW(e) y in liquid effluents and 0.2 Ci per MW(e) y in airborne effluents. For BWRs, the averages are 0.1 and 0.05 Ci per MW(e) y in liquid and airborne effluents respectively.

68. In GCRs, tritium is produced by activation of lithium impurities in the graphite moderator as well as by ternary fission. Use of helium as coolant in HTGRs results in tritium generation by the (n, p) reaction with ^3He. Estimates of the normalized generation rates are 0.5 Ci per MW(e) y from lithium activation (39) and 3-6 Ci per MW(e) y from helium activation (136).

TABLE 11. TRITIUM DISCHARGED IN AIRBORNE EFFLUENTS FROM REACTORS IN VARIOUS COUNTRIES, 1973-1974

	Release (Ci)		*Normalized release (Ci per MW(e) y)*	
Reactor	*1973*	*1974*	*1973*	*1974*
P W R				
Germany, Fed. Rep. of				
Obrigheim	20.2	11.5	0.067	0.039
Stade		11.1		0.018
United States				
Yankee Rowe	8.4	3.8	0.070	0.037
Indian Pt. 1	25.4	0.32		0.0024
San Onofre	268.9	91.4	1.02	0.26
Connecticut Yankee	50.6	0.012	0.18	0.000023
R. E. Ginna	1.1	0.37	0.0028	0.0015
Pt. Beach 1,2	25.5	42.8	0.039	0.056
H. B. Robinson	2.5	51.5	0.0058	0.094
Palisades	0.18	0	0.00066	0
Maine Yankee	1.89	7.2	0.0049	0.017
Surry 1,2	42.4	60.4	0.051	0.090
Turkey Pt. 2,3	4.1	9.2	0.0076	0.010
Indian Pt .2	2.0	19.9	0.050	0.053
Ft. Calhoun	0.33	0.75	0.0048	0.0027
Prairie Island		3.9		0.024
Oconee 1,2	13.1	878	0.049	1.39
Zion 1,2		180		0.34
Arkansas 1		0.030		0.00046
Kewaunee		109		0.60
Three Mile Island		12.7		0.053
Total	466	1 494		
Electrical energy (MW(e) y)	5 393	8 014		
Overall normalized release (Ci per MW(e) y)	0.09	0.19		
B W R				
United States				
Big Rock Pt.	77.1	38.7	1.61	1.00
Humboldt Bay	1.9	1.7	0.040	0.040
Lacrosse	50.6	18.3	2.24	0.49
Oyster Creek	0.32	0.42	0.00078	0.00098
Nine Mile Pt.	26.8	15.8	0.067	0.042
Dresden 2,3	10.0	114	0.010	0.15
Millstone Pt.	1.7	7.9	0.0079	0.019
Monticello				
Quad Cities 1,2	34.0	29.0	0.030	0.031
Pilgrim 1	14.0	8.0	0.030	0.035
Vermont Yankee	1.0	2.2	0.0049	0.0078
Peach Bottom 2,3		5.6		0.0094
Browns Ferry		0.65		0.0015
Cooper Station		0.016		0.000077
Total	217	242		
Electrical energy (MW(e) y)	4 340	5 094		
Overall normalized release (Ci per MW(e) y)	0.050	0.048		

TABLE 11 *(continued)*

Reactor	Release (Ci) 1973	Release (Ci) 1974	Normalized release (Ci per MW(e) y) 1973	Normalized release (Ci per MW(e) y) 1974
H W R				
Argentina				
Atucha		217		2.0
Canada				
Pickering	36 500	24 800	22.4	15.4
Total	36 500	25 017		
Electrical energy (MW(e) y)	1 630	1 723		
Overall normalized release (Ci per MW(e) y)	22.4	14.5		
G C R				
United Kingdom				
Oldbury	30	12	0.10	0.037
Wylfa	200		0.67	
Total	230	12		
Electrical energy (MW(e) y)	588	321		
Overall normalized release (Ci per MW(e) y)	0.39	0.04		

Sources: References 26, 44, 106, 161, 163, 171.

69. The release rate of tritium from GCRs varies with reactor type. Penetration of the Magnox cladding by tritium produced in fuel can be assumed to be about 1 per cent. For HTGRs an estimated 30-90 per cent of the tritium originating in the fuel and graphite moderator may reach the coolant (39, 136). The tritium is removed in coolant-gas purification, but a 4 per cent diffusion loss through the condenser walls is anticipated, or about 3 Ci per MW(e) y (39). Based on the experience with GCRs, primarily for the Magnox reactors in the United Kingdom, tritium release in liquid effluents (table 12) is about 0.2 Ci per MW(e) y, and in airborne effluents it ranges from 0.04 to 0.4 Ci per MW(e) y, on the basis of the limited information available (table 11).

70. The amount of tritium generated in HWR fuel by ternary fission is approximately the same as in LWRs, but activation of deuterium in the D_2O coolant and moderator provides much more. Kouts estimates the tritium production rate in the coolant to be 600 Ci per MW(e) y (76). Tritium concentration in the primary coolant and moderator of a HWR depends upon the irradiation time of the heavy water and the reactor size. The D_2O leakage from HWRs is kept as small as possible for economical and radiological reasons. Leakage from the MZFR reactor in the Federal Republic of Germany averages about 1.5 l d^{-1}, about 0.5 per cent of the total D_2O amount per year (39). For larger reactors, annual losses of from 1 per cent (Atucha reactor in Argentina and Pickering reactors in Canada) to 2-3 per cent can be anticipated. For the optimal loss of 0.5 per cent per year, the normalized tritium release rate from a HWR ranges from 3 Ci per MW(e) y in the first year of operation to about 20 Ci per MW(e) y in the tenth. Based on the latter value as representative of the reactor life, the normalized tritium release is estimated to be 16 Ci per MW(e) y in airborne effluents and 4 Ci per MW(e) y in liquid effluents (39). For larger leakage rates, on the order of 1 per cent per year, these values would be attained after a few years of reactor operation. Information on actual releases of radioactivity from HWRs is limited; however, the data reported for the Pickering reactors in Canada (tables 11 and 12) roughly agree with these estimates (171). For the Atucha reactor in Argentina, normalized tritium release in liquid effluents was 0.8 Ci per MW(e) y during its initial year of operation (1974) and 3 Ci per MW(e) y in 1975 (26). Tritium in airborne effluents from Atucha was 2.0 and 3.8 Ci per MW(e) y in 1974 and 1975, respectively (26).

4. Carbon-14

71. Very little attention has been given to ^{14}C production in and release from reactors. The dose rates associated with the releases are very low; however, with its long half-life (5730 y), ^{14}C can make a significant contribution to the collective dose commitment.

72. Carbon-14 is produced in LWRs and HWRs by (n, α) reactions with ^{17}O present in the oxide fuel and in the moderator, by (n, p) reactions with ^{14}N present in the fuel as impurities, and by ternary fission. Ternary fission production per unit electrical energy generated is practically independent of reactor design, while the normalized production of ^{14}C by the other reactions depends on the enrichment of the fuel, the relative masses of the fuel and moderator, the concentration of nitrogen impurities in the fuel and the temperature of the fuel and moderator.

73. In 1974, Bonka estimated the normalized ^{14}C production in light water reactors to be about 0.03 Ci per MW(e) y (18). Magno, also in 1974, estimated the production to be about 0.05 Ci per MW(e) y (90). Hayes *et al.* (45) estimated the production to be 0.02 Ci per MW(e) y for PWRs and 0.04 Ci per MW(e) y for BWRs. Recent estimates by Davis (29) gives values of 0.02 Ci per MW(e) y in PWRs and BWRs. A study carried out for Swedish power reactors (84) estimated the values to be 0.014 Ci per MW(e) y for PWRs and 0.024 Ci per MW(e) y for BWRs.

74. Assuming, as in the assessments mentioned above, that the average thermal neutron flux density is the same in the fuel and moderator, that the relevant (n, p) and (n, α) reactions follow the $1/v$ law, as several studies indicate (42), and that there are 10 ppm nitrogen impurities in the fuel, production rates of ^{14}C have been estimated from reactor design information compiled by IAEA (57). For recent LWRs, the values estimated are, for PWRs, 0.012 Ci per MW(e) y in the fuel and 0.005 Ci per MW(e) y in the moderator and, for BWRs, 0.016 Ci per MW(e) y in the fuel and 0.008 Ci per MW(e) y in the moderator.

75. These results indicate the normalized ^{14}C production to be about 0.02 Ci per MW(e) y. The amount which can be assumed to be released at the reactor, 30 per cent of the total production, is the amount produced in the moderator, which will vary depending on the moderator size. The ^{14}C produced in the fuel will presumably be released, at least partially, at the reprocessing plant.

76. From measurements of decay-tank gas and containment air at three PWRs, Kunz estimated the ^{14}C release in airborne effluents to be approximately 0.006 Ci per MW(e) y (81). In subsequent analyses of off-gas from the main condenser air ejector of a BWR, Kunz estimated the ^{14}C release in airborne effluents to be 0.016 Ci per MW(e) y (82). This result for the R. E. Ginna reactor in the United States corresponds to a somewhat larger moderator size. From detailed measurements at the Oyster Creek BWR in the United States, Blanchard *et al.* (15) estimate the ^{14}C release to be 0.006 Ci per MW(e) y from the main condenser air ejector and 0.002 Ci per MW(e) y from the building ventilation air. Occasional stack monitoring, however, would indicate, if considered representative, a larger airborne release of 0.018 Ci per MW(e) y. Additional measurements at Oyster Creek indicated ^{14}C discharged in liquid effluents to be $2\ 10^{-5}$ Ci per MW(e) y (15).

77. A ^{14}C airborne normalized release rate of 0.013 Ci per MW(e) y was reported for the Yankee Rowe PWR in the United States for 1972 (146). This reactor reported 0.005 Ci per MW(e) y in airborne effluents in 1974 and $3\ 10^{-5}$ Ci per MW(e) y in liquid effluents (163). Some initial measurements of ^{14}C airborne release from reactors operating in the USSR, however, indicate larger airborne releases, namely 0.2, 0.46 and 0.9 Ci per MW(e) y for a PWR, BWR and LWGR, respectively (121). More recent results are somewhat lower. These measurements presumably reflect different reactor design, moderator volume and nitrogen impurity levels.

78. Of the ^{14}C in the BWR off-gas sample measured by Kunz, 95 per cent was in the form of CO_2, 2.5 per cent, CO and 2.5 per cent, hydrocarbons. Due to the reducing atmosphere of the hydrogen cover gas of the PWR, however, over 80 per cent of the ^{14}C activity released from this reactor type was in organic forms CH_4 and C_2H_6 (81, 82).

79. In gas-cooled, graphite moderated reactors the major source of ^{14}C production is the graphite moderator, due to the ^{13}C (n, γ) ^{14}C reaction and also to the ^{14}N (n p) ^{14}C reaction based on the incorporated nitrogen impurity. Normalized production rates have been estimated to be about 0.18 Ci per MW(e) y in Magnox reactors and 0.3 Ci per MW(e) y in AGRs (74). Production of ^{14}C in the carbon dioxide coolant, mainly from activation of nitrogen impurities and from the ^{17}O (n, α) ^{14}C reaction, is a smaller source estimated to be about $3\ 10^{-3}$ Ci per MW(e) y for Magnox reactors and 10^{-2} Ci per MW(e) y for AGRs (74). Carbon-14 discharges from Magnox reactors and AGRs result from coolant leakage and include ^{14}C released in the coolant from corrosion of the moderator; estimated releases are 0.006 Ci per MW(e) y for Magnox reactors and 0.017 Ci per MW(e) y for AGRs. Assessments of ^{14}C production by HTGRs range from 0.012 Ci per MW(e) y (29) to 0.25 Ci per MW(e) y (90) and originates primarily from the ^{13}C (n, γ) ^{14}C reaction. Insignificant releases of ^{14}C from these reactors are anticipated. Rather, the ^{14}C would be released at the reprocessing plant (17).

80. The production of ^{14}C in HWRs is due to the same type of nuclear reactions described for LWRs (para. 72). However, due mainly to the large moderator mass, the production rate of ^{14}C in HWRs is expected to be considerably larger than in LWRs. Using the assumptions described in paragraph 74, the production rate in the Atucha reactor in Argentina is estimated to be 0.46 Ci per MW(e) y, with 90 per cent generated in the moderator. The production of ^{14}C in CANDU reactors is estimated to be 0.42 Ci per MW(e) y, 95 per cent being produced in the moderator (120).

81. Much more data, particularly from continuous monitoring, must be forthcoming before a reliable assessment of the ^{14}C generation rate in reactors and its release characteristics can be made.

5. Iodine

82. A number of iodine isotopes are produced in reactors by fission and by decay of other fission products. Release estimates have been published for ^{131}I (8.05 d), ^{132}I (2.3 h), ^{133}I (21 h), ^{134}I (53 m), ^{135}I (6.7 h) and ^{129}I ($1.6\ 10^{7}$ y) (16). Equilibrium amounts of all but ^{129}I are rapidly established in the reactor core, and releases are more a function of the integrity of the coolant system than of the amount of electricity generated. Iodine-131, with a half-life of 8 d, is the main concern from an environmental point of view. Its activity per unit of thermal power at equilibrium in uranium fuel varies from about 25 kCi MW^{-1} at the beginning of the fuel irradiation to about 30 kCi MW^{-1} at the end, as a result of the larger fission yields of plutonium, which contributes increasingly to power production as the burn-up proceeds. Long-lived ^{129}I has not been identified in power reactor

TABLE 12. TRITIUM DISCHARGED IN LIQUID EFFLUENTS FROM REACTORS IN VARIOUS COUNTRIES, 1970-1974

Reactor	Start-up year	Net electrical power (MW(e))	Release (Ci)					Normalized release (Ci per MW(e) y)				
			1970	1971	1972	1973	1974	1970	1971	1972	1973	1974
P W R												
France												
SENA, Chooz	1967	270	340	706	1 762	1 849		2.3	3.2	7.2	5.7	
Germany, Fed. Rep. of												
Obrigheim	1968	328		311	243	326	149		1.2	0.89	1.2	0.51
Stade	1972	630			96.7	112	32.2			0.26	0.24	0.05
Biblis	1974	1 147					8.3					0.08
Italy												
Trino, Vercellese	1964	247	135	1 117	1 078			0.95	7.2	4.8		
Japan												
Mihama 1	1970	340	32	140	85	120	47	0.40	0.56	0.67	1.3	1.9
Mihama 2	1972	500			150	190	230			0.63	0.69	0.72
Takahama 1	1974	826					130					0.49
Netherlands												
Borssele	1973	447				1.8	171				0.02	0.53
Sweden												
Ringhals 2	1974	820					6.3					0.27
United States												
Yankee Rowe	1961	175	1 500	1 680	803	694	314	10.3	9.7	10.9	5.8	3.0
Indian Pt. 1	1962	265	410	725	574	138	684	9.4	4.7	4.0	–	5.0
San Onofre	1968	430	4 800	4 570	3 480	4 070	3 810	13.1	11.5	10.8	15.5	10.8
Connecticut Yankee	1968	575	7 400	5 830	5 890	3 900	2 240	17.4	11.6	12.0	14.1	4.5
R. E. Ginna	1970	420	110	154	119	286	195	0.42	0.47	0.43	0.74	0.81
Point Beach, 1,2	1970/72	2 X 497		266	563	556	833		0.68	1.1	0.86	1.1
H. B. Robinson	1971	700		118	405	432	449		0.40	0.81	1.0	0.82
Palisades	1971	700			208	185	8.1			0.96	0.68	0.91
Maine Yankee	1972	790			9.2	154	219			0.17	0.40	0.53
Surry, 1,2	1972/73	2 X 788			5.0	448	245			0.12	0.54	0.36
Turkey Pt. 3,4	1972/73	2 X 693				329	580				0.61	0.64
Indian Pt. 2	1973	873				27.5	47.9				0.69	0.13
Ft. Calhoun	1973	457				15.8	124				0.23	0.45
Prairie Island, 1,2	1973/74	2 X 530				10^{-4}	142				$3.3\ 10^{-5}$	0.89
Oconee 1,2,3	1973/74	3 X 886				70.7	350				0.26	0.55
Zion 1,2	1973	2 X 1 050					2.3					0.0043
Arkansas 1	1974	820					25.6					0.39
Kewaunee	1974	520					92.4					0.51
Three Mile Island	1974	810					130					0.54
		Total	14 727	15 617	15 471	13 905	11 265					
Electrical energy generated (MW(e) y)			1 616	3 124	3 960	6 162	9 069					
Overall normalized release (Ci per MW(e) y)			9.1	5.0	3.9	2.3	1.2					
B W R												
Germany, Fed. Rep. of												
Kahl	1961	15		1.4	1.2	1.7	7.9		0.11		0.30	0.76
Gundremmingen	1966	237		45.6	78.3	148	215		0.20	0.38	0.75	0.98
Lingen	1968	174	31.7		24.0	14.6	9.0	0.28		0.40	0.13	0.17
Würgassen	1972	640			3.2	5.9	3.6			0.05	0.03	0.06
Italy												
Garigliano	1964	152	5.0	5.0	3.0			0.059	0.038	0.062		
Japan												
Tsuruga	1969	331		6.2	5.3	8.2	21.0		0.025	0.020	0.029	0.12

Netherlands												
Dodewaard	1968	52	2.4	1.3	3.2	4.9	4.9	0.056	0.028	0.086	0.12	0.15
Sweden												
Oskarshamn 1	1971	440					10.9					0.071
Ringhals 1	1974	760					2.0					0.23
United States												
Dresden 1	1960	200	5.0	8.7	43.3	18.5	18.8	0.031	0.12	0.34	0.29	0.47
Big Rock Pt.	1962	70	54.0	10.3	10.4	19.7	50.7	1.24	0.27	0.24	0.41	1.31
Humboldt Bay	1963	69	7.0	7.5	13.0	51.3	31.7	0.14	0.19	0.31	1.07	0.73
Lacrosse	1969	53	20.0	91.4	120.0	103.0	115.0	1.31	3.81	4.38	4.56	3.05
Oyster Creek	1969	640	22.0	21.5	61.6	35.9	14.1	0.054	0.047	0.12	0.087	0.033
Nine Mile Pt.	1969	625	20.0	12.4	27.8	46.5	18.7	0.091	0.036	0.075	0.12	0.50
Dresden 2,3	1970/71	2 X 800	31.0	38.5	25.9	25.8	22.6	0.22	0.084	0.028	0.026	0.030
Millstone Pt. 1	1970	652		12.7	20.9	3.7	24.1		0.030	0.058	0.017	0.059
Monticello	1971	545		0.6	0.0001	0	0		0.0036	$2\ 10^{-7}$	0	0
Quad Cities, 1,2	1972	2 X 800			4.7	24.5	34.0			0.011	0.021	0.037
Pilgrim 1	1972	655			4.2	0.4	10.5			0.045	0.00092	0.046
Vermont Yankee	1972	514			0	0.2	0				0.00097	0
Peach Bottom 2,3	1973/74	2 X 1 000					10.0					0.017
Browns Ferry	1973	1 050					2.8					0.0064
Cooper Station	1974	760					1.7					0.0083
		Total	198	263	450	513	629					
Electrical energy generated (MW(e) y)			1 284	2 698	4 072	5 388	5 838					
Overall normalized release (Ci per MW(e) y)			0.15	0.097	0.11	0.095	0.11					
G C R												
Italy												
Latina	1963	153	16.7	13.0	16.9			0.12	0.062	0.12		
United Kingdom												
Berkeley	1962	2 X 138	60.1	43.1	44.2	200	56.7	0.20	0.15	0.17	0.84	0.25
Bradwell	1962	2 X 125	95.3	102.0	251.0	198	117.0	0.45	0.49	1.04	1.08	0.57
Hinkley Pt.	1965	2 X 230	18.6	24.9	38.6	30	39.0	0.11	0.28	0.096	0.11	0.11
Trawsfynydd	1965	2 X 195	67.7	41.9	46.0	116	60.0	0.18	0.11	0.14	0.50	0.16
Dungeness	1965	2 X 205	18.6	35.5	28.9	30.5	20.0	0.051	0.090	0.076	0.083	0.051
Sizewell	1966	2 X 210	20.9	7.0	53.2	208	253	0.049	0.17	0.14	0.63	0.70
Oldbury	1967	2 X 200	17.3	64.4	15.0	13.6	37.4	0.054	0.18	0.048	0.047	0.12
Wylfa	1971	2 X 322	0.55	30.2	82.7	275	134	0.053	0.087	0.25	0.046	0.32
Hunterston	1964	2 X 160	159.0	162.0	37.5	86.7	67.0	0.60	0.63	0.17	0.39	0.28
		Total	475	594	614	1 158	784					
Electrical energy generated (MW(e) y)			2 580	3 004	2 659	2 430	2 887					
Overall normalized release (Ci per MW(e) y)			0.18	0.20	0.23	0.48	0.27					
H W R												
Argentina												
Atucha	1974	320					90.3					0.83
Canada												
Pickering 1,2,3,4	1971/72/73	4 X 508		402	986	5 130	14 400			1.5	3.1	9.0
		Total		402	986	5 130	14 490					
Electrical energy generated (MW(e) y)				344	658	1 630	1 723					
Overall normalized release (Ci per MW(e) y)				1.2	1.5	3.1	8.4					

Sources: References 1, 3, 26, 27, 97, 99, 105, 141, 143, 146, 161, 163, 171.

environs, and its significance, in terms of possible release activities, is much less than that of the other iodine isotopes. However, it is of greater significance in the releases from fuel reprocessing plants and because of its long-term contribution to the collective dose commitment.

83. Iodine measurements at six United States LWRs indicated that on the average 73 per cent of the iodine in reactor off-gas is organic, 22 per cent hypoiodous acid, and 5 per cent elemental (114). All forms were also present in ventilation exhaust air, though the release rate from this source is usually much less than for the reactor off-gas system. The release of iodine nuclides depends strongly on the filter systems used in the installation.

84. Table 13 gives the reported iodine isotope releases in airborne effluents from various reactors. The overall ^{131}I effluent average is (2-5) 10^{-3} Ci per MW(e) y from BWRs and (5-50) 10^{-5} Ci per MW(e) y from PWRs. These values are not necessarily typical for any one reactor. The normalized iodine release amounts for the individual reactors given in table 13 show extremely wide variability. Unusually high results from one or two reactors can easily increase the overall effluent average. The limited data from GCRs and HWRs indicate that the average airborne releases are comparable to that of PWRs.

6. Particulates in airborne effluents

85. Most of the fission and activation nuclides can form aerosols, which may be released with the airborne effluents. Particulates may arise either directly or as decay products of fission noble gases. Aerosols originate particularly from primary coolant leaks, but they can also be generated by working on contaminated components or cleaning contaminated surfaces. High efficiency particulate air (HEPA) filters retain all but the very small fraction of the smallest particles. Released particulate activities are thus very low. Table 14 lists the reported activities and composition of particulates released in airborne effluents from reactors in the United States during 1974 (163). A few additional radionuclides were less frequently identified (163). The average total activities per unit of electrical energy generated are 0.5 mCi per MW(e) y from PWRs and 1.1 mCi per MW(e) y from BWRs. Over 80 per cent of the average PWR release activity is ^{88}Rb, daughter of the noble gas isotope ^{88}Kr. Other small contributors are ^{134}Cs, ^{137}Cs, ^{58}Co, ^{60}Co and ^{54}Mn. For the BWRs, $^{140}Ba + ^{140}La$ and ^{89}Sr each account for about 30 per cent of the total activity, with ^{131}I, ^{58}Co, ^{60}Co, ^{134}Cs and ^{137}Cs each contributing 10 per cent or less.

7. Radionuclides in liquid effluents

86. Radionuclides other than tritium in liquid effluents include a number of fission and activated corrosion products. The amount and composition of the discharge depend strongly on the type of reactor. The available data on discharges during 1974 are listed in table 15. The average normalized releases, based on operating experience, are approximately 0.008, 0.06 and 0.15 Ci per MW(e) y for PWRs, BWRs and GCRs, respectively. The averages for earlier data (1972 liquid effluents) are similar for BWRs and GCRs but somewhat higher (0.03 Ci per MW(e) y) for PWRs (27, 146). The radionuclides ^{137}Cs and ^{134}Cs account for 30-50 per cent of the total activity discharged by PWRs and GCRs and 70 per cent of that from BWRs: ^{131}I and ^{133}I make up 10-40 per cent and ^{58}Co and ^{60}Co about 15 per cent of the activity in liquid effluents from LWRs. Dissolved noble gases are also present in liquid effluents from LWRs, and in addition several less commonly identified radionuclides have been reported (163).

87. The activity of ^{137}Cs reported as discharged is slightly greater than that of ^{134}Cs. For reactors reporting the release of both caesium isotopes, the $^{134}Cs/^{137}Cs$ activity ratio is 0.6 for the PWRs and 0.7 for the BWRs. For the GCRs in the United Kingdom the ratio is 0.2. On the basis of an analysis of several years of liquid effluent release data, primarily from reactors in the Federal Republic of Germany, Schiesser estimates that typical normalized releases of ^{137}Cs and ^{134}Cs from large LWRs and 5.0 and 3.1 mCi per MW(e) y, respectively, and of ^{89}Sr and ^{90}Sr, 0.63 and 0.063 mCi per MW(e) y, respectively (125).

88. The iodine isotopes ^{131}I and ^{133}I are released in liquid effluents in amounts comparable to the airborne release from BWRs. Iodine is readily soluble and with little hold-up of liquid releases would be expected to be prevalent in liquid effluents. The iodine isotopes are not reported in liquid discharges from GCRs.

89. The activated corrosion products present in liquid effluents can be expected to vary widely, even among reactors of the same type. In addition to ^{58}Co and ^{60}Co, the isotopes ^{51}Cr and ^{54}Mn are quite prevalent in liquid effluents from LWRs. The reported activities of ^{99}Mo, ^{65}Zn and ^{59}Fe are somewhat less. The isotopes ^{55}Fe and ^{63}Ni are not routinely reported in LWR releases, but Hutchinson *et al.* (56) measured activities comparable to other corrosion products in liquid-waste samples. Blanchard *et al.* (15, 72), however, did not detect ^{63}Ni in liquid effluents from PWRs and BWRs. The Palisades PWR in the United States reported relatively high releases of activated corrosion products, including ^{63}Ni, during 1974, associated with a relatively long maintenance period (163).

90. Most of the activity in liquid effluents from GCRs arise from spent-fuel storage pools. Additional sources are the reactor-vessel cooling system, the coolant-drying installation and various other low-level sources. Liquid streams are collected, treated and released with the condenser coolant water. In GCR liquid effluents, the activation products include ^{35}S, ^{45}Ca and ^{32}P. Activity released in liquid effluents from gas-cooled Magnox reactors (table 15) is somewhat higher than from LWRs. In the United Kingdom all releases are to the sea, except for Trawsfynydd, from which releases are to a fresh-water lake. Liquid wastes are filtered and treated additionally by filtration in non-regenerable ion-exchange beds (60).

TABLE 13. IODINE DISCHARGED IN AIRBORNE EFFLUENTS FROM REACTORS IN VARIOUS COUNTRIES, 1970-1974

	Iodine-131										*Iodine-133*				*Iodine-135*			
	Release (Ci)					*Normalized release (10^{-5} Ci per MW(e) y)*					*Release (Ci)*		*Normalized release (10^{-5} Ci per MW(e) y)*		*Release (Ci)*		*Normalized release (10^{-5} Ci per MW(e) y)*	
Reactor	*1970*	*1971*	*1972*	*1973*	*1974*	*1970*	*1971*	*1972*	*1973*	*1974*	*1972*	*1974*	*1972*	*1974*	*1972*	*1974*	*1972*	*1974*
P W R																		
Belgium																		
BR-3, Mol	0.063	$2\ 10^{-5}$	0.001			970		80										
France																		
SENA, Chooz			0.023					9.4										
Germany, Fed. Rep. of																		
Obrigheim	0.045	0.015	0.006	0.005	0.005	15.6	5.8	2.2	1.8	1.7								
Stade			0.047	0.043	0.011			12.7	9.1	1.8								
Biblis					$6\ 10^{-5}$					0.06								
Italy																		
Trino, Vercellese	0.0006	0.001	$1\ 10^{-6}$			0.42	0.65	0.0004										
Netherlands																		
Borssele				0.0025	0.034				10.4	4.5								
United States																		
Yankee Rowe			0.00023	0.0027	0.00071			0.32	2.25	0.68		0.00029		0.28		0.00039		0.37
Indian Pt. 1			0.058	0.012	0.09			40.8		65.7		0.0045		3.25				
San Onofre			$4.4\ 10^{-5}$	0.42	0.00019			0.013	160	0.053		$1.2\ 10^{-5}$		0.0034		$3.1\ 10^{-5}$		0.0088
Connecticut Yankee			0.01	0.0013	$4.6\ 10^{-6}$			2.04	0.47	$9.1\ 10^{-6}$	$6.3\ 10^{-5}$		0.013					
R. E. Ginna			0.034	0.00053	0.00028			12.1	0.14	0.12	0.0015	0.00017	0.54	0.069				
Point Beach 1,2			0.0097	0.011	0.088			1.82	1.69	11.5		0.038		5.02				
H. B. Robinson				0.30	0.046				68.2	8.47		0.0034		0.63		0.00095		0.17
Palisades			0.0087	0.29	0.0099			4.0	104	112		0.010		112		0.0019		21.8
Maine Yankee			$1.7\ 10^{-6}$	0.0016	0.054			0.0032	0.41	13.2	0.0042	0.0019	7.9	0.46	0.0011		2.1	
Surry 1,2			$1.2\ 10^{-5}$	0.042	0.10			0.029	5.04	15.0	$4.5\ 10^{-5}$	0.020	0.11	2.90		0.0042		0.63
Turkey Pt. 2,3				0.055	3.41				10.3	378		0.034		3.74		0.0052		0.57
Indian Pt. 2				0.00029	0.37				0.73	98.0		0.056		14.9				
Ft. Calhoun				$4.3\ 10^{-5}$	0.00042				0.063	0.15		$5.0\ 10^{-5}$		0.018		$4.2\ 10^{-5}$		0.015
Prairie Island				$1.3\ 10^{-5}$	0.00045				0.58	0.28		0.00014		0.086		$1.6\ 10^{-5}$		0.010
Oconee 1,2				0.012	0.032				4.47	5.01		0.00037		0.059		$8.1\ 10^{-6}$		0.0013
Zion 1,2				$6.7\ 10^{-7}$	0.014				0.00083	2.65		0.0011		0.21				
Arkansas 1					0.053					81.4								
Kewaunee					0.024					13.1		0.0027		1.46		0.0023		1.25
Three Mile Island					0.028					1.18		0.00013		0.052		$2.0\ 10^{-7}$		$8.2\ 10^{-5}$
Total	0.11	0.02	0.20	1.20	4.37						0.058	0.17			0.011	0.015		
Electrical energy generated (MW(e) y)	438	412	3 133	5 471	8 436						863	6 544			53	4 079		
Overall normalized release (10^{-5} Ci per MW(e) y)	25	3.9	6.3	22	52						0.67	2.6			2.1	0.37		

TABLE 13 *(continued)*

	Iodine-131										*Iodine-133*				*Iodine-135*			
	Release (Ci)					*Normalized release (10^{-3} Ci per MW(e) y)*					*Release (Ci)*		*Normalized release (10^{-3} Ci per MW(e) y)*		*Release (Ci)*		*Normalized release (10^{-3} Ci per MW(e) y)*	
Reactor	*1970*	*1971*	*1972*	*1973*	*1974*	*1970*	*1971*	*1972*	*1973*	*1974*	*1972*	*1974*	*1972*	*1974*	*1972*	*1974*	*1972*	*1974*
B W R																		
Germany, Fed. Rep. of																		
Kahl	0.005	0.0025		0.002	0.003	0.38	0.19		0.32	0.29								
Gundremmingen	0.20	0.34	0.20	1.96	0.12	0.94	1.5	0.94	9.9	0.53								
Lingen	0.26	0.38	0.15	0.016	0.002	2.3	3.3	2.5	0.15	0.038								
Würgassen			$< 10^{-4}$	$< 10^{-4}$	< 0.0007			< 0.002	< 0.0004	< 0.01								
Italy																		
Garigliano	0.06	0.13	0.06			0.71	0.98	1.2										
Japan																		
Tsuruga	0.38	1.06	0.24	0.20	0.28	1.4	4.2	0.92	0.70	1.6								
Fukushima 1,2		0.06	0.25	0.79	0.34		0.19	0.84	3.5	0.69								
Netherlands																		
Dodewaard	0.0005	0.009	0.0015	0.001	0.0095	0.012	0.020	0.040	0.024	0.03								
United States																		
Dresden 1				0.04	0.41				1.1	10.3		4.41		110		8.66		220
Big Rock Pt.			0.12	4.6	0.09			2.8	96.0	2.3	0.017	0.26	0.39	6.8		0.00063		0.016
Humboldt Bay			0.40	0.17	0.50			9.7	3.5	11.6	1.7	1.19	41.1	27.4		0.012		0.28
Lacrosse			0.69	0.18	0.033			25.3	8.0	0.87	0.47	0.019	17.2	0.49	0.012		0.44	
Oyster Creek			6.26	6.7	2.31			12.6	16.0	7.8	7.04	10.5	14.1	24.9	5.82	9.54	11.7	22.6
Nine Mile Pt.			0.89	1.96	0.72			2.4	4.9	1.9	0.55	1.66	1.5	4.4	0.28	0.17	0.76	0.45
Dresden 2,3				0.49	3.98			0.99		5.3		14.7		19.5		19.3		25.6
Millstone 1			1.23	0.15	3.18			3.4	0.70	7.7								
Monticello			0.58	1.2	5.63			1.4	3.2	17.2	1.16	11.0	2.9	33.2	2.26	12.0	5.6	36.2
Quad Cities 1,2			0.73	5.5	8.82			1.6	4.7	9.5	0.60	16.0	1.4	17.3	0.070	11.8	0.16	12.8
Pilgrim 1			0.03	0.46	1.44			0.3	0.97	6.3	0.92	1.12	9.9	4.9		1.87		8.2
Vermont Yankee			0.17	0.06	0.35			3.5	0.29	1.2	0.16	0.12	3.3	0.42				
Peach Bottom 2,3					0.0066					0.11								
Browns Ferry 1					0.38					0.086		0.045		0.10		0.41		0.92
Cooper Station					0.13					0.062		0.086		0.42		3.44		16.7
Total	0.91	1.98	12.0	24.5	29.7						12.6	61.1			8.4	67.2		
Electrical energy generated (MW(e) y)	747	1 094	3 312	5 509	6 134						1 972	4 129			1 746	3 806		
Overall normalized release (mCi per MW(e) y)	1.2	1.8	3.6	4.4	4.8						6.4	15.0			4.8	18.0		

Reactor	Iodine-131										Iodine-133				Iodine-135			
	Release (Ci)					Normalized release (10^{-5} Ci per MW(e) y)					Release (Ci)		Normalized release (10^{-5} Ci per MW(e) y)		Release (Ci)		Normalized release (10^{-5} Ci per MW(e) y)	
	1970	1971	1972	1973	1974	1970	1971	1972	1973	1974	1972	1974	1972	1974	1972	1974	1972	1974
G C R																		
France																		
Chinon			0.027					5.4										
St. Laurent			0.065					9.9										
Bugey			0.0001					0.08										
Total			0.09															
Electrical energy generated (MW(e) y)			1 285															
Overall normalized release (10^{-5} Ci per MW(e) y)			7.2															
H W R																		
Argentina																		
Atucha					0.0098					9.1								
Canada																		
Pickering			0.13	0.0055	0.0040			20.0	0.34	0.25								
Total			0.13	0.0055	0.0138													
Electrical energy generated (MW(e) y)			658	1 630	1 723													
Overall normalized release (10^{-5} Ci per MW(e) y)			20.0	0.34	0.80													

Sources: References 1, 26, 27, 43, 44, 99, 146, 161, 163, 171.

TABLE 14. PARTICULATES IN AIRBORNE EFFLUENTS FROM UNITED STATES REACTORS

Reactor	Electrical energy generated in 1974 (MW(e) y)	Amount released (mCi) during 1974											
P W R		^{88}Rb	^{137}Cs	^{54}Mn	^{58}Co	^{60}Co	^{134}Cs	^{59}Fe	^{89}Sr	^{138}Cs	^{51}Cr	^{140}Ba	^{90}Sr
Yankee Rowe	103.9		0.016	0.41	0.95	2.18	0.0081		0.74		0.5	0.52	0.11
Indian Pt. 1	137.0	542	7.26	0.84	0.85	7.05	2.74	0.047	0.052				0.023
Connecticut Yankee	502.3	0.16											
R. E. Ginna	239.7		0.020	$6.3\ 10^{-4}$	0.0023	0.012	0.0049	$2.5\ 10^{-4}$			$7.8\ 10^{-4}$		
Pt. Beach 1,2	764.8	0.92	0.23		28.0	37.2				0.14			
H. B. Robinson	547.9			0.024	0.70	0.36	0.066					0.091	
Palisades	8.9		0.12	0.60	2.0	0.58	0.042						
Maine Yankee	411.0		0.016		0.41	0.19	$9.3\ 10^{-4}$				0.0046		
Surry 1,2	673.5		1.71	37.4	1.16	1.16	0.0001						
Turkey Pt. 3,4	901.8		88	2.91	17.7	15.8	52	0.018	0.092			0.11	0.012
Indian Pt. 2	376.7	170	0.53	7.67	41.6	7.06	0.43	3.08	1.05				0.27
Ft. Calhoun	274.0				0.023				$3.7\ 10^{-4}$			0.011	$3.4\ 10^{-4}$
Oconee 1,2,3	632.4		0.032		0.070	0.010	$5.5\ 10^{-4}$		0.012	0.40	0.0039	0.042	$1.2\ 10^{-7}$
Zion 1,2	536.5		0.040		0.27				0.0005				0.034
Arkansas 1	65.1								0.0025				
Kawaunee	182.6	136			0.37					0.14			
Three Mile Island	239.7				0.0023				$3.4\ 10^{-4}$				$7.1\ 10^{-4}$
Total		849	98.0	49.9	94.1	71.6	55.3	3.1	1.9	0.68	0.51	0.78	0.46
Corresponding electrical energy (MW(e) y)		1 963	4 786	2 989	6 030	4 798	4 033	1 655	3 267	1 580	1 387	2 460	3 202
Normalized release (μCi per MW(e) y)		430	21.0	17.0	16.0	15.0	14.0	1.9	0.60	0.43	0.37	0.32	0.14
B W R		^{140}Ba	^{89}Sr	^{131}I	^{60}Co	^{134}Cs	^{51}Cr	^{137}Cs	^{58}Co	^{54}Mn	^{90}Sr	^{59}Fe	^{65}Zn
Dresden 1	40.0	74.4	78.1	32.9	45.0			3.6	5.5		1.0		
Big Rock Pt.	38.8				5.23	1.59	7.69	7.79		1.29			0.040
Humboldt Bay	43.4	126	202		0.35	0.27		4.47		0.47	0.17		0.14
Lacrosse	37.7	1.2	4.7			1.2		1.2			1.5		
Oyster Creek	422.4	58.1	47.4	33.4	8.4	1.7	1.5	2.6	1.6	3.3	1.2	0.20	
Nine Mile Pt.	376.7		3.65		7.54	3.66	4.58	7.41	0.16	1.7	4.61	0.18	0.056
Dresden 2,3	753.4	886	991	334	267	15.6	49.2	33.2	47.4	9.3	11.0		
Millstone Pt.	411.0		3.35	29.6	12.9	2.76	2.68	3.67	0.79	6.13	0.41	0.63	0.046
Quad Cities 1,2	924.7	6.9	5.83	34.0	3.5	3.44	6.1	4.9	0.65	0.71	0.095	0.0056	0.21
Pilgrim 1	228.3	4,7	0.89		1.38	0.15	0.014	0.44	0.31	0.99	0.0055	0.098	0.052
Vermont Yankee	285.4	1.63			0.031	1.1		0.78		0.0077			0.089
Browns Ferry	593.6	35.9	0.16			38.4		9.15			0.030		
Cooper Station	205.5	195	0.023			28.8					0.012		
Total		1 390	1 337	464	351	98.7	71.8	79.2	56.4	23.9	20.0	1.1	0.63
Corresponding electrical energy (MW(e) y)		3 534	4 037	2 552	3 524	4 321	3 155	4 155	3 157	3 484	4 037	2 363	2 308
Normalized release (μCi per MW(e) y)		390	330	180	100.0	23.0	23.0	19.0	18.0	6.9	5.0	0.47	0.27

Source: Reference 163.

TABLE 15. RADIONUCLIDES OTHER THAN TRITIUM DISCHARGED IN LIQUID EFFLUENTS FROM VARIOUS REACTORS DURING 1974

Reactor	Electrical energy generated (MW(e) y)	Amount discharged (Ci)																	
		^{131}I	^{137}Cs	^{133}I	^{134}Cs	^{58}Co	^{60}Co	^{51}Cr	^{54}Mn	^{124}Sb	^{144}Ce	^{103}Ru	^{110m}Ag	^{89}Sr	^{132}I	^{59}Fe	^{95}Nb	^{95}Zr	^{99}Mo	^{90}Sr
P W R																				
Germany, Fed. Rep. of																				
Obrigheim	293.5	0.083	0.61		0.40	0.64	0.27	0.019	0.073	0.018				0.0056						0.001
Stade	608.2	0.0007	0.041		0.013	0.013	0.015	0.0046	0.0043	0.020	0.0025	0.0010	0.027	0.0011			0.0029	0.0011		0.0004
Biblis	100.8	0.0011				0.040	0.0032		0.0034	0.27				0.0001						$9\ 10^{-6}$
United States																				
Yankee Rowe	103.9	0.0006	0.0032	$5\ 10^{-5}$	0.0020	0.0001	0.0003	$5\ 10^{-5}$	0.0003				$4\ 10^{-6}$	0.0003						$7\ 10^{-5}$
Indian Pt. 1	137.0	0.40	0.45		0.20	0.12	0.16							0.0062		0.0077				0.0008
San Onofre	353.9	0.047				0.35	0.070	0.19	0.011	0.013			0.017	0.0020	0.032	0.018				0.0044
Conn. Yankee	502.3	$9\ 10^{-5}$	0.27		0.0030	0.42	0.68	0.51	0.0045		0.28	0.048								
Ginna	239.7	0.0001	0.039		0.013	0.014	0.032		0.0034		0.015	0.0040	0.0002					0.0064		
Pt. Beach 1,2	764.8	0.018	0.098	0.029	0.038	0.0013	0.0002		$2\ 10^{-5}$		$8\ 10^{-6}$	0.0005		0.0009	0.0012		0.0001	$8\ 10^{-5}$		0.0002
H. B. Robinson	547.9	0.82	0.15		0.14	0.22	0.16	0.0081	0.022	0.0002			0.0003	0.0032		$2\ 10^{-5}$			$8\ 10^{-5}$	0.0011
Palisades	8.9	0.0056	1.48	0.0005	0.70	0.70	0.43	0.014	0.29							0.0012	0.0076	0.0021		
Maine Yankee	411.0		0.99	0.14	1.49	0.27			0.0025									0.0016		$1\ 10^{-5}$
Surry 1,2	673.5	11.0	6.83	4.67	3.73	1.93	1.00		0.36					0.020						0.0015
Turkey Pt. 3,4	901.8	1.07	0.068	0.099	0.036	0.16	0.029	0.021	0.0082	0.019	0.0077			0.0094	0.0007	0.0026		0.0028	0.0051	0.0002
Indian Pt. 2	376.7	2.18	0.24		0.056	1.34	0.14		0.062					0.0019		0.012				0.0003
Ft. Calhoun	274.0			0.017		0.14	0.0029		0.011					$4\ 10^{-5}$						$7\ 10^{-5}$
Prairie Island	160.0					0.0003	$4\ 10^{-5}$													
Oconee 1,2,3	632.4	0.11	0.060	0.092	0.040	0.47	0.028	0.017	0.0077	0.0002	0.0005		$1\ 10^{-6}$	0.016	0.0030	$3\ 10^{-5}$	0.0002	0.0001	0.0029	0.0020
Zion 1,2	536.5					0.0008														
Arkansas 1	65.1	0.019	0.0002	0.0003		0.033	0.0006	0.0091	0.0021		0.0015	$6\ 10^{-7}$	0.0013	0.017	0.0001	0.0018	0.0003	0.0002	$2\ 10^{-5}$	0.0025
Kewaunee	182.6	0.021	0.0072	0.0027	0.0011	0.29	0.017	0.0045	0.0089	0.0090					$6\ 10^{-5}$	0.0001	0.0024	0.0017	0.0007	
Three Mile Island	239.7	0.0092	0.0035		$3\ 10^{-5}$	0.018	0.0001	0.0053	0.0002					$2\ 10^{-5}$				0.0003	$4\ 10^{-6}$	$2\ 10^{-6}$
Total		15.78	11.34	5.05	6.85	7.17	3.03	0.803	0.874	0.354	0.304	0.0531	0.0458	0.0835	0.0370	0.0437	0.0135	0.0165	0.0088	0.0144
Corresponding electrical energy (MW(e) y)		6 733	6 689	4 018	6 624	8 114	7 167	4 440	7 281	3 621	3 714	2 180	2 551	6 073	2 836	3 206	2 262	4 054	2 570	6 484
Normalized release (mCi per MW(e) y)		2.3	1.7	1.3	1.0	0.88	0.42	0.18	0.12	0.098	0.082	0.024	0.018	0.014	0.013	0.013	0.0060	0.0041	0.0034	0.0022

		^{137}Cs	^{134}Cs	^{60}Co	^{131}I	^{54}Mn	^{58}Co	^{89}Sr	^{51}Cr	^{144}Ce	^{65}Zn	^{24}Na	^{99}Mo	^{133}I	^{90}Sr	^{59}Fe	^{95}Zr	^{141}Ce	^{110m}Ag
B W R																			
Germany, Fed. Rep. of																			
Kahl	10.4	0.0017	0.0002	0.0028	0.0002			$2\ 10^{-5}$							0.0010				
Gundremmingen	219.1	0.12	0.059	0.040	0.11	0.0098	0.057	0.53		0.0007	$6\ 10^{-5}$				0.052	0.0015	0.0006	0.0030	0.011
Lingen	54.9	0.0044	0.00012	0.0057				0.0021							$3\ 10^{-5}$	$1\ 10^{-5}$			
Würgassen	55.7	0.0005	0.0005	0.36		0.014	0.16	0.0028	0.10		0.33				$2\ 10^{-5}$	0.0004	0.0041	0.0004	0.0009
United States																			
Dresden 1	40.0	1.37	0.67	0.72	0.034	0.036	0.0060	0.0098						0.023	0.0019	0.0022			
Big Rock Pt.	38.8	0.18	0.075		0.0052	0.049					0.021			0.0002		0.010			
Humboldt Bay	43.3	2.10	1.37	0.28	0.034	0.23	0.0031	0.074		0.12	0.14			0.0015	0.018				
Lacrosse	37.7	2.72	1.51	0.53		0.079	6.81	0.013	0.061		0.096				0.0012				
Oyster Creek	422.4	0.015	0.026	0.074	0.014	0.044	0.0092	0.012	0.11	0.0031	0.0020		0.11	0.016	0.0062	0.012	0.0077	0.0041	
Nine Mile Pt.	376.7	9.78	4.64	5.16	1.01	2.46	0.015	0.85	0.27			0.17	0.36	0.48	0.12	0.010	0.029	0.0080	
Dresden 2,3	753.4	6.79	2.77	12.3	0.55	0.72	0.23	0.62	0.059	0.65			0.0016	0.0032	0.028		0.0023		
Millstone Pt.	411.0	95.2	72.1	9.67	13.4	6.18	0.50	1.62			0.17				0.21	0.13			
Monticello	331.1	no liquid releases																	
Quad Cities 1,2	924.7	6.00	2.95	3.01	2.09	0.38	0.43	0.24	1.10		0.12			0.0087	0.045	0.0002	0.0008		$8\ 10^{-5}$

TABLE 15 *(continued)*

Reactor	*Electrical energy generated (MW(e) y)*	*Amount discharged (Ci)*																
		^{137}Cs	^{134}Cs	^{60}Co	^{131}I	^{54}Mn	^{58}Co	^{89}Sr	^{51}Cr	^{144}Ce	^{65}Zn	^{24}Na	^{99}Mo	^{133}I	^{90}Sr	^{59}Fe	^{95}Zr	^{141}Ce	^{110m}Ag
United States *(continued)*																			
Pilgrim 1	228.3	1.58	0.50	0.96	0.17	0.28	0.30	0.016	0.12	0.0008	0.056		0.010	0.0011	0.0027	0.023	0.0010	$7\ 10^{-5}$	0.0002
Vermont Yankee	285.4	no liquid releases																	
Browns Ferry 1	593.6	0.0011	0.0081	0.18	0.10	0.014	0.014	0.0052	0.091		0.30	0.017			0.0051	0.016			
Peach Bottom 2,3	441.8			0.0075		0.0052	0.045		0.069		0.0030	0.21	0.0018			0.0006	0.0034		
Cooper Station	205.5	0.0019	0.22	0.077	0.0028	0.0024	0.57	0.0098	0.72		0.020		0.010		0.0009	0.0087	0.0020	0.0038	
	Total	125.87	86.90	33.21	17.44	10.50	9.13	4.00	2.70	0.775	0.994	0.399	0.497	0.528	0.490	0.212	0.0510	0.0194	0.0121
Corresponding electrical energy (MW(e) y)		5 032	5 032	5 435	4 884	5 409	5 370	4 993	4 656	2 283	4 239	2 029	3 045	3 444	4 993	4 629	4 244	2 124	2 044
Normalized release (mCi per MW(e) y)		25.0	17.3	6.1	3.6	1.9	1.7	0.80	0.58	0.34	0.23	0.20	0.16	0.15	0.098	0.046	0.012	0.0091	0.0059

		^{137}Cs	^{35}S	^{134}Cs	^{90}Sr	^{90}Y	^{125}Sb	^{147}Pm	^{55}Fe	^{106}Ru	^{106}Rh	^{125m}Te	^{45}Ca	^{144}Ce
GCR														
United Kingdom														
Berkeley	224.9	11.3	3.26	2.19	1.99	1.99	0.092	0.25	0.12	0.092	0.092	0.023	0.85	0.069
Bradwell	204.3	27.5	7.11	3.33	16.6	16.6	0.36	4.50	4.86	1.71	1.71	0.090	0.63	1.08
Hinkley Pt.	350.5	61.8	4.13	5.63	6.25	6.25	16.0	4.75	2.13	4.00	4.00	4.13	0.25	1.25
Trawsfynydd	369.9	2.20	11.1	0.32	0.17	0.17	3.14	0.095	0.019	0.30	0.30	0.76	0.019	0.019
Dungeness	388.1	43.0	6.07	13.0	1.45	1.45	0.069	0.14	1.86	< 0.035	< 0.035	< 0.035	0.62	0.069
Sizewell	360.7	6.49	4.69	1.10	0.70	0.70	0.048	0.095	0.59	0.048	0.048	0.016	0.52	0.016
Oldbury	320.8	12.6	6.68	2.28	4.24	4.24	0.16	0.098	0.20	0.033	0.033	0.033	0.52	0.033
Wylfa	424.7	0.036	0.26	0.008	0.024	0.024	0.001	0.008	0.056	0.004	0.004	0.001	0.001	0.004
Hunterston	243.2	32.5	8.58	11.4	1.94	1.94							0.41	
	Total	197.3	51.84	39.24	33.32	33.32	19.87	9.94	9.82	6.19	6.19	5.05	3.83	2.54
Corresponding electrical energy (MW(e) y)		2 887	2 887	2 887	2 887	2 887	2 644	2 644	2 644	2 664	2 664	2 664	2 887	2 644
Normalized release (mCi per MW(e) y)		68.3	18.0	13.6	11.5	11.5	7.5	3.8	3.7	2.3	2.3	1.9	1.3	0.96

		^{144}Pr	^{32}P	^{60}Co	^{89}Sr	^{51}Cr	^{124}Sb	^{91}Y	^{154}Eu	^{95}Nb	^{14}C	^{65}Zn	^{54}Mn	^{59}Fe
Berkeley	224.9	0.069	0.069	0.023	0.28	0.16	0.069	0.046	< 0.012	0.023	0.046	< 0.012	< 0.012	< 0.012
Bradwell	204.3	1.08	0.72	1.53	< 0.045	< 0.045	0.18	< 0.045	0.27	< 0.045	< 0.045	0.18	0.09	< 0.045
Hinkley Pt.	350.5	1.25	0.25	0.13	0.38	1.00	0.25	0.88	0.13	0.13	0.13	< 0.063	< 0.063	< 0.063
Trawsfynydd	369.9	0.019	0.25	0.038	< 0.0095	< 0.0095	0.057	< 0.0095	< 0.0095	0.019	< 0.0095	0.019	< 0.0095	0.019
Dungeness	388.1	0.069	0.21	0.069	0.21	0.35	0.35	< 0.035	< 0.035	0.069	< 0.035	< 0.035	< 0.035	< 0.035
Sizewell	360.7	0.016	0.43	0.048	0.080	0.11	0.064	0.032	< 0.008	0.016	< 0.0080	0.016	0.016	0.016
Oldbury	320.8	0.033	0.13	0.033	0.85	0.13	0.13	0.033	< 0.016	0.033	0.065	< 0.016	< 0.016	0.033
Wylfa	424.7	0.004	< 0.0003	0.008	0.001	0.016	0.004	0.001	< 0.0003	0.004	0.001	0.004	0.004	0.005
Hunterston	243.2		0.18											
	Total	2.54	2.23	1.87	1.79	1.76	1.10	0.987	0.395	0.289	0.237	0.219	0.110	0.725
Corresponding electrical energy (MW(e) y)		2 644	2 887	2 644	2 644	2 644	2 644	2 644	2 644	2 644	2 644	2 644	2 644	2 644
Normalized release (mCi per MW(e) y)		0.96	0.77	0.71	0.68	0.67	0.42	0.37	0.15	0.11	0.090	0.083	0.042	0.027

Sources: References 3, 106, 163.

B. LOCAL AND REGIONAL COLLECTIVE DOSE COMMITMENT

91. Routine environmental monitoring is conducted to a greater or lesser extent around all reactor installations. More detailed, investigative studies to characterize reactor environmental contamination caused by releases have been conducted around specific types of reactors (15, 70, 71, 72). Except in the immediate vicinity of the reactor, the levels of radioactive contamination are not usually readily detectable. Dose assessments must therefore rely primarily on calculations of the environmental dispersion of the released radioactivity. Generalized calculations can be expected to indicate roughly the relative significance of the release amounts and of the exposure pathways. More specific dose assessments at a given site may require a different selection of model parameters to fit the local conditions.

1. Fission noble gases

92. The noble gases released from reactors usually make the largest contribution to the dose to the local population. Considerable effort has been devoted to the development and application of calculational methods to estimate the airborne dispersion (23, 96), and in a few cases careful attempts to measure the actual exposure from the noble gas plume have been successful (9, 37, 98).

93. Bryant has calculated the gonad dose per unit activity discharged that would be received by the population at distances from 1 to 1000 km for each of noble gas nuclides (23). The calculations assume a 30 m effective stack height and average weather conditions. Assuming a population density of 100 km^{-2} in the region from 1 to 100 km and 25 km^{-2} at greater distances, the corresponding collective doses per unit activity discharge have been calculated (table 16). When these results are applied to actual or generalized released amounts, the total dose and the relative contributions of the various nuclides can be obtained. The specific noble gas release composition can vary substantially, depending on how the waste gas is processed.

94. Using the average release composition based on operating experience (table 9), the examples of table 17 have been calculated. In the computation for the BWR given in table 17, the gonad doses at 1 and 10 km are due primarily to ^{88}Kr, ^{87}Kr, ^{138}Xe and ^{135}Xe. The ^{88}Kr daughter, ^{88}Rb, although largely prevented from being released by the particle filters, builds up as the parent decays and is an important dose contributor at 10 km. The same holds for the ^{138}Xe daughter, ^{138}Cs. At 100 km, ^{135}Xe (9.2 h) becomes the dominant contributor. The fractional contribution from the relatively long-lived ^{133}Xe (5.3 d) increases with distance. At 1000 km, only ^{135}Xe and ^{133}Xe make significant dose contributions. Estimates of the corresponding collective doses per unit of noble gas activity released are 4.5 10^{-4} man rad Ci^{-1} within 100 km, and an additional 0.4 10^{-4} man rad Ci^{-1} in the region from 100-1000 km. For the average BWR total normalized release based on operating experience, 1100 Ci per MW(e) y (table 8), the local collective dose would be 0.5 man rad per MW(e) y (to 100 km), and the additional regional contribution would be 0.05 man rad per MW(e) y (100-1500 km), including the contribution from ^{133}Xe beyond 1000 km.

TABLE 16. GONADAL DOSE FACTORS FOR NOBLE GASES RELEASED IN AIRBORNE EFFLUENTS[a]

		Dose per unit release (10^{-9} rad Ci^{-1})				*Collective dose per unit release (10^{-3} man rad Ci^{-1})[b]*		
Radionuclide	*Half-life*	*1 km*	*10 km*	*100 km*	*1000 km*	*1-10 km*	*10-100 km*	*100-1000 km*
^{83m}Kr	1.86 h	3.2	0.16			0.014	0.015	
^{85m}Kr	4.4 h	18.4	0.92	0.010		0.069	0.18	0.0078
^{85}Kr	10.76 y	0.18	0.012	0.00076	0.000048	0.00080	0.0050	0.0080
^{87}Kr	76 m	66.6	2.2	0.0016		0.20	0.20	
^{88}Kr	2.8 h	101.0	5.4	0.025		0.40	0.78	0.012
^{88}Rb[c]	17.8 m	8.2	1.7	0.0079		0.095	0.29	
^{89}Kr	3.2 m	76.1	0.0032					
^{89}Rb[d]	15.4 m	23.8	0.27					
^{131m}Xe	11.8 d	13.3	0.76	0.044	0.0023	0.055	0.31	0.41
^{133m}Xe	2.26 d	22.5	1.3	0.067	0.0011	0.092	0.47	0.46
^{133}Xe[e]	5.27 d	0.0014	0.00079	0.00043	0.00012	0.000028	0.0016	0.014
^{133}Xe	5.27 d	2.3	0.14	0.0065	0.00026	0.0094	0.050	0.054[f]
^{135m}Xe	15.6 m	38.1	0.24			0.052	0.0051	
^{135}Xe	9.2 h	25.4	1.3	0.032	0.00029	0.097	0.34	0.11
^{137}Xe	3.9 m	4.8	0.00041					
^{138}Xe	17 m	72.9	0.70			0.16	0.018	
^{138}Cs[g]	32.2 m	12.0	1.3	0.000070		0.098	0.066	
^{41}Ar	1.83 h	85.6	3.2	0.0057		0.26	0.22	0.0023

Source: Reference 23.

[a] Effective stack height of 30 m; average weather conditions.

[b] Assumed 100 man km^{-2} in the region 1-100 km and 25 man km^{-2} at distances > 100 km.

[c] Per unit activity of ^{88}Kr released.

[d] Per unit activity of ^{89}Kr released.

[e] Per unit activity of ^{133m}Xe released.

[f] The extrapolated collective dose in the region 1000-1500 km, per unit activity of ^{133}Xe released, is 0.017 10^{-3} man rad Ci^{-1}.

[g] Per unit activity of ^{138}Xe released.

TABLE 17. GONADAL DOSE FROM NOBLE GASES RELEASED IN AIRBORNE EFFLUENTS FROM REACTORS[a]

Type of reactor	Dose per unit release (10^{-9} rad Ci^{-1}) 1 km	10 km	100 km	1 000 km	Collective dose per unit release (10^{-3} man rad Ci^{-1}) 1-10 km	10-100 km	100-1 000 km
BWR	44	2.0	0.015	0.00012	0.16	0.29	0.041
PWR	5.7	0.26	0.0079	0.00027	0.020	0.070	0.059
GCR	86	3.2	0.0057		0.26	0.22	0.0023

Radionuclide	Fraction of total release (%)	Relative contribution to dose (%) 1 km	10 km	100 km	1 000 km	Relative contribution to collective dose (%) 1-10 km	10-100 km	100-1 000 km
BWR								
^{135}Xe	26	15	17	55	63	16	30	70
^{88}Kr	14	32	39	23		35	37	4.1
^{88}Rb[b]		2.6	12	7.4		8.3	14	
^{133}Xe[c]	14	0.7	1	6.1	30	0.8	2.4	18
^{138}Xe	13	21	4.7			13	0.8	
^{138}Cs[b]		3.5	8.7	0.06		7.9	2.9	
^{87}Kr	12	18	14	1.3		15	8.2	
^{83m}Kr	7	0.5	0.6			0.6	0.4	
^{85m}Kr	5	2.1	2.4	3.3		2.2	3.1	1.0
^{135m}Xe	4	3.5	0.5			1.3	0.07	
^{85}Kr	2	0.008	0.01	0.1	0.8	0.01	0.03	0.4
^{137}Xe	0.9	0.1	0.0002					
^{133m}Xe	0.6	0.3	0.4	2.7	5.5	0.3	1.0	6.7
^{133}Xe[b]			0.0003	0.02	0.6		0.003	0.2
PWR								
^{133}Xe[c]	90	37	48	74	86	42	64	82
^{135}Xe	3	13	15	12	3.2	15	14	5.6
^{138}Xe	1	13	2.7			8.0	0.3	
^{85}Kr	1	0.03	0.05	0.1	0.2	0.04	0.07	0.1
^{131m}Xe	1	2.4	2.9	5.6	8.5	2.8	4.4	6.9
^{88}Kr	0.9	16	19	2.8		18	10	0.2
^{135m}Xe	0.8	5.4	0.7			2.1	0.06	
^{85m}Kr	0.6	2.0	2.1	0.8		2.1	1.5	0.08
^{133m}Xe	0.5	2.0	2.5	4.2	2.0	2.3	3.3	3.9
^{133}Xe[b]			0.002	0.03	0.2		0.01	0.1
^{87}Kr	0.4	4.7	3.4	0.08		4.0	1.1	
^{41}Ar	0.3	4.5	3.7	0.2		3.9	0.9	0.01
GCR								
^{41}Ar	100	100	100	100	100	100	100	100

[a] The dose factors of table 16 were used; therefore, the results apply to a 30-m effective stack height and average weather conditions.

[b] Formed after release and decay of parent radionuclide.

[c] The extrapolated collective dose in the region 1 000-1 500 km due to ^{133}Xe is 0.0024 10^{-3} and 0.015 10^{-3} man rad Ci^{-1} for the BWR and PWR, respectively.

95. Using reported noble gas release data and actual average local meteorology and population factors, Martin has computed the collective dose to the population within 80 km of several BWRs in the United States (96). The results for 1971 ranged from 0.04 to 4.0 man rad per MW(e) y for eight reactor sites. The average noble gas release was 1718 Ci per MW(e) y. The collective dose was 900 man rad from 1.85 GW(e) y of electrical energy generated, corresponding to 0.5 man rad per MW(e) y. Approximately similar results were obtained for 11 BWR sites in 1972 (94). Preliminary results for 1973 indicated a probable slight reduction in the collective dose due to the longer hold-up times of the newer BWRs (95). The results of Martin, which are based on actual population and meteorology data, are in good agreement with the estimates of the previous paragraph.

96. Attempts to evaluate the absorbed dose rates in air from released noble gas by actual measurements within a few kilometres of BWRs have met with success (9, 98). Sensitive ionization chambers clearly register the overhead passage of the plume; however, some care is needed to distinguish similar abrupt changes in the background exposure rate due to changes in the radon-daughter contribution during and shortly after a rainfall.

97. Gogolak has used the results of a monitoring network of continuously operating ionization chambers to evaluate model dispersion calculations (37). Seven ionization chambers were placed at distances of 1.3-8 km from a BWR located at a sea-coast site. In the most prominent wind direction, the absorbed dose in air per unit of activity released, measured over a 200-d period, averaged $4.2\ 10^{-9}$ rad Ci^{-1} at 2.6 km and $1.5\ 10^{-9}$ rad Ci^{-1} at 8 km. The computed absorbed doses in air, with careful correlation of stack-effluent release monitoring and local meteorology, agreed very well with the measurements. For the actual population around the reactor, Gogolak determined the whole-body collective dose per unit of electrical energy generated to be 0.02 man rad per MW(e) y from 0 to 16 km and estimated it to be 0.05 from 0 to 80 km and 0.09 man rad per MW(e) y overall. The estimates include a shielding and occupancy factor of 0.5 and a tissue screening and absorption factor of 0.8. The collective dose estimates of Martin and the example in table 17 have not been corrected for shielding by buildings.

98. The main contributor to the collective dose from noble gases released from a PWR (table 17) is expected to be primarily ^{133}Xe, due to the long hold-up of the primary gaseous-waste processing system, but leakages also result in some release of shorter-lived noble gas nuclides. The collective dose appears to be primarily due to ^{133}Xe, ^{135}Xe and ^{88}Kr, with ^{133}Xe becoming increasingly a more important contributor to the dose at greater distances. Small releases of the longer-lived ^{133m}Xe (2.3 d) and ^{133m}Xe (12.0 d) occur, but their contributions to the collective dose remain small out to 1000 km. The contribution from ^{85}Kr (10.76 y) to the collective dose in the local and regional areas is insignificant.

99. The collective dose per unit of noble gas activity released by PWRs is $0.9\ 10^{-4}$ man rad Ci^{-1} within 100 km and $0.6\ 10^{-4}$ man rad Ci^{-1} from 100 to 1000 km (table 17). For the average PWR normalized release based on operating experience, about 15 Ci per MW(e) y (table 8), the local collective dose would be 0.0014 man rad per MW(e) y (to 100 km), with an additional regional contribution of 0.0011 man rad per MW(e) y (100-1500 km), including the extrapolated contribution from ^{133}Xe beyond 1000 km. The total of these two contributions is 0.0025 man rad per MW(e) y. Using actual population data and reported releases for two United States PWRs for 1972, Martin computed the collective dose to the population within 80 km of the reactors to be 0.005 man rad per MW(e) y (94).

2. Activation gases

100. Due to the short half-life of ^{41}Ar (1.83 h), the dose decreases quite rapidly with distance. A calculation of the individual gonad dose and collective dose is given in table 17 for the GCR, assuming the noble gas release to be 100 per cent ^{41}Ar. For a population density of 100 km^{-2}, the collective dose per unit activity released to 100 km is $4.8\ 10^{-4}$ man rad Ci^{-1}. For an ^{41}Ar release from GCRs of 200 Ci per MW(e) y, the collective dose is estimated to be 0.1 man rad per MW(e) y. Clarke has calculated collective doses from ^{41}Ar released from Magnox reactors in the United Kingdom (24). His results are $(4.8\text{-}30)\ 10^{-4}$ man rad Ci^{-1}, depending on the reactor site, corresponding on the average to 0.13 man rad per MW(e) y. Reductions by factors of two to three would be appropriate to account for indoor shielding. Nagel has discussed initial attempts to compare calculations with measurements of the gamma dose from ^{41}Ar (103).

101. The behaviour in the environment of ^{35}S released from GCRs is not well understood. Ingestion of milk is thought to be the significant pathway to man; there are, however, uncertainties in estimating the deposition velocity and the transfer to milk. Passant has given a value of 0.023 rad per curie released as a rough estimate of the dose to bone marrow per unit activity released at the reactor boundary (113). Vennart and Ash have recently reviewed the dosimetry of inhaled and ingested ^{35}S (168).

102. The absorbed dose rate at the site boundary from ^{16}N released from GCRs is given as $5\ 10^{-5}$ rad y^{-1} (whole-body) for a 2000 Ci y^{-1} release (113). Absorbed dose rates in air from ^{16}N radiation originating from the turbine buildings of BWRs (about 5 mrad y^{-1} at 0.5 km) are quite dependent on source and field geometry (86, 87).

3. Tritium

103. Tritium present in airborne effluents from reactors can contribute to the local collective dose primarily through the inhalation pathway and secondarily through the ingestion pathway. The local collective dose contribution after deposition through the ingestion pathway may be quite variable from site to site owing to differences in local hydrology and water usage. This pathway is accounted for in the general assessment of the global collective dose commitment in chapter VI. The intake of airborne tritium occurs by inhalation (20 m^3 air inhaled per day) and by passage through skin. Intake through the skin is assumed to be equal to that through inhalation. The dose to soft tissue per unit activity intake in the form of tritiated water is 84 rad Ci^{-1} (12). Assuming an atmospheric dispersion factor of $5\ 10^{-7}$ s m^{-3} at 1 km from the release and a reduction in concentration due to further dispersion inversely proportional to the 1.5 power of the distance expressed in kilometres, the local collective dose per unit activity released can be assessed by integration over the local area. Integrating from 1 to 100 km for a population density of 100 km^{-2} and including the above factors, we obtain the estimated local collective dose from airborne tritium per unit activity released:

$$S = (5\ 10^{-7}\ \mathrm{s\ m^{-3}})(40\ \mathrm{m^3\ d^{-1}})\left(\frac{1}{86\,400}\ \mathrm{d\ s^{-1}}\right)$$

$$(84\ \mathrm{rad\ Ci^{-1}})(100\ \mathrm{man\ km^{-2}})\int_1^{100} r^{-1.5}\,2\pi r\,dr$$

the local collective dose from airborne tritium per unit activity released is estimated to be $2\ 10^{-4}$ man rad per Ci.

104. The average discharges of airborne tritium based on operating experience (table 11) are (Ci per MW(e) y), for PWRs and GCRs, 0.2; for BWRs, 0.05; for HWRs, 18. Using the above value of collective dose per unit release,

the estimated local collective doses, for the assumed local situation, are $4\ 10^{-5}$, $1\ 10^{-5}$, and $4\ 10^{-3}$ man rad per MW(e) y for the PWR and GCR, the BWR, and the HWR, respectively.

105. Tritium in liquid effluents from reactors can contribute most directly to the local collective dose if the discharge is to a river that provides a drinking water supply. The collective dose per unit activity released, estimated from the drinking water intakes given in table 22 (discussed in paragraph 126) is 0.007 man rad Ci^{-1}. The tritium releases reported from the most recent operating experience (table 12) are about 1 and 0.1 Ci per MW(e) y from PWRs and BWRs, respectively. From HWRs the release is assumed to be 4 Ci per MW(e) y. The local collective dose estimates would thus be 0.007, 0.0007, and 0.03 man rad per MW(e) y for the PWR, BWR, and HWR, respectively.

4. Carbon-14

106. Carbon-14 makes a very small contribution to the local collective dose. It is of more significance in terms of entering the carbon cycle and contributing to the global collective dose, as discussed in chapter VI. The local collective dose due to ^{14}C airborne releases from reactors can be estimated by comparing the resulting specific activity in air (which contains 0.16 g of C per cubic metre) to the natural specific activity (and thus the natural ^{14}C dose rate). Using the same atmospheric dispersion model and the same population assumptions as in the case of airborne tritium (para. 103), the local collective dose commitments per unit activity released are estimated to be 0.12, 0.1, 0.37, and 0.40 man rad Ci^{-1} for the lung, gonads, bone lining cells and bone marrow, respectively.

107. For a normalized ^{14}C release from a light-water reactor of $6\ 10^{-3}$ Ci per MW(e) y (para. 76), the local collective dose commitments are estimated to be $7\ 10^{-4}$, $6\ 10^{-4}$, $2.2\ 10^{-3}$ and $2.4\ 10^{-3}$ man rad per MW(e) y for the lungs, gonads, bone lining cells and bone marrow, respectively. As the inhalation intake of carbon is about 3 g d^{-1} and only 1 per cent of this intake is retained in the body (13), whereas the ingestion intake is 300 g d^{-1} with 100 per cent retention (68), the inhalation pathway can account for only 10^{-4} of the local collective dose. Regional contributions to the collective dose have been assessed by Kelly *et al.* (74), considering the first passage of the released material over a country or region. These contributions are also very small compared to the global collective dose commitment from ^{14}C.

5. Iodine

108. Assessment of local dose from ^{131}I released from reactors is complicated by the various forms that iodine may take—particulate, elemental, organic or as hypoiodous acid. Elemental iodine readily deposits on forage and enters the cow-milk-man pathway. Organic iodine, however, is retained much less efficiently by vegetation, and its deposition velocity is 200-1000 times smaller than that of the elemental form (2, 47). Particulate-associated iodine will be deposited at rates intermediate between those for the elemental and organic forms. The behaviour of hypoiodous acid is uncertain; it may simply decompose to the elemental and organic forms (114). Physico-chemical transformations occurring during atmospheric transport may also affect the amount of iodine in its various organic forms, since these are not stable in sunlight. The elemental form would be expected to become rapidly associated with airborne aerosols, so that deposition at distances beyond the immediate vicinity of the release would be largely governed by the particulate behaviour. This is also shown by fallout measurements (116).

109. A recent reassessment by Hoffman (53) of iodine deposition factors for predicting environment transfer has shown that the experimentally derived values of the deposition velocity have frequently been misinterpreted. As the measurements relate directly the actual deposition rate on vegetation to the concentration in air, the use of an additional factor to account for the intercepted fraction of the total deposition is therefore inappropriate.

110. Recent determinations of deposition velocities as the ratio of the total deposition on vegetation per unit ground surface area to the time-integrated concentration in air give 2 cm s^{-1} for the deposition of elemental iodine on grass and 0.01 cm s^{-1} or less for methyl iodide (47). In the case of particulates (mean aerosol particle diameter 4 μm), a value of 0.1 cm s^{-1} was found representative for grass, about 0.2 cm s^{-1} for clover and about 0.03 cm s^{-1} for vegetation-free soil (54). Since the deposition velocity varies with the vegetation density, less variability is encountered by normalizing the values by the mass of dry vegetation per unit area (52). For the conditions under which the particulate deposition velocities were measured, the normalized value for grass is 0.005 $m^3\ kg^{-1}\ s^{-1}$ (54).

111. The assessment of the transfer of iodine to milk, which is the main pathway to man, requires the knowledge of the value of the following parameters in addition to the deposition velocity: the residence half-time of particulates on vegetation (14 d), corresponding to an effective mean-life of 20.2 d for ^{129}I and 7.36 d for ^{131}I; the average mass of grass consumed per cow and per day under average agricultural conditions during the grazing season, taken to be 11 kg (dry) per day (51); the fractional transfer of the daily ingested activity by the cow per unit volume of produced milk, 0.01 d l^{-1}; and the fractional pasture-grazing time, assumed to be 0.5 for ^{131}I and 1.0 for ^{129}I. Taking account of all these parameters, an integrated air concentration of 1 pCi d m^{-3} of ^{131}I or ^{129}I would thus result in an integrated milk concentration for ^{131}I of 175 pCi d l^{-1} and for ^{129}I of 960 pCi d l^{-1}. Transfer via wet deposition is usually insignificant over the course of a year. For specific times or locations, however, it may indeed be significant.

112. To assess the transfer of iodine from air to fresh leafy vegetables, the required parameters are: the deposition velocity and the residence time on the vegetation (same values as discussed above); the fractional removal by washing, 0.4 (157); the decay due to an average 7-d marketing delay, if applicable, 0.55 for ^{131}I (157); and a dry-to-wet vegetation weight ratio of 0.5. Time-integrated concentrations of 350 pCi d kg^{-1}

(fresh weight) for ^{131}I and 1740 pCi d kg^{-1} (fresh weight) for ^{129}I are calculated for the case of a time-integrated air concentration of 1 pCi d m^{-3}.

113. An estimate of the transfer of ^{129}I to beef can also be made. The parameters required are: the deposition velocity, 0.005 m^3 kg^{-1} s^{-1}; residence mean-time on grass, 20.2 d; grass consumption rate, 11 kg (dry) per day; fractional transfer of daily ingested activity per unit mass of meat, 0.003 d kg^{-1} (111); and the fractional pasture time, 1.0. The resulting transfer factor is 290 pCi d kg^{-1} per 1 pCi d m^{-3} of ^{129}I in air.

114. The estimated transfer factors from air to milk, leafy vegetables or meat have not been verified in the case of actual radioiodine releases from reactors. A careful attempt to measure ^{131}I in the environment around a reactor during normal operation has been reported (170). Low levels of ^{131}I in air were detected near three BWRs, but only a few samples of vegetation and milk showed ^{131}I activity above the detection limit. The transfer of ^{131}I from deposition on grass to milk has also been estimated from fallout field measurements (see Annex C). These estimates of the transfer factor are somewhat lower than the value given in paragraph 11, but it has been suggested that the availability of fallout ^{131}I might be reduced because of its physical form (140). Because of the variability of all of the intervening factors, the assessment of transfer factor given in the preceding paragraphs can be expected to give only a general indication of the doses from airborne releases of iodine.

115. In a review of the iodine metabolic parameters certain values have been suggested for use in computing the age-dependent doses to the thyroid gland following an ingestion or inhalation intake (51). The values for ^{131}I and ^{129}I are given in table 18.

TABLE 18. DATA RELATING TO THE AGE-DEPENDENT DOSE TO THE THYROID GLAND FROM ^{131}I AND ^{129}I INTAKES

	Age			
	6 months	*4 years*	*14 years*	*Adult*
Thyroid mass (g)	2.0	4.0	14	20
Fractional uptake by the thyroid				
Ingestion	0.40	0.35	0.35	0.35
Inhalation	0.30	0.26	0.26	0.26
^{131}I				
Energy per disintegration (MEV)	0.18	0.18	0.19	0.19
Effective half-time in the thyroid (d)	6.0	6.3	6.9	7.6
Dose per unit intake (rad μCi^{-1})				
Ingestion	16	7.3	2.4	1.9
Inhalation	12	5.5	1.8	1.4
^{129}I				
Energy per disintegration (MEV)	0.060	0.061	0.063	0.064
Effective half-time in the thyroid (d)	23	28	48	136
Dose per unit intake (rad μCi^{-1})				
Ingestion	20	11	5.6	1.1
Inhalation	15	8.3	4.2	8.4

Source: Reference 51.

116. The average consumption rate of milk (68), leafy vegetables (157) and beef (one third of maximum meat consumption) (132) and the inhalation rate (68) for representative ages are given in table 19. These intake rates and the transfer factors estimated for the various pathways were used to compute the thyroid doses per unit time-integrated activity concentration in air, also listed in table 19. The highest dose is to the infant and is due almost entirely to milk consumption.

TABLE 19. DATA RELATING TO THE ENVIRONMENTAL PATHWAYS AND THYROID DOSES FROM ^{131}I and ^{129}I

	Age			
	6 months	*4 years*	*14 years*	*Adult*
Inhalation pathway				
Breathing rate (m^3 y^{-1})	1 150	3 530	6 440	8 030
Ingestion pathway consumption rate				
Milk (l/d)	0.9	0.5	0.4	0.25
Leafy vegetables (kg/y)	0	13	20	30
Beef (kg/y)	0	8	15	27
Dose per unit integrated concentration in air (mrad per pCi y m^{-3})				
^{131}I				
Inhalation	14	19	12	11
Ingestion[a]				
Milk	920	230	61	30
Leafy vegetables	0	33	17	20
Total[b]	930	280	90	61
^{129}I				
Inhalation	17	29	27	67
Ingestion[a]				
Milk	6 300	1 900	780	960
Leafy vegetables	0	250	190	570
Beef	0	26	24	86
Total[b]	6 300	2 200	1 000	1 700

[a] Particulate form assumed. Environmental transfer and therefore dose ~ 20 times higher for the elemental form and ~ 20 times less for the organic form.

[b] Rounded.

117. A population-weighted dose factor can be obtained by assuming that the doses to the three groups of children are representative of the age groups 0-1, 1-9, and 10-19 y, respectively, and that these groups contain respectively 2, 16 and 20 per cent of the population (157), the population-weighted thyroid dose factor is 120 mrad per pCi y m^{-3} for ^{131}I and 1700 mrad per pCi y m^{-3} for ^{129}I.

118. The local thyroid collective dose commitment per unit activity of ^{131}I released from the reactor can be calculated using the same dispersion assumptions and population density values discussed previously:

$$S = (5\ 10^{-7}\ \text{s m}^{-3})\left(\frac{1}{3.15\ 10^{7}}\ \text{y s}^{-1}\right)$$

$$(120\ \text{mrad pCi}^{-1}\ \text{y}^{-1}\ \text{m}^3)(100\ \text{man km}^{-2})$$

$$\int_1^{100} r^{-1.5}\, 2\pi r\, dr$$

$$= 22\ \text{man rad per Ci}$$

On the basis of average operating experience (table 13), the normalized airborne release of ^{131}I from BWRs is $5\ 10^{-3}$ Ci per MW(e) y. The thyroid collective dose commitment per unit of electrical energy generated is therefore estimated to be 0.11 man rad per MW(e) y. The normalized collective dose commitments for PWRs, GCRs and HWRs are smaller by two orders of magnitude.

6. Particulates in airborne effluents

119. The activities of particulates released in airborne effluents may be quite variable but are relatively low. From releases based on average operating experience (table 14), estimates may be made of the local collective dose commitments from immersion and from inhalation intake while the radioactive material remains airborne and from the ingestion pathway and the exposure to contaminated ground following deposition.

120. The highest particulate activity discharge from PWRs was 0.0004 Ci per MW(e) y of ^{88}Rb. This would correspond to 0.004 Ci per MW(e) y of the precursor ^{88}Kr. Compared to ^{88}Kr activity releases of 280 Ci per MW(e) y from BWRs and 0.09 Ci per MW(e) y at PWRs, the release amounts and therefore the collective doses from ^{88}Rb particulate discharge are one or more orders of magnitude lower than those from ^{88}Rb that arise from discharge of ^{88}Kr.

121. Estimates of the collective dose commitments by the various pathways following unit release of activity in airborne effluents, are listed in table 20. The external

TABLE 20. LOCAL COLLECTIVE DOSE COMMITMENT FACTORS FOR RADIONUCLIDES IN AIRBORNE PARTICULATE EFFLUENTS

	Collective dose commitment per unit activity released (man rad Ci^{-1})						
		Inhalation		*Ingestion*			*Exposure to contaminated ground*
Radionuclide	*Air immersion total body*	*Lung (whole)*	*Bone marrow*	*Total body*	*Bone marrow*	*Bone lining cells*	*Total body*
^{58}Co	0.001	0.09	0.005				1.2
^{60}Co	0.003	1.9	0.08				80.0
^{89}Sr		0.01	0.02		0.06		
^{90}Sr		0.03	1.0		100	140	
^{106}Ru	0.0002	5.6	0.009				1.9
^{134}Cs	0.002	0.07	0.07	30			21.0
^{137}Cs	0.0007	0.06	0.05	20			46.0
^{140}Ba	0.0003	0.009	0.005				0.5

gamma dose from the passing cloud (immersion exposure) makes a minor contribution to the collective dose commitment. The dose assessments from immersion and from inhalation assume decreasing concentrations with distance integrated to 100 km and a population density of 100 man km^{-2} in the local region. The dose estimates from the ingestion pathway and from exposure to contaminated ground do not require the deposition regions to be specified, provided that the population density can be assumed to be constant in the relevant area (100 km^{-2} is assumed). The transfer factors from deposition to diet and to man for strontium and caesium nuclides are derived from fallout field studies (see Annex C). The assessment of the exposure to contaminated ground is also discussed in Annex C for most of the radionuclides in table 20. The additional dose factors for ^{60}Co and ^{134}Cs assume a plane-source distribution maintained in time (10) and may thus be slight overestimates, as some downward movement in soil is expected over the mean-lives of these radionuclides.

122. Estimate of the collective dose commitments due to radioactive particulates released in airborne effluents from reactors per unit electrical energy generated are given in table 21, obtained by applying the dose factors of table 20 to the releases representing average operating experience. The collective dose commitments are somewhat higher for BWRs than PWRs, ranging from $3\ 10^{-5}$ to $2\ 10^{-4}$ man rad per MW(e) y to the lung, due primarily to ^{60}Co, and $3\ 10^{-3}$ to $1\ 10^{-2}$ man rad per MW(e) y to total body, due to ^{60}Co from external exposure and to ^{134}Cs and ^{137}Cs from external exposure and through the ingestion pathway. The dose commitments to bone marrow and bone lining cells are due almost entirely to the small amounts of ^{90}Sr released.

TABLE 21. LOCAL COLLECTIVE DOSE COMMITMENTS FROM PARTICULATES IN AIRBORNE EFFLUENTS FROM REACTORS

	Normalized activity released (Ci per MW(e) y)	*Collective dose per unit electrical energy generated (man rad per MW(e) y)*							
		Total body		*Lung (whole)*		*Bone marrow*		*Bone lining cells*	
PWR									
^{137}Cs	$2.1\ 10^{-5}$	1.4	10^{-3}	0.1	10^{-5}	0.1	10^{-5}		
^{60}Co	$1.5\ 10^{-5}$	1.2	10^{-3}	2.9	10^{-5}	0.1	10^{-5}		
^{134}Cs	$1.4\ 10^{-5}$	0.7	10^{-3}	0.1	10^{-5}	0.1	10^{-5}		
^{58}Co	$1.6\ 10^{-5}$	0.02	10^{-3}	0.1	10^{-5}	0.08	10^{-6}		
^{140}Ba	$3.2\ 10^{-7}$	0.02	10^{-5}	0.03	10^{-7}	0.02	10^{-7}		
^{90}Sr	$1.4\ 10^{-7}$			0.04	10^{-7}	1.4	10^{-5}	2.0	10^{-5}
^{89}Sr	$6.0\ 10^{-7}$			0.06	10^{-7}	0.05	10^{-6}		
	Total	3	10^{-3}	3	10^{-5}	2	10^{-5}	2	10^{-5}
BWR									
^{60}Co	$1.0\ 10^{-4}$	8.0	10^{-3}	1.9	10^{-4}	0.08	10^{-4}		
^{134}Cs	$2.3\ 10^{-5}$	1.2	10^{-3}	0.02	10^{-4}	0.02	10^{-4}		
^{137}Cs	$1.7\ 10^{-5}$	1.1	10^{-3}	0.01	10^{-4}	0.09	10^{-5}		
^{140}Ba	$3.9\ 10^{-4}$	0.2	10^{-3}	0.04	10^{-4}	0.02	10^{-4}		
^{58}Co	$1.8\ 10^{-5}$	0.02	10^{-3}	0.02	10^{-4}	0.09	10^{-6}		
^{90}Sr	$5.0\ 10^{-6}$			0.02	10^{-5}	5.1	10^{-4}	7.0	10^{-4}
^{89}Sr	$3.3\ 10^{-4}$			0.03	10^{-4}	0.3	10^{-4}		
	Total	1	10^{-2}	2	10^{-4}	5	10^{-4}	7	10^{-4}

7. Radionuclides in liquid effluents

123. Radionuclides discharged in liquid effluents may result in doses to man through the pathways of drinking water and fish consumption for releases to fresh water, and of ocean fish and shellfish consumption for releases to salt water. A portion of the population may also be exposed on shorelines to external irradiation from sediments. In areas where irrigation of crops is practised, especially when sprinkling methods are utilized, a significant contribution to the collective dose could result. This pathway should then also be considered. Ingestion of water fowl and immersion exposure from swimming are other pathways, but these have generally been found to be insignificant contributors to the collective dose (19).

124. Assessments for specific reactors can be performed by means of rather specific transfer models and using the information provided by environmental monitoring. This monitoring is usually carried out along the critical pathways leading to human exposures. Site-specific assessments for the liquid discharges of nine GCRs in the United Kingdom (106) show that the local annual collective dose to the gonads in the vicinity of these reactors is in the range of 10^{-1} to 1 man rad. Combining these values with the electrical energy generated in each case (106), the normalized gonad collective dose is estimated to be in the range of $5\ 10^{-4}$ to $4\ 10^{-3}$ man rad per MW(e) y.

125. In the general case, the dose assessments require information on the discharged activity of each radionuclide, the volume of the receiving water into which the radioactivity is diluted, the concentration levels which are reached in fish and shellfish, the factors regarding removal to sediments and exchange rates of water bodies, and the number of individuals in the populations who use the water for drinking purposes and who consume fish.

126. The local and regional collective dose commitments from radionuclides in liquid effluents can be estimated using the expression

$$S_i^c = \frac{A_i}{V(\tau+\lambda_i)} \sum_k N_k f_{k,i} I_k D_i$$

where

A_i (pCi) = activity of nuclide i released to water

V (l) = volume of receiving water

τ (y^{-1}) = turnover time of receiving water

λ_i (y^{-1}) = radioactive decay constant for nuclide i

N_k (man) = number of individuals for pathway k

$f_{k,i}$ (pCi kg^{-1} per pCi l^{-1}) = concentration factor for item in pathway k for nuclide i

I_k (kg y^{-1}) = individual consumption rate of pathway item k

D_i (rad Ci^{-1}) = tissue dose per unit activity ingested.

By using the normalized release rate for A_i (Ci per MW(e) y), the collective dose will be expressed in units of man rads per MW(e) y. The total collective dose commitment per unit of electrical energy generated S^c is obtained by a further summation over all radionuclides.

127. The quantity $\frac{A}{V(\tau+\lambda)}$ (pCi y l^{-1}) is the integral water concentration for release of an activity A (pCi) or, alternatively, the equilibrium concentration in water $C_{w,i}$ (pCi l^{-1}), for a constant continuing release rate (Ci y^{-1}). The equilibrium concentration in fish or shellfish is $C_{w,i} f_{k,i}$ (pCi/kg fish), where $f_{k,i}$ is the appropriate fresh water or salt water concentration factor.

128. For radionuclide releases to small volumes of water, the concentrations in water or fish may be high, but the population which can be served with drinking water or by fish production will be limited. For releases to larger water volumes, the concentrations will be less, but the populations involved will be correspondingly larger. In fact, the N_k/V relationship could be taken, in a crude approximation, as relatively constant, the inverse of which indicates the water utilization with regard to the specific pathway k per individual in the population.

129. For the drinking water pathway, a fresh water utilization ratio of $3\ 10^7$ l man^{-1} will be assumed in estimating collective dose commitments from generalized liquid releases. This value of V/N_k is assumed to be a global average, obtained from an estimated global total of $1.3\ 10^{17}$ l of fresh water in lakes ($1\ 10^{17}$ l) and rivers (annual flow $0.3\ 10^{17}$ l) (5), serving the world population of $3.8\ 10^9$. Similar results are obtained for regional areas. Martin (93) estimates that a population of $3.1\ 10^6$ derives drinking water from Lake Ontario and the St. Lawrence River, comprising an available volume of $2.2\ 10^{14}$ l. This gives a water utilization factor of $7\ 10^7$ l man^{-1}. In the Danube River studies, Ruf (122) quotes annual flows of (3-7) 10^{12} l, from which several million derive their drinking water. This gives a factor of about $2\ 10^6$ l man^{-1}. For the large flow of the Mississippi River, the estimated factor is $3\ 10^8$ l man^{-1} (159). Even more widely varying results would be possible for more localized situations.

130. Average fish plus sea-food consumption per individual is about 8 kg y^{-1}, ranging from 4 to 6 kg y^{-1} in the Near East and Africa to 10-14 kg y^{-1} in the Far East and Europe (68). It may be assumed that the annual consumption is 6 kg y^{-1} ocean fish, 1 kg y^{-1} fresh water fish and 1 kg y^{-1} shellfish. Total fresh water fish consumption by the world population is thus $3.8\ 10^9$ kg y^{-1}, which, when a correction is made for edible weight, agrees well with the estimated annual global harvest of 10^{10} kg landed weight (5). Dividing by the global fresh water volume given in the above paragraph, we obtain $3\ 10^{-8}$ man kg y^{-1} l^{-1}, which will be assumed to be the factor $N_k I_k / V$ needed in estimating collective doses from fresh water fish consumption.

131. Similarly, ocean-fish consumption by the world population is $22.8\ 10^9$ kg y^{-1}. The annual global ocean fish harvest is estimated to be $60\ 10^9$ kg landed weight (5). The ocean surface area is $3.6\ 10^8$ km^2, and assuming the depth for fish production extends to 30 m, the water volume is 10^{19} l. Of course, most of the fish are taken from coastal regions, comprising only about 10 per cent of the ocean's surface. However, most of the larger water volume can by expected to circulate through the fish production regions. Thus, the factor $N_k I_k/V$ which is required for the salt water fish pathway is $2\ 10^{-9}$ man kg y^{-1} l^{-1}. For the shellfish pathway, with consumption one sixth that of ocean fish, a value of the factor $N_k I_k/V$ of $3\ 10^{-10}$ man kg y^{-1} l^{-1} will be used in this Annex.

132. For estimating collective doses from exposure to sediments, rather more specific assumptions must be made regarding the receiving waters and the potential population involved. Booth *et al.* (19) have calculated sediment exposure rates based on releases to a water volume of 10^{12} l with a water turnover rate of 0.1 y^{-1}. This corresponds to an annual dilution volume of 10^{11} l. Dividing by the fresh water utilization factor derived above of $3\ 10^7$ l man^{-1}, it can be assumed that the exposures apply to a population of 3000. These values will be used to obtain collective dose estimates for sediment exposure in the general release situation.

133. For assessments involving releases to the sea, the dilution volume will be assumed to be 10^{15} l, with a turnover of 1 y^{-1}. The salt water utilization factor from global values of ocean volume and population is 10^{19} l per $3.8\ 10^9$ man, or $3\ 10^9$ l man^{-1}. Thus, for a dilution volume of 10^{15} l, the corresponding population is 300 000. For releases to salt water, this value will be used to obtain collective doses from the individual dose rates from sediment exposure calculated by Booth *et al.* (19). The estimates of populations exposed to sediments are admittedly rather arbitrarily selected and should certainly be adjusted for estimating the collective dose at specific sites.

134. Correction factors to account for removal of radionuclides from water to sediments depend on the turnover rate, that is, the flow-through or replacement rate of the receiving water. The correction becomes less important for fast moving water (τ = 10 or 100 y^{-1}). For releases to salt water, in which depths greater than 10 m can be assumed, the correction is also negligible (19). This, however, will depend on how the effluents are admitted to the water. For near-shore releases not far from the bottom, sediment removal is considerable for many radionuclides. Even for surface releases, sedimentation may in some cases be an important process, ultimately removing the activity from the water. Whether sediments once deposited might eventually become resuspended by storms or by winds from shore areas is a question that is being studied.

135. In the case of releases to fresh water, a turnover rate of 0.1 y^{-1} will be assumed for the generalized assessments. For ^{137}Cs, the correction for sediment removal is taken to be 0.29 (19); therefore, the time-integrated activity for an activity release of 1 Ci is $0.29(\tau + \lambda)^{-1}$ = 2.4 Ci y. For Lake Huron, which was analysed by Barry (4), the integrated value for a unit activity release of ^{137}Cs was 1.4 Ci y, in reasonable agreement with the assumed generalized case. Mitchell and Jeffries (101), however, estimate a more rapid turnover rate for Lake Trawsfynydd, the half-time being 50 d, corresponding to τ= 5 y^{-1}. For releases to salt water, a turnover rate of 1 y^{-1} will be assumed with no additional removal of activity to sediments. Kautsky (73) estimates the turnover of water in the North Sea to be of this order, and Hetherington (48) reports the residence half-time of water in the Irish Sea to be approximately 1 y.

136. The factors which are required to estimate collective doses (using the formula in paragraph 126) for a number of radionuclides that may be present in liquid effluents released to fresh and salt water are listed in table 22. The corrections to account for removal to sediments are also included, and in addition, factors are given for the removal of activity during treatment of drinking water (30, 122). The concentration factors for fresh-water fish are those compiled by Thompson (135) and for marine fish and shellfish by Freke (35). The factors relating dose to activity intake included in table 22 have the follow characteristics: (a) values for the total body (TB) from ^3H, ^{14}C, ^{65}Zn, ^{134}Cs, and ^{137}Cs apply approximately equally to most single-organ exposures; (b) the dose factors for thyroid (Thy) are taken from table 18; (c) for ^{90}Sr the dose factor used refers to exposure of bone lining cells; the dose to bone marrow would be 30 per cent smaller; (d) the doses from ^{32}P, ^{89}Sr, and ^{239}Pu are in total bone; (e) for the other radionuclides the highest doses are experienced in the lower large intestine (LLI).

137. Collective dose estimates for the composition and amounts of radionuclides other than ^3H in liquid effluents from reactors reported from operating experience (table 15) are given in table 23. The collective doses to the total body include contributions from ingestion of ^{137}Cs, ^{134}Cs and ^{65}Zn, and from external exposure of ^{137}Cs, ^{134}Cs, ^{60}Co, ^{54}Mn, ^{144}Ce, ^{51}Cr, ^{125}Sb, and ^{106}Ru in sediments. The dose to the lower large intestine is due primarily to ^{60}Co and ^{54}Mn for PWRs and BWRs and to ^{125}Sb for GCRs. The dose to bone from ^{32}P in releases to salt water from GCRs is estimated to be comparable to the ^{90}Sr dose, but is much less for release to fresh water. Since the average radionuclide release from GCRs applies chiefly to reactors which discharge to the sea, a separate example is included in table 23 for discharges to fresh water from the GCR at Lake Trawsfynydd.

138. The estimates of collective dose in table 23 correspond to average release amounts from reactors and for generalized release situations. The collective doses for specific reactor situations may differ strongly from them. There may also be particular radionuclides or special pathways which might be overlooked. In general, however, the results seem to be consistent with the dose estimates from environmental sampling (15, 70, 71, 100).

TABLE 22. COLLECTIVE DOSE FACTORS FOR RADIONUCLIDES IN LIQUID EFFLUENTS RELEASED TO FRESH AND SALT WATER

Radionuclide	Radioactive half-life $T_{½}$	Sediment removal correction factor s_i	Time integral of unit activity in water W_i (Ci y)	Drinking-water treatment removal factor f_{1i}	Concentration factor, fish f_{2i} (pCi kg^{-1} fish per pCi l^{-1} water)	Dose per unit activity ingested D_i (10^{-6} rad Ci^{-1})	External dose from sediment per unit activity released (10^{-6} rad Ci^{-1})	Collective dose per unit activity released (man rad Ci^{-1})				
								Drinking water S_{1i}	Fish S_{2i}	Total (internal)		Sediment exposure (external)
					Fresh water							
^{3}H	12.26 y	1.0	6.39	1.0	0.9	0.000084		0.0071	1.4 10^{-5}	0.0071	TB	
^{14}C	5 730 y	0.78	7.79	1.0	4 600	0.00056		0.057	0.60	0.66	TB	
^{32}P	14.3 d	1.0	0.056	0.4	100 000	0.038		0.011	6.4	6.4	Bone	
^{51}Cr	27.7 d	0.97	0.105	0.9	40	0.00097	0.0023	0.0012	0.00012	0.0013	LLI	6.8 10^{-6}
^{54}Mn	313 d	0.83	0.914	0.5	100	0.019	2.76	0.11	0.052	0.16	LLI	0.0083
^{60}Co	5.26 y	0.33	1.43	0.5	20	0.039	162	0.37	0.033	0.40	LLI	0.48
^{65}Zn	244 d	0.96	0.845	0.4	1 000	0.0065	0.30	0.029	0.16	0.19	TB	0.00090
^{89}Sr	50.5 d	1.0	0.196	0.5	5	0.062		0.080	0.0018	0.082	Bone	
^{90}Sr	28.5 y	0.78	6.27	0.5	5	0.7		29.0	0.66	30.0	Bone	
^{95}Zr	63 d	0.81	0.197	0.1	3.3	0.032	1.13	0.0083	0.00062	0.0089	LLI	0.0034
^{95}Nb	35 d	1.0	0.136	0.1	30 000	0.019	0.0090	0.0034	2.3	2.3	LLI	2.7 10^{-5}
^{103}Ru	41 d	0.92	0.147	0.1	10	0.024	0.11	0.0046	0.0011	0.0057	LLI	0.00032
^{106}Ru	1.0 y	0.59	0.743	0.1	10	0.19	1.73	0.19	0.042	0.23	LLI	0.0052
^{110m}Ag	270 d	1.0	0.964	0.5	2.3	0.065	0.84	0.41	0.0043	0.41	LLI	0.0025
^{125}Sb	2.7 y	0.94	2.63	0.5	1	0.019	2.15	0.33	0.0015	0.33	LLI	0.0065
^{129}I	1.6 10^{7} y	1.0	10.0	0.8	15	10.0		1 050	45	1 100	Thy	
^{131}I	8.05 d	1.0	0.032	0.8	15	3.1	6.7 10^{-5}	1.0	0.045	1.1	Thy	2.0 10^{-7}
^{134}Cs	2.1 y	0.51	1.19	0.2	400	0.075	36	0.23	1.1	1.3	TB	0.11
^{137}Cs	30.0 y	0.29	2.36	0.2	400	0.043	235	0.27	1.2	1.5	TB	0.70
^{144}Ce	290 d	0.63	0.648	0.1	25	0.19	0.33	0.16	0.092	0.25	LLI	0.00099
^{239}Pu	24 400 y	1.0	10.0	0.1	10	0.019		0.25	0.06	0.31	Bone	
						Salt water						
				Concentration factor				*Concentration factor*				
				Fish C_{3i}	*Shellfish* C_{4i}			*Fish* S_{3i}	*Shellfish* S_{4i}			
^{3}H	12.26 y		0.946	1	1	0.000084		1.6 10^{-7}	2.4 10^{-8}	1.8 10^{-7}	TB	
^{14}C	5 730 y		1.0	1	1	0.00056		1.1 10^{-6}	1.7 10^{-7}	1.3 10^{-6}	TB	
^{32}P	14.3 d		0.056	10 000	10 000	0.038		0.043	0.0064	0.049	Bone	
^{51}Cr	27.7 d		0.099	100	1 000	0.00097	1.1 10^{-6}	1.9 10^{-5}	2.9 10^{-5}	4.8 10^{-5}	LLI	3.3 10^{-7}
^{54}Mn	313 d		0.553	3 000	50 000	0.019	0.0006	0.063	0.16	0.22	LLI	0.00018
^{60}Co	5.26 y		0.884	100	10 000	0.039	0.0052	0.0069	0.10	0.11	LLI	0.0016
^{65}Zn	244 d		0.491	5 000	50 000	0.065	0.00016	0.032	0.048	0.082	TB	4.8 10^{-5}
^{89}Sr	50.5 d		0.166	1	1	0.062		2.1 10^{-5}	3.1 10^{-6}	2.4 10^{-5}	Bone	
^{90}Sr	28.5 y		0.976	1	1	0.7		0.0014	0.00020	0.0016	Bone	
^{95}Zr	63 d		0.199	30	100	0.032	0.0042	0.00038	0.00019	0.00057	LLI	0.0013
^{95}Nb	35 d	1.0	0.122	100	200	0.019	0.00004	0.00046	0.00014	0.00060	LLI	1.2 10^{-5}
^{103}Ru	41 d		0.139	3	100	0.024	0.000012	0.00002	0.0001	0.00012	LLI	3.6 10^{-6}
^{106}Ru	1.0 y		0.591	3	100	0.19	0.000076	0.00067	0.0034	0.0041	LLI	2.3 10^{-5}
^{110m}Ag	270 d		0.516	1 000	5 000	0.065	0.00074	0.067	0.050	0.12	LLI	0.00022
^{125}Sb	2.7 y		0.796	1 000	1 000	0.019	0.00025	0.030	0.0045	0.035	LLI	7.5 10^{-5}
^{129}I	1.6 10^{7} y		1.0	20	100	10.0		0.40	0.30	0.70	Thy	
^{131}I	8.05 d		0.031	20	100	3.1	3.6 10^{-7}	0.0038	0.0029	0.0067	Thy	1.1 10^{-7}
^{134}Cs	2.1 y		0.752	30	50	0.075	0.0016	0.0034	0.00085	0.0043	TB	0.00049
^{137}Cs	30.0 y		0.977	30	50	0.043	0.0082	0.0025	0.00063	0.0031	TB	0.0025
^{144}Ce	290 d		0.534	30	100	0.19	0.0028	0.0061	0.0030	0.0091	LLI	0.00084
^{239}Pu	24 400 y		1.0	3	300	0.019		0.00011	0.0017	0.0018	Bone	

Notes: i = radionuclide; k = pathway = 1, 2, 3, 4 for drinking water, fresh-water fish, salt-water fish and shellfish, respectively; λ_i = decay constant = $0.693/T_{½}$; τ = water turnover rate = 0.1 y^{-1} (fresh water), 1.0 y^{-1} (salt water); $S_{k,i} = W_i f_{k,i} N_k I_k D_i / V_i$; where $W_i = \iota A_i s_i (\tau + \lambda_i)^{-1}$; $I_1 = 438$ l y^{-1}, $N_1/V = 3\ 10^{-8}$ man l^{-1}; $I_2 = 1$ kg y^{-1}, $N_2 I_2/V = 3\ 10^{-8}$ man kg l y^{-1} l^{-1}; $I_3 = 6$ kg y^{-1}, $N_3 I_3/V = 2\ 10^{-9}$ man kg y^{-1} l^{-1}; $N_4 I_4/V = 3\ 10^{-10}$ man kg y^{-1} l^{-1}.

TABLE 23. COLLECTIVE DOSE FROM RADIONUCLIDES OTHER THAN TRITIUM IN LIQUID EFFLUENTS FROM REACTORS

		Normalized collective dose (man rad per MW(e) y)													
		Release to salt water								*Release to fresh water*					
	Normalized activity released (Ci per MW(e) y)	*Total body*		*Lower large intestine*		*Bone*		*Thyroid*		*Total body*		*Lower large intestine*		*Bone*		*Thyroid*	
P W R																	
^{137}Cs	0.002	1.1	10^{-5}							4.4	10^{-3}						
^{134}Cs	0.001	0.5	10^{-5}							1.4	10^{-3}						
^{60}Co	0.0004	0.06	10^{-5}	4.4	10^{-5}					0.2	10^{-3}	1.6	10^{-4}				
^{54}Mn	0.0001	0.02	10^{-6}	2.2	10^{-5}					0.08	10^{-5}	1.6	10^{-5}				
^{144}Ce	0.00008	0.07	10^{-6}	0.07	10^{-5}					0.08	10^{-6}	0.2	10^{-4}				
^{51}Cr	0.0002	0.01	10^{-8}	0.01	10^{-6}					0.01	10^{-7}	0.03	10^{-5}				
^{90}Sr	0.000002					3.2	10^{-9}							6.0	10^{-5}		
^{131}I	0.002							1.3	10^{-5}							2.2	10^{-3}
	Total	2	10^{-5}	7	10^{-5}	3	10^{-9}	1	10^{-5}	6	10^{-3}	2	10^{-4}	6	10^{-5}	2	10^{-3}
B W R																	
^{137}Cs	0.025	1.4	10^{-4}							5.5	10^{-2}						
^{134}Cs	0.017	0.8	10^{-4}							2.4	10^{-2}						
^{60}Co	0.006	0.1	10^{-4}	6.6	10^{-4}					0.3	10^{-2}	2.4	10^{-3}				
^{54}Mn	0.002	0.04	10^{-5}	4.4	10^{-4}					0.02	10^{-3}	0.3	10^{-3}				
^{51}Cr	0.0006	0.02	10^{-8}	0.03	10^{-6}					0.04	10^{-7}	0.08	10^{-5}				
^{90}Sr	0.0001					1.6	10^{-7}							3.0	10^{-3}		
^{89}Sr	0.0008					0.2	10^{-7}							0.07	10^{-3}		
^{131}I	0.004							2.7	10^{-5}							4.4	10^{-3}
	Total	2	10^{-4}	1	10^{-3}	2	10^{-7}	3	10^{-5}	8	10^{-2}	3	10^{-3}	3	10^{-3}	4	10^{-3}
G C R																	
	Salt water / *Fresh water*																
^{137}Cs	0.068 / 0.006	3.8	10^{-4}							1.3	10^{-2}						
^{134}Cs	0.014 / 0.0009	0.7	10^{-4}							0.1	10^{-2}						
^{65}Zn	0.00008 / 0.00005	0.06	10^{-4}														
^{60}Co	0.0007 / 0.0001	0.01	10^{-4}	0.8	10^{-4}												
^{125}Sb	0.008 / 0.008	0.08	10^{-5}	2.8	10^{-4}					0.05	10^{-3}	2.6	10^{-3}				
^{144}Ce	0.001 / 0.00005	0.08	10^{-5}	0.09	10^{-4}					0.05	10^{-6}	0.01	10^{-3}				
^{106}Ru	0.002 / 0.0008	0.05	10^{-6}	0.08	10^{-4}					0.04	10^{-4}	0.2	10^{-3}				
^{32}P	0.0008 / 0.0007					3.9	10^{-5}							0.4	10^{-2}		
^{90}Sr	0.01 / 0.0005					1.6	10^{-5}							1.5	10^{-2}		
^{89}Sr	0.0007					0.02	10^{-6}										
	Total	5	10^{-4}	4	10^{-4}	6	10^{-5}			1	10^{-2}	3	10^{-3}	2	10^{-2}		

IV. FUEL REPROCESSING

139. At the fuel reprocessing stage of a completely integrated nuclear fuel cycle, the uranium and plutonium in the irradiated fuel are recovered for reuse from the fission products that have accumulated during fuel burn-up in the reactor. The spent fuel received at the reprocessing plant is stored under water, which serves both as a transparent radiation shield and as a coolant. The fuel elements to be processed are transferred to a head-end cell, where they are disassembled, and the individual rods are treated mechanically to expose the fuel. The fuel is then leached with nitric acid

140. A solvent extraction process is then used to separate the uranium and plutonium from the fission and activation products. Nearly all fuel reprocessing facilities employ some form of the Purex process, which uses the organic complexing compound tributyl phosphate to extract both the uranium and the plutonium into the organic phase. The uranium and plutonium can be separately back-extracted from the organic solution with nitric acid. The product nitrates are further purified and converted to oxides suitable for refabrication into fuel elements.

A. EFFLUENTS

141. Waste processing to prevent large releases of radioactivity to the environment is a complex task at reprocessing plants. The gaseous and volatile fission products (I, ^{3}H, Kr, Xe, Ru, Te and Cs) are largely separated from the fuel during the fuel dissolution step. The dissolver off-gas is treated for nitric acid recovery and for iodine removal before being blended with the off-gas from other vessels in the plant. The vessel off-gas is usually treated by caustic scrubbing, drying and filtering through high efficiency filters before discharge from a stack. The aqueous wastes, containing almost all of the fission products, are generally concentrated by evaporation and stored in underground tanks and will eventually be solidified. The evaporator overheads are usually sufficiently decontaminated of radioisotopes to permit their discharge to the environment under existing regulations.

TABLE 24. RADIONUCLIDES DISCHARGED FROM VARIOUS FUEL REPROCESSING PLANTS, 1960-1974

Year	Electrical energy equivalent of fuel processed (MW(e) y)	Activity released (Ci)								
		(a) In airborne effluents								
		^{85}Kr	^{3}H	^{90}Sr	^{106}Ru	^{131}I	^{129}I	^{89}Sr	^{137}Cs	^{134}Cs
		Windscale (United Kingdom)								
1972	~ 2 500	1 000 000		0.097		23.6	0.004			
1973				0.75		1.2				
1974				0.15		0.01				
Total (Ci)		1 000 000		1.0		24.8	0.004			
Normalized release 1972 (Ci per MW(e) y)		400		$4\ 10^{-5}$		$9\ 10^{-3}$	$2\ 10^{-6}$			
		Nuclear Fuel Services (United States)								
1966	210	77 000								
1967	900	328 000	~ 500			< 0.06				
1968	530	193 000	~ 500			0.0066				
1969	830	300 000	~ 500			< 0.03				
1970	660	180 000	~ 500			< 0.03				
1971	720	221 000	1 070	0.00036	0.0013	0.0024	0.0026	0.00027	0.0009	0.0006
1972	0	0	5.5	0.041	0.029	0.00096		0.0021		
Total (Ci)		1 299 000	~3 075	0.041	0.030	0.01	0.0026	0.0024	0.0009	0.0006
Normalized release 1966-1972 (Ci per MW(e) y)		340	0.84	$6\ 10^{-5}$	$4\ 10^{-5}$	$8\ 10^{-6}$	$4\ 10^{-6}$	$3\ 10^{-6}$	$1\ 10^{-6}$	$8\ 10^{-7}$

(b) In liquid effluents

		La Hague (France)				
		^{106}Ru	^{137}Cs	^{144}Ce	^{110m}Ag	^{95}Zr-Nb
1971		7 900	6 700	3 900		90
1972		7 600	1 200	1 400		340
1973		7 000	2 000	1 700	1 450	70
	Total (Ci)	22 500	9 900	7 000	1 450	500

		Windscale (United Kingdom)										
		^{137}Cs	^{3}H	^{106}Ru	^{95}Zr	^{95}Nb	^{90}Sr	^{144}Ce	^{134}Cs	^{239}Pu	^{103}Ru	^{89}Sr
1960		910		39 600	2 400	6 300	520	890			11 600	980
1961		1 100		25 300	1 700	7 900	490	2 200			3 200	1 370
1962		1 100		23 000	940	4 300	1 020	2 400			1 800	500
1963		370		33 400	560	3 300	550	1 400			9 600	170
1964		1 300		23 100	21 600	20 800	970	3 200			1 200	190
1965		1 200		21 000	17 700	33 700	1 160	3 500			1 800	170
1966		1 200		24 900	14 100	23 400	910	6 900			2 500	90
1967		1 600	16 100	17 200	18 800	25 700	1 390	13 700		492	2 200	140
1968		1 500	20 300	24 200	28 100	37 100	1 370	10 000		828	1 800	40
1969		12 000	24 800	22 900	31 600	30 000	2 950	13 500	630	816	1 400	230
1970		30 100	32 000	27 600	9 100	9 900	6 000	12 400	7 010	936	890	470
1971		35 800	31 500	36 400	18 000	17 300	12 300	17 200	6 370	1 128	830	390
1972	≈ 2 500	34 800	33 600	30 500	25 600	23 500	15 200	13 700	5 820	1 558	1 160	1 080
1973				37 800			7 450	14 600		1 776		
1974				29 200			10 600	6 530		1 248		
Total (kCi)		123.0	158.3	416.1	190.2	243.2	62.9	122.0	19.8	8.8	40.0	5.8
Normalized release 1972 (Ci per MW(e) y)		13.9	13.4	12.2	10.2	9.4	6.1	5.5	2.3	0.62	0.46	0.43

TABLE 24 *(continued)*

Year	Electrical energy equivalent of fuel processed (MW(e) y)	Activity released (Ci)								
		Nuclear Fuel Services (United States)								
		^{3}H	^{106}Ru	^{137}Cs	^{90}Sr	^{89}Sr	^{134}Cs	^{129}I	^{239}Pu	^{238}Pu
1966	210	290								
1967	900	4 200			9.9			0.07		
1968	530	2 650			5.0			0.03		
1969	830	5 980			10.1			0.2		
1970	660	4 520			14.2			0.34		
1971	720	3 850	48.2	10.0	6.6	2.27	1.83	0.21	0.0048	0.0042
1972	0	600	6.1	1.1	0.7	0.08	0.19	0.06	0.0005	0.0007
	Total (Ci)	22 090	54.3	11.1	46.5	3.35	2.02	0.91	0.0053	0.0049
Normalized release 1966-1972 (Ci per MW(e) y)		5.7	0.075	0.015	0.013	0.0033	0.0028	$2.5\ 10^{-4}$	$7.4\ 10^{-6}$	$6.8\ 10^{-6}$

Sources: References 21, 48, 50, 93, 100, 106, 123, 134, 147, 172.

142. The radionuclides of concern in reprocessing plant effluents include primarily ^{3}H, ^{14}C, ^{85}Kr, ^{129}I, ^{131}I, ^{106}Ru, ^{134}Cs, ^{137}Cs, and the actinides. General discussions of the occurrence and release pathways from reprocessing plants have appeared in several reports (8, 83, 107, 109, 151, 158), and more detailed accounts have been published for tritium (39, 80), noble gases (49, 80), and iodine (16, 118). Specific information available on radionuclide discharges from reprocessing plant operating experience is given in table 24. The release data from the NFS plant in the United States represent a completed experience, as this plant was closed for modifications in 1972.

143. The release of radioactive materials from the fuel reprocessing plant depends upon the type of fuel, irradiation history, cooling time and the specific waste processing systems of the reprocessing installation. The typical radionuclide composition of LWR fuel following an average burn-up of 33 000 MW(t) d per tonne and a cooling time of 150 d is given in table 25 (107). Burn-up differs for the various light-water reactor types. The burn-up levels achieved in presently operating reactors, and therefore the amounts of longer-lived radionuclides generated, have been somewhat less than the example given in table 25. The cooling time has also been on the average much longer than 150 d (167).

TABLE 25. RADIONUCLIDE CONTENT OF LWR FUEL

Burn-up, 33 000 MW(t) d t^{-1}; cooling time, 150 d

Radionuclide	Per unit mass of fuel (Ci t^{-1})	Per unit electricity generated[a] (Ci per MW(e) y)	Radionuclide	Per unit mass of fuel (Ci t^{-1})	Per unit electricity generated[a] (Ci per MW(e) y)
^{3}H	692	23	^{134}Cs	213 000	7 140
^{85}Kr	11 200	375	^{137}Cs	106 000	3 550
^{89}Sr	96 000	3 220	^{137m}Ba	99 600	3 340
^{90}Sr	76 600	2 570	^{140}Ba	430	14.4
^{90}Y	76 600	2 570	^{140}La	495	16.6
^{91}Y	159 000	5 330	^{141}Ce	56 700	1 900
^{95}Zr	276 000	9 250	^{144}Ce	770 000	25 810
^{95}Nb	518 000	17 360	^{143}Pr	694	23.3
^{95m}Nb	5 860	196	^{144}Pr	770 000	25 810
^{103}Ru	89 100	2 986	^{147}Pm	99 400	3 330
^{106}Ru	410 000	13 740	^{151}Sm	1 150	38.5
^{103m}Rh	89 100	2 990	^{154}Eu	6 820	229
^{106}Rh	410 000	13 740	^{155}Eu	6 370	214
^{110m}Ag	261	8.7	^{160}Tb	300	10.1
^{125}Sb	8 130	272	^{239}Np	17.4	0.6
^{125m}Te	3 280	110	^{238}Pu	2 810	94
^{127m}Te	6 180	207	^{239}Pu	330	11
^{127}Te	6 110	205	^{240}Pu	478	16
^{129m}Te	6 690	224	^{241}Pu	115 000	3 850
^{129}Te	4 290	144	^{241}Am	200	6.7
^{129}I	0.038	0.0013	^{242}Cm	15 000	503
^{131}I	2.17	0.073	^{244}Cm	2 490	84

Source: Reference 107.
[a] Assuming a reactor thermal efficiency of 0.33.

1. Krypton-85

144. The thermal fission yield for ^{85}Kr is 0.285 per cent for ^{235}U and 0.144 per cent for ^{239}Pu (31), corresponding to activities per unit of thermal energy of 0.415 and 0.210 Ci per MW(t) d or per unit electricity generated of 505 and 255 Ci per MW(e) y for ^{235}U and ^{239}Pu, respectively. Assuming that 41 per cent of the fissions are fissions of ^{239}Pu in LWR fuel with a burn-up of 33 000 MW(t) d per tonne (31), the ^{85}Kr activity generated per unit electricity generated is about 400 Ci per MW(e) y. A more detailed calculation estimates the generation per unit mass to be 11 200 Ci/t^{-1} (107), corresponding to about 375 Ci per MW(e) y, assuming a thermal efficiency of 33 per cent. Almost all (>99 per cent) of the ^{85}Kr generated by fission in zircaloy-clad LWR fuels is expected to be released at the reprocessing plant (80). The operating experience shown in table 24 confirms this expectation.

2. Tritium

145. Most of the tritium separated from fuel during dissolution appears in the liquid-waste stream. Some is carried into the dissolver off-gas stream. For the NFS plant in the United States only about 7 per cent of the tritium in the fuel was released through the stack (25). More recent reprocessing-plant designs call for about 75 per cent of the tritium present in fuel to be released to the air and liquid waste discharges to be prevented entirely (80).

146. A portion of the tritium in fuel elements is immobilized as a solid zirconium compound in the zircaloy cladding. The fraction thus retained with the hulls is a function of the linear power rating of the fuel. For present LWR fuel this amounts to about 15 per cent (80). Of an estimated 19 Ci per MW(e) y generation rate, Grathwohl (39) estimates that 1.2 Ci per MW(e) y are released at the reactor (PWR), 16 Ci per MW(e) y are released at the reprocessing plant and 1.8 Ci per MW(e) y are retained with solid wastes. Similar released amounts are expected in reprocessing HWR fuel, while about one half of this amount is expected for AGR fuel and one tenth for HTGR fuel (39). Operating experience (table 24) shows ^{3}H release in liquid effluents to be about 13 Ci per MW(e) y for Windscale and about 6 Ci per MW(e) y for the NFS plant. An additional 1 Ci per MW(e) y was estimated released in airborne effluents from NFS.

3. Carbon-14

147. There are no data available on actual ^{14}C discharges from fuel reprocessing plants. In this Annex it is assumed that all of the ^{14}C present in spent fuel is discharged in the airborne effluents during reprocessing, probably in the form of CO_2.

4. Iodine

148. A tonne of reference LWR fuel (table 25) contains 2.17 Ci of ^{131}I and 0.038 Ci of ^{129}I, corresponding to normalized contents of approximately 0.073 and 0.0013 Ci per MW(e) y for ^{131}I and ^{129}I, respectively. The ^{131}I content depends very much on the cooling time. In current practice, the fuel is still held for at least 150 d before reprocessing, and in many cases the spent fuel is stored for much longer periods.

149. Airborne release of ^{129}I at the Windscale and NFS reprocessing plants has been reported to be $(2\text{-}4)10^{-6}$ Ci per MW(e) y (table 24). The normalized liquid release of ^{129}I at NFS, $2.5\ 10^{-4}$ Ci per MW(e) y, corresponds to about 25 per cent of the total in the fuel. Release of iodine to the sea from Windscale can be as much as 75 per cent of the throughput (22). The global collective dose estimates for ^{129}I are thus strongly dependent on the liquid releases. The chemical form of the iodine is of importance, particularly for the airborne releases. Haller (41) has reported a wide variation in chemical form of ^{131}I discharged from a fuel reprocesssing plant.

5. Caesium, ruthenium, strontium

150. Other radionuclides released from fuel reprocessing plants include ^{137}Cs, ^{134}Cs, ^{106}Ru and ^{90}Sr. For the airborne effluents, the decontamination factors (ratio of activity processed to activity released) are of the order of 10^{7}-10^{10}, based on the NFS experience (^{90}Sr, $4\ 10^{7}$; ^{106}Ru, $3\ 10^{8}$; ^{137}Cs, $4\ 10^{9}$; ^{134}Cs, $9\ 10^{9}$). In liquid effluents, somewhat greater fractions of the processed amounts of these fission products were released. For release to fresh-water streams at NFS, the decontamination factors were 10^{5}-10^{6}. Liquid wastes from NFS were passed through a series of three small lagoons before discharge to the stream. This system provided a 30-60 d hold-up of the liquids and, in addition, removed considerable amounts of activity by sedimentation: >90 per cent of ^{144}Ce, ^{147}Pm, ^{95}Zr and ^{239}Pu, and 60-75 per cent of ^{134}Cs, ^{137}Cs and ^{60}Co (89). Releases of ^{106}Ru, ^{125}Sb and ^{90}Sr were less affected by the lagoon hold-up.

151. For the Windscale situation, in which release is to the sea, the achievement of decontamination factors of 10^{2}-10^{3} is practised. Ratios of ^{89}Sr, to ^{90}Sr and ^{103}Ru to ^{106}Ru in liquid discharges indicate fuel-cooling times of the order of 1 y (125). After 1969/70, releases of long-lived radionuclides, particularly ^{137}Cs, from Windscale increased, due primarily to leakage from fuel elements in the storage pools.

6. Plutonium, americium, curium

152. Considerable attention has recently been focused on the transuranic elements, particularly plutonium: large amounts would become available as a result of increased reprocessing. It could be used in the operation of breeder reactors or in thermal reactors as recycle fuel. Included in table 25 are the activities of transuranic isotopes in the fuel elements of LWRs.

153. During reactor operation, ^{239}Pu is formed in the uranium fuel by neutron capture by ^{238}U, followed by relatively rapid beta decays of ^{239}U and ^{239}Np. Generally more than half of the ^{239}Pu undergoes fission, thus contributing to the energy produced by the reactor. A small amount is transformed by successive neutron capture to ^{240}Pu, ^{241}Pu, ^{242}Pu and ^{243}Pu. Beta decay of ^{241}Pu and ^{243}Pu produce ^{241}Am and ^{243}Am which, following subsequent neutron capture and beta decay, give rise to ^{242}Cm and ^{244}Cm. These interactions are illustrated in figure I.

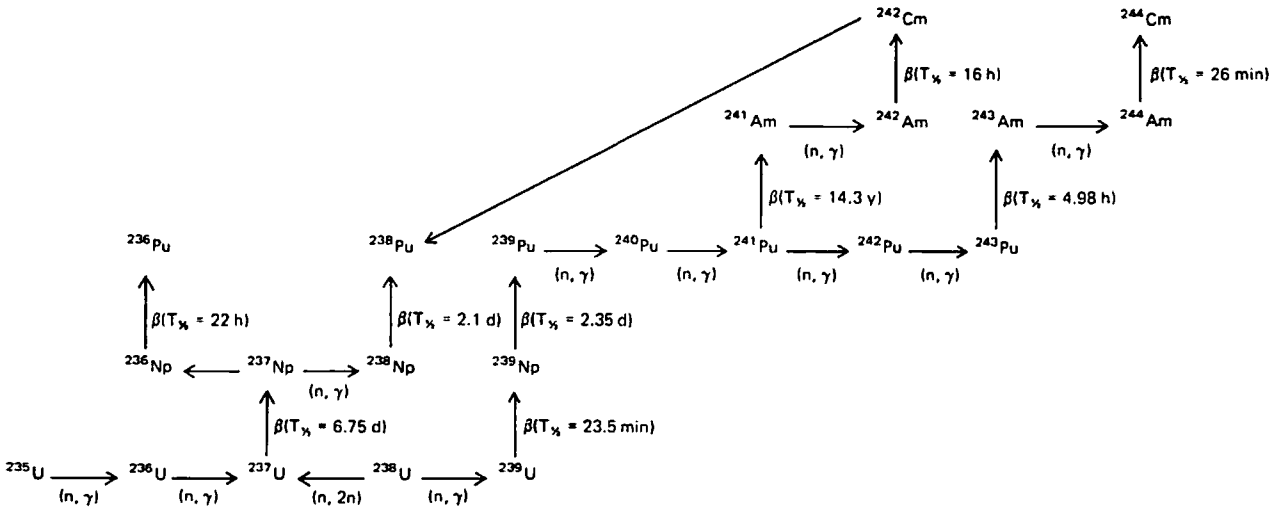

Figure I. Formation scheme for important transuranic radionuclides (31)

154. The isotopic composition of the plutonium in a spent fuel of high burn-up is as follows (weight per cent): ^{239}Pu, 60; ^{240}Pu, 22; ^{241}Pu, 12; ^{242}Pu, 4.5; ^{238}Pu, 1.5 (31). The composition changes with time however. Plutonium-238 activity increases as ^{242}Cm decays, ^{240}Pu increases as ^{244}Cm decays, and ^{239}Pu increases slightly as ^{243}Am decays to ^{239}Np, which subsequently decays to ^{239}Pu. The amounts of ^{241}Am increase significantly as ^{241}Pu decays.

155. Most of the half-lives of the transuranic isotopes are quite long: ^{239}Pu (24 400 y), ^{240}Pu (6580 y), ^{238}Pu (86 y), ^{241}Pu (13.2 y), ^{241}Am (458 y) and ^{244}Cm (17.6 y). Relatively short-lived is ^{242}Cm (163 d), which forms a significant fraction of the alpha activity in spent fuel.

156. Measurements at the NFS fuel reprocessing plant in the United States showed that small amounts of plutonium were discharged in the liquid effluent stream (table 24). In a paper published in 1974, it was suggested that 0.1-1 per cent of the plutonium throughput was being released in liquid effluents from the Windscale reprocessing plant (102).

B. LOCAL AND REGIONAL COLLECTIVE DOSE COMMITMENT

157. The evaluation of the total collective dose from radionuclides released from fuel reprocessing plants requires consideration of the exposure of the local population surrounding the plant and the long-term global exposure. The global dose estimates are presented in a subsequent section. The local environment around the NFS plant, being the first commercial fuel reprocessing plant in the United States, has been studied in considerable detail. A comprehensive review of the population doses from radioactivity discharged from the plant has recently been presented by Martin (93). More detailed surveys to evaluate the doses incurred through the ingestion pathway were made by Magno *et al.* (91). The releases of radioactivity into the Irish Sea from the Windscale plant and the corresponding exposures are still being closely studied (106). Considerable detail in obtaining inventories of activity in the sea and sediments and in tracing the activity in its passage into the North Sea are being achieved (100). Some results of environmental surveys around the reprocessing plant at La Hague have also been published (123).

1. Krypton-85

158. The collective dose commitment from ^{85}Kr released from reprocessing plants is most significant from the global standpoint. As discussed in chapter VI, it is estimated that the collective dose to the gonads due to the release of 375 Ci per MW(e) y of ^{85}Kr is 0.01 man rad per MW(e) y during the first two years, until uniform atmospheric concentrations are achieved. The collective dose received as the ^{85}Kr initially disperses through the local and regional area surrounding the reprocessing plant is much smaller. Using the same local and regional dispersion assumptions as in previous sections of this Annex, namely a dispersion factor of $5\ 10^{-7}$ s m^{-3} at 1 km and a concentration decreasing as the inverse 1.5 power of the distance, a population density of 100 km^{-2}, and a gonadal dose factor (average for testes and ovaries) of $1.1\ 10^{4}$ rad m^3 Ci^{-1} y^{-1} (104), the gonadal collective dose in the local region (1-100 km from the plant) per unit ^{85}Kr activity released is estimated to be $2\ 10^{-6}$ man rad Ci^{-1}. If all the ^{85}Kr present in the spent fuel were released, the estimated local normalized collective dose to the gonads would be 0.0007 man rad per MW(e) y. For other tissues the dose factors are $1.8\ 10^{4}$, $3.1\ 10^{4}$, $1.8\ 10^{6}$ rad m^3 Ci^{-1} y^{-1} for red bone marrow, whole lung, and skin, respectively (104). The local normalized collective doses are 0.001, 0.002, and 0.1 man rad per MW(e) y for bone marrow, lung, and skin, respectively.

2. Tritium

159. An estimated 16 Ci of ^{3}H per MW(e) y could be released at fuel reprocessing plants (para. 146), primarily in liquid effluents. For a release of 1 Ci per MW(e) y in airborne effluents, as was the NFS experience (table 24), and assuming a collective dose factor of $2\ 10^{-4}$ man rad per curie released (para. 103), the local collective dose would be $2\ 10^{-4}$ man rad per MW(e) y. For liquid releases the factors for ^{3}H in table 22 can be applied. For the release to salt water (Windscale) of 13 Ci per MW(e) y, the collective dose is $2\ 10^{-6}$ man rad per

MW(e) y, and to fresh water (NFS), of 6 Ci per MW(e) y, the collective dose estimate is 0.04 man rad per MW(e) y.

3. Carbon-14

160. In paragraph 106 the local collective dose commitments per unit activity released following airborne releases of ^{14}C were estimated to be 0.1, 0.12, 0.37 and 0.40 man rad Ci^{-1} for gonads, lung, bone lining cells, and bone marrow, respectively. For an anticipated release of 0.014 Ci per MW(e) y from the reprocessing plant (paras. 73 and 147) the local collective dose commitments are estimated to be as follows (man rad per MW(e) y): gonads, $1\ 10^{-3}$; lungs, $2\ 10^{-3}$; bone lining cells, $5\ 10^{-3}$; bone marrow, $6\ 10^{-3}$.

4. Iodine

161. Members of the public can incur thyroid doses from ^{131}I discharges in airborne effluents from fuel reprocessing plants. A spent-fuel cooling time of 150 d and a fractional release of the order of 10^{-3} for airborne releases of iodine would imply a release of $7\ 10^{-5}$ Ci per MW(e) y, of the same order as releases by PWRs and GCRs and much smaller than BWR releases. The NFS reprocessing plant reported ^{131}I releases of $1\ 10^{-5}$ Ci per MW(e) y in 1968 and $0.3\ 10^{-5}$ Ci per MW(e) y in 1972. From the Windscale reprocessing plant the ^{131}I release was $9\ 10^{-3}$ Ci per MW(e) y in 1972 (table 24), but was lower by factors from 20 to 2000 in subsequent years (106). The local collective dose to the thyroid, using a dose factor averaged for the age distribution given in paragraph 117, is estimated to be 22 man rad Ci^{-1} for ^{131}I released in airborne effluents. The local collective dose per unit of electricity generated would therefore be expected to be of the order of 0.002 man rad per MW(e) y for spent fuel held 150 d, and about 100 times more for the highest reported releases in reprocessing plants. Since large amounts of fuel are being held in storage for much longer periods than 150 d, local doses from ^{131}I should generally be insignificant when this fuel is reprocessed.

162. The dosimetry of ^{129}I was considered in table 18 and the thyroid doses based on representative food consumption estimates were given in table 19. The thyroid dose per unit integrated ^{129}I concentration in air through the inhalation and ingestion pathways, weighted for the assumed population age distribution (para. 117), is 1700 mrad per pCi y m^{-3}, which is the same as for the adult thyroid. Using the same dispersion assumptions and population density as in paragraph 103, it is possible to estimate the local collective dose from ^{129}I in airborne effluents to be 300 man rad Ci^{-1}. This is approximately equal to the local collective dose commitment provided that soil accumulation does not greatly increase the levels of ^{129}I in plants. Soldat estimates that soil accumulation of ^{129}I adds 1 per cent per year to the leafy vegetable pathway and 1.3 per cent per year for milk consumption, assuming that all of the iodine in soil is retained in the root zone (132). Kühn *et al.* (79), however, report that iodine penetrates into soil more rapidly and more deeply than other fission products. The global contribution to the collective dose commitment from ^{129}I released to the environment is considered in chapter VI.

163. For an ^{129}I airborne release (table 24) of $4\ 10^{-6}$ Ci per MW(e) y, the local collective dose commitment to thyroid is 0.001 man rad per MW(e) y. The local and regional collective dose per unit release of ^{129}I in liquid effluents is 1100 man rad Ci^{-1} for fresh water and 0.7 man rad Ci^{-1} for salt water (table 20). For the reprocessing plant release experience of $2.5\ 10^{-4}$ Ci per MW(e) y to fresh water (table 24), and $9.8\ 10^{-4}$ Ci per MW(e) y to salt water (para. 149), the local and regional collective dose is estimated to be 0.3 and 0.0007 man rad per MW(e) y for fresh and salt water releases, respectively.

5. Caesium, ruthenium, strontium

164. The fission products ^{137}Cs, ^{134}Cs, ^{106}Ru, ^{89}Sr and ^{90}Sr are important components of fuel reprocessing plant releases and contributors to the collective dose. Caesium-137 and ^{134}Cs may concentrate in fish and result in total body doses to the consumers of the fish. In the past few years, ^{137}Cs has contributed the largest component of the collective dose from radioactive releases from the Windscale reprocessing plant (100, 106). Ruthenium-106 is known to accumulate in the seaweed *Porphyra* growing near the Windscale discharge area in the North Irish Sea, from which the foodstuff laverbread is produced. However, recent changes in the harvesting practice of the seaweed have considerably reduced the ^{106}Ru contribution to the collective dose (100). Caesium, ^{106}Ru, ^{95}Zr-^{95}Nb and ^{144}Ce in sediments cause external exposures. All of these nuclides may contribute small collective doses from inhalation following airborne release from reprocessing plants.

165. Approximate estimates of local collective doses due to the release of airborne particulates can be obtained by using dose factors derived as for reactor releases (table 20). These dose factors account for direct exposure to the radioactive cloud, exposure by the inhalation and ingestion pathways, and by external exposure to deposited radioactivity. Data on typical releases of radioactive particulates in airborne effluents from reprocessing plants are available from the NFS experience (table 24). These average release amounts are used in the example of local collective dose determination given in table 26. The local collective dose commitments are of the order of 10^{-4} man rad per MW(e) y. Ruthenium-106 is an important contributor to the collective dose commitment to the lung via inhalation and to the total body from exposure to contaminated ground. Caesium-137 and ^{134}Cs also contribute to the total body dose through the ingestion pathway and by external exposure. Strontium-90 is responsible for the dose to bone marrow and bone lining cells through the ingestion pathway.

166. Approximate estimates of the collective doses from radionuclides in liquid effluents can be obtained using the dose factors of table 20 and the reported releases from fuel reprocessing plants (table 24). The results are given in table 27. The collective doses from ^{3}H and ^{129}I in liquid effluents, which were considered separately above, are also listed, as are those from ^{95}Zr, ^{95}Nb, ^{144}Ce, and ^{239}Pu. The estimates are based on the operating experience of the Windscale plant for releases to salt water and of the NFS plant for releases to fresh water. For most radionuclides, they are somewhat

TABLE 26. LOCAL COLLECTIVE DOSE COMMITMENTS FROM PARTICULATES IN AIRBORNE EFFLUENTS FROM A FUEL REPROCESSING PLANT[a]

Radionuclide	Normalized activity released (Ci per MW(e) y)	Collective dose (man rad per MW(e) y)			
		Total body	Lung (whole)	Bone marrow	Bone lining cells
^{106}Ru	$4\ 10^{-5}$	$7.6\ 10^{-5}$	$2.2\ 10^{-4}$	$0.04\ 10^{-5}$	
^{137}Cs	$1\ 10^{-6}$	$6.6\ 10^{-5}$	$0.06\ 10^{-6}$	$0.05\ 10^{-6}$	
^{134}Cs	$8\ 10^{-7}$	$4.1\ 10^{-5}$	$0.06\ 10^{-6}$	$0.06\ 10^{-6}$	
^{90}Sr	$6\ 10^{-5}$		$0.02\ 10^{-4}$	$6.1\ 10^{-3}$	$8.4\ 10^{-3}$
^{89}Sr	$3\ 10^{-6}$		$0.03\ 10^{-6}$	$0.02\ 10^{-5}$	
	Total	$2\ 10^{-4}$	$2\ 10^{-4}$	$6\ 10^{-3}$	$8\ 10^{-3}$

[a]Example based on NFS data, 1971-1972 (table 24).

TABLE 27. COLLECTIVE DOSE FROM RADIONUCLIDES IN LIQUID EFFLUENTS FROM FUEL REPROCESSING PLANTS

Radionuclide	Normalized activity released (Ci per MW(e) y)	Collective dose (man rad per MW(e) y)			
		Total body	Large lower intestine	Bone	Thyroid
		Release to salt water			
^{3}H	13	0.000002			
^{137}Cs	14	0.08			
^{95}Zr	10	0.01	0.006		
^{134}Cs	2.3	0.01			
^{144}Ce	5.5	0.005	0.05		
^{106}Ru	12	0.0003	0.05		
^{95}Nb	9.4	0.0001	0.006		
^{103}Ru	0.5	0.000002	0.00006		
^{90}Sr	6.1			0.01	
^{89}Sr	0.4			0.00001	
^{239}Pu	0.6			0.001	
^{129}I	~ 0.001				0.0007
	Total	0.1	0.1	0.01	0.0007
		Release to fresh water			
^{3}H	6	0.04			
^{137}Cs	0.015	0.03			
^{134}Cs	0.0028	0.004			
^{106}Ru	0.075	0.0004	0.02		
^{90}Sr	0.013			0.4	
^{89}Sr	0.0033			0.0003	
^{239}Pu	$7.4\ 10^{-6}$			0.000002	
^{129}I	$2.5\ 10^{-4}$				0.3
	Total	0.07	0.02	0.4	0.3

larger than the previously published estimates (91, 100, 140), primarily because only small, identifiable, local populations had been taken into account in making the earlier estimates. Generalized environmental dispersion has been assumed in the assessments of table 27, however, and differences from more realistic site-specific analyses are expected. For example, the ^{137}Cs releases in liquid effluents from the Windscale plant during 1972/73 have resulted in an estimated collective dose to the entire fish-consuming population in Western Europe (106) of 3000 man rad (half of which is to the United Kingdom population), corresponding to about 1.2 man rad per MW(e) y.

6. Plutonium, americium, curium

167. Both the inhalation and the ingestion pathways to man of the transuranic elements have been investigated, with important data on widespread environmental effects coming from fallout studies (Annex C). Extremely low concentrations were found in foods; this fact, combined with a very low uptake from the gut, indicates that ingestion contributes very little to body content. Inhalation intake could conceivably be of more significance. Annex C discusses the inhalation pathway and the problems of resuspension of plutonium deposited on the soil. Plutonium in airborne effluents has not been reported for fuel reprocessing plants. However, there are data available on total alpha activity released (106).

168. For releases in liquid effluents, no unusual concentrating mechanisms seem to exist, although some high concentration factors have occasionally been reported (154). Plutonium is largely removed to sediments. Hetherington *et al.* (48) have discussed some of the detailed studies of plutonium behaviour in the marine environment following discharge from the Windscale reprocessing plant. Approximate estimates of the local and regional collective dose commitments are included in table 27.

V. RADIOACTIVE WASTE STORAGE AND DISPOSAL

169. Only a small fraction of the radioactivity generated in the nuclear fuel cycle is released to the environment during normal operations. Except for uranium, plutonium, and certain other useful nuclides present in spent fuel, the radioactivity associated with the fuel cycle is considered waste, which must be subjected to suitable treatment and storage or disposal. Storage is taken to mean any arrangement intended to allow the waste to be retrieved if necessary at any future time; the waste may be temporarily inaccessible, but its position and other details have been documented and the means are available to retrieve it. Disposal implies a relinquishing of control over the waste.

A. LOW- AND INTERMEDIATE-LEVEL WASTE

170. The tailings from uranium mills are one example of low-activity solid waste. Common forms of solid waste arising in most types of reactors include spent ion-exchange resins, air and liquid filters, reactor components (control rods, replaced pressure tubes), reactor instruments, protective clothing and miscellaneous paper, plastic and metal wastes. In addition, miscellaneous wastes (e.g., obsolete buildings and equipment) may arise from any installation.

171. Solid wastes can often be reduced in volume, either by compression or incineration. They are then placed in storage or disposed of at surface- or deep-burial sites. Most nuclear sites have some provision for storage of solid wastes. Some reactors provide for storage of solid wastes throughout the reactor lifetime. The final disposition of these wastes will depend on the decision as to the final method of disposal of the reactor itself.

172. It is common practice to dump low-activity solid waste untreated into trenches and cover with earth. At less suitable sites, or if more hazardous materials are to be buried, additional barriers are needed to retard the transfer of activity from the waste to water supplies. These may be provided by constructing concrete wells or pits, or by incorporating the waste in concrete or bitumen.

173. The limitations of shallow burial have been noted. In particular, if significant quantities of long-lived radioisotopes such as ^{90}Sr and ^{137}Cs are included, satisfactory containment is required for a period sufficient for decay. Surface burial is generally considered unsuitable for waste significantly contaminated with transuranium elements, except as temporary storage (108). Since 1970 it has been a requirement in the United States that all solid wastes with significant contamination of transuranium nuclides be segregated and stored retrievably (142).

174. Suitable conditions for a surface-burial site cannot always be found owing to dense population or unfavourable geological or hydrological conditions. The possibility of using abandoned mine workings and natural geological formations as possible sites has therefore been investigated.

175. One of the most thoroughly investigated repositories is the Asse II salt mine in the Federal Republic of Germany. After acquisition of the mine in 1965, studies were made of the stability of the mine room, pillars and safety roofs, the safety of the shaft, and the hydrogeology of the environs. The completion of the studies and a radiological safety assessment enabled the first batch of low-level wastes to be deposited in 1967. The depth of storage of these wastes is about 750 metres. The mine has been used for both low- and intermediate-level radioactive wastes, which generate negligible heat. It is estimated that this one mine will suffice for the low- and intermediate-level wastes generated in the Federal Republic of Germany until 2000 (109).

176. Out of many sites explored in Austria, a gypsum mine and an artificial cavern of 20 000 m^3 were found suitable for permanent storage of low- and intermediate-level radioactive waste, provided that certain additional construction work was undertaken (108).

177. In the south of Spain, several old mines (in particular the Beta mine north of Cordoba) were also suitable for the permanent storage of low- and intermediate-level wastes.

178. The possibility of using the sea to receive and dilute low- and intermediate-level radioactive wastes has been recognized for several decades. The first deliberate introductions of packaged radioactive material into the sea were probably by the United States into the Pacific in 1946. Since about 1949, the United Kingdom and other European countries have made similar disposals in the deep waters of the north-eastern Atlantic Ocean. As a result of the United Nations Conference on the Law of the Sea in 1958, IAEA has produced recommendations that form the basis for deep-sea disposal operations.

B. HIGH-LEVEL WASTE

179. The high-level liquid waste, generated if fuel is reprocessed, contains more than 99 per cent of the fission product and actinide activity in the fuel, except for plutonium and uranium, which are present to the extent of less than 1 per cent. Although some may be disposed of in the liquid state, it appears likely that the rest will be solidified in some manner to render its handling, transport and storage safer and to facilitate its eventual disposal. By the end of the century, the total high-level liquid waste produced throughout the world concomitantly with about 10^7 MW(e) y of nuclear electric power will be equivalent to about 10^4 m^3 of solidified material.

180. The view has been expressed that present storage methods are satisfactory, both on economic and on safety grounds, as an interim measure for the present and near future.

181. Various disposal strategies for these high-level liquid wastes are discussed in detail in several publications (6, 7, 75, 152, 167). Those alternative strategies which have been subjected to the most

intensive scientific and engineering study on the basis of their promise of providing satisfactory isolation of the wastes from man's environment and of being feasible economically include:

Solidification, followed by eventual disposal into geological formations

Solidification, followed by eventual disposal under or on to the sea bed

Storage, followed by disposal of the liquid wastes directly into geological formations

These three alternatives remain the subject of intensive scientific and engineering study. In addition, some other methods have been examined for their scientific and economic feasibility including disposal of solidified waste in the polar ice caps; extra-terrestrial disposal; and separation, and nuclear transmutation, of the actinide content of the waste.

182. To date, no national authority has reached a final decision on the precise future strategy that it will follow on storage and disposal of high-level waste. Indeed, no major disposal operation involving high-level waste from nuclear power production has yet been undertaken by any country, and in all countries generating this waste it remains in storage.

183. Doses resulting from occupational exposure in waste-storage operations are covered in Annex E. Because high-level wastes from nuclear power production continue to be maintained in storage by national authorities, with the precise method of eventual disposal undecided, the Committee feels that it is unable at this stage to make an adequate assessment of collective dose commitment for the world population from disposal of these wastes. However, the Committee is satisfied that the collective dose contribution from present waste-storage practices is very small compared to the contributions from other parts of the nuclear fuel cycle.

VI. COLLECTIVE DOSE COMMITMENT FROM GLOBALLY DISPERSED RADIONUCLIDES

184. The radionuclides that contribute to the global collective dose are those which are sufficiently long-lived to achieve widespread distribution in the environment. These include ^{3}H, ^{14}C, ^{85}Kr and ^{129}I. Other longer-lived radionuclides, such as ^{137}Cs and ^{239}Pu, probably become less widely dispersed after deposition in soil or sediments following release in a local region. Consideration of the global dispersion and the potential dose contributions has appeared in several reports (5, 11, 22, 74, 88, 92). Estimates of the individual and collective dose commitments from ^{3}H and ^{85}Kr are becoming fairly well established, as experience has led to a good understanding of their environmental behaviour. For radionuclides discharged in liquid effluents, the methods discussed in chapter IV may be applied as a first approximation.

185. The very long-lived nuclides, ^{14}C (5730 y) and ^{129}I ($1.6\ 10^{7}$ y), pose a special problem. Rather extensive extrapolation into the future is necessary to cover their mean lifetime. In this regard the concept of the incomplete dose commitment, introduced in Annex A, is of special utility for assessing the future maximum *per caput* annual doses resulting from a continuing but finite practice. Thus, if one can foresee that power production by nuclear fission will have a finite duration, which could be of the order of several hundred years, the incomplete dose commitment can be used to estimate the maximum annual *per caput* dose that will be experienced in the future due to that practice. Although the exercise of computing the complete collective doses can be carried out, assuming an ultimate size for the world population, the significance of the results cannot be readily interpreted.

A. TRITIUM

186. The collective dose to the global population from reactor and reprocessing plant releases of tritium can be assessed from the relationships determined for the ^{3}H released into the environment by nuclear explosions. The dose commitment in that case is estimated to be 2 mrad from 2500 MCi released, or $0.8\ 10^{-12}$ rad Ci^{-1} for the northern hemisphere (Annex C). This estimate was derived from measurements of the environmental persistence of fallout ^{3}H in surface waters.

187. A rough estimate of the dose commitment for ^{3}H can be obtained by noting that fallout tritium reached levels of around 4000 pCi l^{-1} in surface waters and that subsequent decline of concentration was exponential with a half-time of 3.2 y (12). This corresponds to an integrated concentration of 18 400 pCi y l^{-1}, or about 20 000 pCi y l^{-1} including levels occurring prior to the maximum concentration. Assuming that the total water intake by man in food, air and drinking water is about 3.1 l d^{-1}, and that the tissue dose per unit activity of tritium intake is 84 rad Ci^{-1} (12), a transfer factor of $9.5\ 10^{4}$ rad per Ci y l^{-1} is estimated. The dose commitment from the integrated fallout tritium levels is thus estimated to be about 2 mrad, in agreement with the estimate of the previous paragraph.

188. An alternate approach to estimate the dose commitment (11, 22) consists of assuming that all significant discharges of ^{3}H as tritiated water in the near future will occur in the northern hemisphere, and that the tritiated water will be dispersed in the circulating waters of that hemisphere (about 10^{22} g). It is also assumed that the time of exchange with the southern hemisphere and with waters below the thermocline is substantially larger than the half-life of tritium. This approach leads to a lower estimate for the dose commitment, because the higher concentrations of ^{3}H in surface waters before complete mixing occurs are neglected.

189. The collective dose commitment per unit activity of ^{3}H released can be assessed by the procedures outlined in Annex A. In the time scale of interest, the function describing the population growth can be approximated by an exponential with a fractional

increase rate a about 2 per cent per year. The present northern hemisphere population N_0 is estimated to be about $3.2\ 10^9$ (100). The collective dose commitment S^c is related in this case to the dose commitment D^c by the equation

$$S^c = \int_0^\infty \bar{D}\,(t)\,N\,(t)\,dt = \frac{\lambda_E D^c N_0}{\lambda_E - a}$$

where λ_E is the effective decrease constant of ^3H in surface waters. For assessments based on the model presented in paragraphs 186 and 187, λ_E is equal to 1/4.6 y (the effective mean life). With the value of D^c given in paragraph 186, the collective dose commitment is estimated to be about $3\ 10^{-3}$ man rad per curie of tritium released. For assessments based on the model outlined in paragraph 188, λ_E is the decay constant of ^3H. The collective dose commitment for this model is about $1\ 10^{-3}$ man rad Ci^{-1}, probably an underestimate for the reasons given in paragraph 188.

190. Using the value of $3\ 10^{-3}$ man rad Ci^{-1} for the estimated reprocessing plant release of 16 Ci per MW(e) y (para. 146), the collective dose commitment is assessed to be about $5\ 10^{-2}$ man rad per MW(e) y. Releases of tritium from reactors (tables 11 and 12) make additional contributions of the order of 1 per cent of this value in the case of BWRs and GCRs, 20 per cent in the case of PWRs, and on the average 130 per cent in the case of HWRs.

B. KRYPTON-85

191. Krypton-85 (10.7 y half-time) decays 99.57 per cent of the time by beta-ray emission (mean energy 0.251 MeV). In 0.43 per cent of the disintegrations a lower-energy beta ray (mean energy 0.0475 MeV) and a photon (0.514 MeV) are emitted. The dose to the gonads and bone marrow is primarily due to photons from ^{85}Kr decay in air. When a person is immersed in a large volume of air containing ^{85}Kr, the dose rates per unit concentration of ^{85}Kr in air are $0.62\ 10^4$, $1.6\ 10^4$, and $1.8\ 10^4$ rad y^{-1} per Ci m^{-3} in testes, ovaries, and red bone marrow, respectively (104). Beta decay of ^{85}Kr in air contributes almost 100 per cent of the dose in skin, and beta rays originating in the airways of lung account for 58 per cent of the lung dose. The doses per unit concentration of ^{85}Kr in air are $1.8\ 10^6$ rad m^3 Ci^{-1} y^{-1} for skin and $3.1\ 10^4$ rad m^3 Ci^{-1} y^{-1} for lung (104).

192. The collective dose commitment from ^{85}Kr generated during nuclear power production is due almost entirely to the release from reprocessing plants, the release from reactors being quite small in comparison. As the solubility of krypton in water is negligible, there is no sink for the krypton released into the atmosphere, and rather uniform concentrations are achieved in a period of about two years. In the 1972 report of the Committee, the distribution of krypton was taken to be almost homogeneous over the surface of the globe and throughout the troposphere. This assumption is substantiated by results of measurements of ^{85}Kr in surface air at different latitudes (33, 112).

193. Machta has developed a model which takes account of dispersion in the first 2 y after release (88). The local wind-rose is used for the first 6 h (about 100 km of travel), air trajectory climatology from 6 h to about 3 d, mean low-level airflow from 3 to 30 d, constituting the first hemispheric pass, and finally north-south and vertical mixing until uniform air concentrations are achieved. For the reprocessing plant release of 375 Ci per MW(e) y, the combined collective dose contribution of these steps in the first two years is about 0.01 man rad per MW(e) y, using an average gonadal dose factor of $1.1\ 10^4$ rad m^3 Ci^{-1} y^{-1}. Variations in the local population around the release point can introduce variations of about 10-20 per cent in the estimated collective dose contribution during the first two years following release, but there is little difference (1-2 per cent) in the subsequent collective dose contribution.

194. From the third year after release on, the air concentration is subject only to radioactive decay. The collective dose commitment can be calculated by the procedures given in Annex A, assuming an exponential population growth in the time scale of interest, with a fractional increase rate a of about 2 per cent per year and a population at the beginning of the third year N_0 of about $3.9\ 10^9$. As 1 Ci of ^{85}Kr after uniform mixing in the atmosphere ($4\ 10^{18}$ m^3) gives an average gonadal dose rate $R = 2.8\ 10^{-15}$ rad y^{-1}, the collective dose commitment per unit activity released is

$$S^c = \int_0^\infty \bar{D}\,(t)\,N\,(t)\,dt = \frac{R_0 N_0}{\lambda - a} = 2.4\ 10^{-4} \text{ man rad } Ci^{-1}$$

195. For the reprocessing plant release of 375 Ci per MW(e) y, the activity remaining after two years is about 330 Ci per MW(e) y and the resulting collective dose commitment is about 0.08 man rad per MW(e) y. The total collective gonadal dose commitment from ^{85}Kr, including the contribution of the first two years, is therefore estimated to be 0.09 man rad per MW(e) y. The corresponding values for bone marrow and lung are 0.15 and 0.25 man rad per MW(e) y.

C. CARBON-14

196. The dose commitment from ^{14}C releases from nuclear power installations can be assessed by assuming that the environmental distribution and behaviour will follow that of natural ^{14}C. The dose commitment per unit activity released has been estimated by this procedure to be approximately $4.6\ 10^{-8}$ rad Ci^{-1} for the whole body, $2\ 10^{-8}$ rad Ci^{-1} for gonads and lung, and about $7\ 10^{-8}$ rad Ci^{-1} for endosteal cells and bone marrow (Annexes B and C).

197. As this dose is delivered over a very long time, much longer than the time required by the world population to reach an equilibrium value, it can be shown (Annex A) that the collective dose commitment is, very approximately, given by $S^c \simeq D^c N_\infty$, where N_∞ is the assumed upper bound of the population size. Assuming a value of 10^{10} for N_∞, the collective dose commitment per unit activity release is 460 man rad

Ci^{-1} for the whole body, 200 man rad Ci^{-1} for gonads and lung, and 700 man rad Ci^{-1} for endosteal cells and bone marrow.

198. The combined ^{14}C release from light-water reactors and reprocessing plants (about 0.02 Ci per MW(e) y) gives therefore a whole-body collective dose commitment of 9 man rad MW(e) y, while the value for gonads and lung is about 4 man rad per MW(e) y and the value for endosteal cells and bone marrow is about 14 man rad per MW(e) y. As is discussed in Annex A, it would not be realistic to use these collective dose commitments to assess the maximum *per caput* annual dose in the future, because it cannot be assumed that the practice will continue for the long time required to achieve equilibrium. The incomplete collective dose commitment is the proper quantity for this purpose.

199. Assuming that power production by nuclear fission will last for a few hundred years (for example 500 y) it is possible to calculate the incomplete collective dose commitment by an appropriate model for the carbon cycle in the environment. Using the environmental model that incorporates a thick diffusive layer between the surface and deep oceans, discussed in Annex C, the incomplete whole-body collective dose commitment is estimated to be about 2 man rad per MW(e) y. For gonads and lung, the corresponding value is 0.9 man rad per MW(e) y and for endosteal cells and bone marrow 3 man rad per MW(e) y.

D. IODINE-129

200. The extent to which locally released ^{129}I participates in the global iodine cycle is not certain, but because of its very long half-life ($1.6\ 10^{7}$ y) it may be considered to become widely distributed. The specific-activity approach has been the usual method to assess the thyroid dose commitment from ^{129}I discharges. A specific activity of 1 pCi g^{-1} stable iodine in thyroid tissue results in an absorbed dose rate of $0.9\ 10^{-7}$ rad y^{-1} in the thyroid of a 6-month-old child, $2.1\ 10^{-7}$ rad y^{-1} in a 4-y-old, $3.5\ 10^{-7}$ rad y^{-1} in a 14-year-old, and $7.2\ 10^{-7}$ rad y^{-1} in the adult thyroid. The absorbed dose rate increases with age because the iodine concentration increases, being 80, 180 and 300 ppm at ages 6 months, 4 y and 14 y respectively (119), and 600 ppm in the adult thyroid (68). An average absorbed dose rate, weighted for an assumed population age distribution (para. 117), is $5.5\ 10^{-7}$ rad y^{-1} per pCi g^{-1}.

201. Stable iodine is non-uniformly distributed in nature. The largest fraction, however, is in sea water. Evaporation of sea water contributes most of the exchange between hydrosphere and atmosphere. Atmospheric water is exchanged within about 10 d, and it follows therefore that there is a rapid exchange of iodine. Assuming 10^{22} g to be the mass of circulating water with an iodine concentration of 0.064 ppm (139), there is an initial mixing capacity for ^{129}I of $6.4\ 10^{14}$ g of stable iodine. Over the mean life of ^{129}I, exchange with the deep ocean must also be considered. Uniform mixing is achieved within 100-200 y. The mixing capacity for ^{129}I is thereby increased by a factor of 60. For computing the dose commitment, therefore, the release of 1 Ci of ^{129}I can be considered to result in a specific activity of $2.6\ 10^{-17}$ Ci g^{-1}, giving an average absorbed dose rate to thyroid of $1.4\ 10^{-11}$ rad y^{-1}.

202. Assuming that about half of the ^{129}I present in spent fuel is discharged in liquid releases (para. 149), that 10^{10} is the upper bound of the world population, and that only decay decreases the availability of ^{129}I, the collective dose commitment to the thyroid is estimated to be

$$S^c = \left(6.5\ 10^{-4}\ \frac{\text{Ci}}{\text{MW(e)}\,\text{y}}\right)\left(1.4\ 10^{-11}\ \frac{\text{rad}}{\text{y Ci}}\right)\left(\frac{1.6\ 10^{7}\ \text{y}}{0.693}\right)$$

$$(10^{10}\ \text{man}) = 2100\ \text{man rad per MW(e) y}$$

As discussed in the case of ^{14}C, a dose commitment delivered over such an enormous amount of time is of doubtful meaning. In particular, it cannot be used for assessing future maximum *per caput* annual doses resulting from a continuing practice. A more useful quantity in this case, the incomplete collective dose commitment, can be calculated with the assumption that power generation by nuclear fission will last for a few hundred years. Using 500 y as a representative value, the incomplete collective dose commitment to the thyroid is estimated to be 0.05 man rad per MW(e) y.

VII. MISCELLANEOUS CONTRIBUTIONS

203. Several operations conducted in support of fuel cycle installations may make additional contributions to the collective dose commitment from nuclear power production. Examples of such operations are the transportation of materials between fuel cycle installations and some research and development activities.

A. TRANSPORTATION

204. Part of the operating requirement of the nuclear fuel cycle is the need to transport radioactive materials: unirradiated fuel from the fabrication plant to the reactor, spent fuel from the reactor to the reprocessing plant, and solid wastes from the reactor and reprocessing plant to waste storage or burial grounds. During this transportation, two groups of people will receive radiation doses: the transport workers and the general public. The contribution made by the exposure of transport workers to the total collective dose resulting from the generation of nuclear power is discussed in Annex E.

205. Nuclear fuel and radioactive waste materials are usually shipped by truck, rail or barge. The transport of radioactive material is subject to regulations, which in virtually all countries are based on the IAEA model regulations (58). The number of shipments and the shipping distances may vary greatly from installation to installation and from country to country. Typical distances and numbers of shipments to support a large reactor have been published in the United Kingdom (169) and the United States (145).

TABLE 28. ESTIMATED COLLECTIVE DOSE TO THE PUBLIC DUE TO SHIPMENTS TO AND FROM REACTORS

(man rad per MW(e) y)

Country	*Reactor type*	*Population group*[a]	*Unirradiated fuel*		*Irradiated fuel*		*Solid waste*		*Total*
United Kingdom	GCR	A	$2\ 10^{-5}$	(500)	$1\ 10^{-4}$	(10^3)			$4.3\ 10^{-4}$
		B	$1\ 10^{-5}$	($1\ 10^6$)	$3\ 10^{-4}$	($3\ 10^6$)			
United States	LWR	A	$4\ 10^{-7}$	(60)	$1.2\ 10^{-3}$	(700)	$9.1\ 10^{-4}$	(600)	$4.4\ 10^{-3}$
		B	$1.3\ 10^{-6}$	($3\ 10^5$)	$1.6\ 10^{-3}$	($7\ 10^5$)	$6.5\ 10^{-4}$	($3\ 10^5$)	

Note: The number in parentheses is the number of individuals involved.

[a] A = individuals in close proximity; B = individuals along the route.

206. For purposes of estimating the collective dose, the public may be divided into two groups: those individuals along the route who may come into relatively close proximity to the shipment and those at some distance from the shipment as it passes. The collective doses to the first group are estimated by the same procedure as that described in Annex E. The collective doses to the second group are estimated by calculating the dose rate as a function of distance from the package out to about 1 km, multiplying the average dose rate by the population density along the route and integrating the result over the distance travelled. A summary of the calculated doses to the public is given in table 28.

207. The estimated total collective dose to the public from normal transportation associated with reactor operations is in the range of $4\ 10^{-4}$ to $4\ 10^{-3}$ man rad per MW(e) y. The risk of additional radiation exposure from accidents is extremely small. The probability of a transportation accident, of which less than 1 per cent involve a severe impact or fire, is about 10^{-6} per vehicle-mile (145). Combining the low probability of accident occurrence with the low probability of radioactivity release in the event of an accident, it has been concluded that collective doses from transport accidents are an insignificant addition to the collective doses from normal transportation (145).

B. NUCLEAR RESEARCH LABORATORIES

208. A portion of the radioactivity released to the environment from nuclear research laboratories may be attributed to support for continued operation or future development of the nuclear fuel cycle. However, other activities at nuclear centres, such as for example radioisotope production and processing, and other types of research, are usually responsible for a large portion of the radioactive releases.

209. Reported estimates of collective dose to the local population during 1973 from 28 research and operational installations in the United States range from 10^{-6} to 200 man rad (160). The highest values are for the largest research and production centres, Savannah River, Argonne, Mound, and Hanford. The total collective dose from all installations (about 450 man rad) divided by the electrical energy generated by nuclear reactors in the country in the same year gives 0.05 man rad per MW(e) y. A much smaller, but indeterminate value represents the portion of this collective dose incurred only in support of nuclear fuel cycle operations.

210. The collective dose to gonads from radionuclides in liquid effluents from the research reactor installations Winfrith and Dounreay in the United Kingdom have been estimated not to exceed 0.1 and 1 man rad, respectively, during 1972-1973 by the shellfish pathway (100). From the Harwell Laboratories the estimated collective dose is 100 man rad by the drinking water pathway from radioactivity released to the River Thames (100). Contributing to this value is the radioactivity, primarily tritium, released from the radioisotope production plant at Amersham (106).

211. Data on radioactive materials released from the nuclear research centres Jülich and Karlsruhe and from research reactor sites in the Federal Republic of Germany have been reported (55). Only for the Karlsruhe laboratories are the releases of any significance. Individuals in the vicinity of the centre may receive an estimated annual dose of 0.3 mrad due primarily to fish consumption (55). The fraction attributable to support of the nuclear fuel cycle cannot be readily estimated.

212. In general, it can be concluded that this component of the collective dose commitment is very small compared to the contribution of other phases of nuclear power production. The collective dose contribution of research and development through occupational exposure is discussed in Annex E.

VIII. SUMMARY OF COLLECTIVE DOSE COMMITMENTS TO THE PUBLIC FROM NUCLEAR POWER PRODUCTION

213. The preceding sections of this Annex contain the results of the Committee's assessments of the collective dose commitments, excluding the contribution of occupational exposure, associated with nuclear power production. These collective dose commitments, per unit electrical energy generated, are summarized in table 29.

TABLE 29. SUMMARY OF NORMALIZED COLLECTIVE DOSE COMMITMENTS TO THE PUBLIC DUE TO NUCLEAR POWER PRODUCTION

(man rad per MW(e) y)

	Gonads	*Whole lung*	*Thyroid*	*Bone marrow*	*Bone lining cells*
Local and regional contribution					
Mining and milling					
U, Ra, Th[a]	0.00001	0.00004	0.00001	0.00002	0.0002
Rn[a]	0.0008	0.1	0.0008	0.0008	0.0008
Fuel fabrication					
U[a]		0.00001		0.000004	0.00002
Reactor operation[b]					
Atmospheric pathways					
Kr, Xe, ^{41}Ar	0.2	0.2	0.2	0.2	0.2
^{3}H	0.004	0.004	0.004	0.004	0.004
^{14}C	0.0006	0.0007	0.0006	0.002	0.002
^{131}I			0.1		
Cs, Sr, Co, Ru	0.006	0.006	0.006	0.006	0.006
Water pathways					
^{3}H	0.03	0.03	0.03	0.03	0.03
Cs, Co, Mn, I	0.01	0.01	0.02	0.01	0.01
Fuel reprocessing					
Atmospheric pathways					
^{85}Kr	0.0007	0.002	0.0007	0.001	0.001
^{3}H	0.0002	0.0002	0.0002	0.0002	0.0002
^{14}C	0.001	0.002	0.001	0.006	0.005
^{131}I, ^{129}I			0.2		
Cs, Ru, Sr	0.0002	0.0004	0.0002	0.006	0.008
Water pathways					
^{3}H	0.04	0.04	0.04	0.04	0.04
^{129}I			0.3		
Cs, Ru, Sr	0.09	0.09	0.09	0.2	0.2
Transportation					
External	0.003	0.003	0.003	0.003	0.003
Global contribution					
Fuel reprocessing and reactor operation					
^{3}H	0.1	0.1	0.1	0.1	0.1
^{85}Kr	0.09	0.25	0.09	0.15	0.15
^{14}C[a]	0.9	0.9	0.9	3.0	3.0
^{129}I[a]			0.5		
Total	1.5	1.7	2.0	3.8	3.8

[a] The values are the incomplete collective dose commitments. The complete dose commitments delivered over thousands to millions of years are as follows (man rad per MW(e) y):

Mining and milling:
U lung, 37; bone marrow, 65; bone lining cells, 280
Rn lung, 100

Fuel fabrication
U lung, 120, bone marrow, 220; bone lining cells, 920

Global
^{14}C gonads and lung, 4; bone marrow and bone lining cells, 14
^{129}I thyroid, 2100

[b] Values are averages based on the reactor-type distribution given in table 7.

For the contributions of the very long-lived nuclides, the values in the table are the incomplete collective dose commitments, the complete commitments being given in the footnotes. The use of these quantities is discussed in Annex A, the incomplete commitments being of particular interest for assessing the future maximum annual *per caput* doses in the case of continued practices. The other required inputs for these assessments are the nuclear installed capacity and the world population size. Considerable caution, however, is required for extrapolation into the future. The activity discharged per unit electricity generated has generally decreased during the past several years because of improvements in technology and increases in regulatory control. Since it is very difficult to predict what the future course of technology and control will be, the extrapolation of the dose commitments to future power production may not necessarily be valid.

214. The data summarized in table 29 indicate that more than 50 per cent of the collective dose commitment to the world population from nuclear power production is due to the global dispersion of the long-lived radionuclides ^{14}C, ^{85}Kr and ^{3}H. In some countries, technologies are under development for restricting the release of these radionuclides and also

^{129}I. While collection and retention of these radionuclides will reduce the projected global collective dose commitments, it can also present additional radiation sources for potential local and regional exposures from processing operations, handling, transportation, storage and disposal of the collected concentrated radionuclides.

215. The collective dose commitment can be expressed as the period of time during which natural radiation would have to be doubled to give an equivalent dose increase. The collective dose commitments to various organs shown in table 29 for the production of 1 MW(e) y range from about 2 to about 4 man rad. For the present installed capacity of 80 GW(e) (table 7), and assuming a utilization factor of 70 per cent, the whole body collective dose commitment per year of electric energy production is about 1.3 10^5 man rad, corresponding to about 3.5 h of natural radiation exposure.

Appendix

COLLECTIVE DOSE COMMITMENT FROM RELEASE OF RADIOACTIVE MATERIALS DUE TO ACCIDENTS

216. Although accidents involving the release of radioactive material or unplanned personal exposure can occur at any stage of the fuel cycle, most attention has been focused on reactor accidents. This is not because reactor accidents are more likely, but because the potential consequences for the general public of some reactor accidents are much greater than from accidents at other stages in the fuel cycle. In view of the low accident frequency and limited consequences of non-reactor accidents, only reactor accidents will be covered in this appendix.

217. So far, in several hundred reactor-years of operation, there has not been an accident in a commercial power reactor which has led to any exposure of the public. The frequency of accidents involving radioactivity in the entire nuclear industry, including research and development, has been very low and most of those which have occurred have been at experimental or pilot plants. Of these, only a few have involved exposures of members of the public.

218. Although no power reactor accidents involving exposure of the public have occurred, the commitment to a large nuclear programme implies a commitment to a certain accident probability. In this sense, therefore, there exists an "accident dose commitment" which is incurred by the operation of power reactors. Since the past experience does not provide estimates of the frequency of extremely unlikely events, any accident analysis must be based on a probability approach which takes into account reliability considerations.

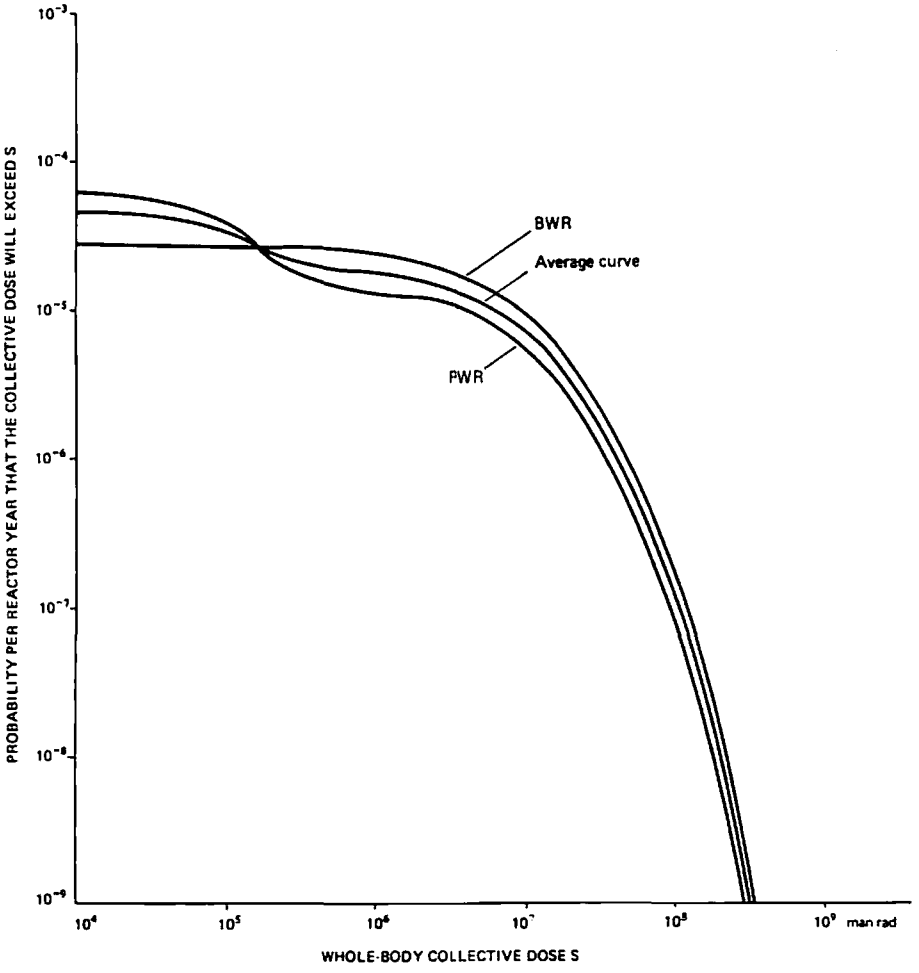

Figure II. Probability distribution for the whole-body collective dose per reactor year. Reactor of 1000 MW(e). (Uncertainties can be accommodated by allowing variations in the average curve of factors of 1/3 and 6 in probability and 1/3 and 3 in consequence.) (155)

219. The most comprehensive analysis to date (155), based on a detailed study of the sequence of events or faults that might lead to release, expressed its main conclusions in terms of the probabilities of different accident releases per reactor-year of operation of large light-water reactors. The doses and collective doses that would result from a given release were assessed by the use of a consequence model, also stochastic in nature, which took account of different weather conditions and population distributions.

220. The probability of incurring an accidental collective dose of a given value (or within a given range) can be obtained from the convolution of the functions representing the release model and the consequence model. An example of such a combined function is represented in figure II, which gives the probability of exceeding selected collective dose values.

221. In the example quoted above, the probability density function (the probability increment per unit collective dose) $f(S)$ can be obtained by differentiation of the function of figure II. The accident collective dose commitment S^c_{acc}, defined as the expectation of collective dose due to accidents, is the integral

$$S^c_{acc} = \int_0^\infty Sf(S)dS$$

where, in practice, the integration is carried out over the possible range of collective doses. For large light-water reactors (1000 MW(e)), this integration gives a value of about 250 man rad per reactor-year, implying a normalized accident collective dose commitment of 0.25 man rad per MW(e) y.

222. It should be pointed out that the value quoted above includes individual doses for which proportionality of dose and risk does not apply, e.g., in the case of acute effects. Therefore, it is not possible to assess the relative detriment by comparing this accident collective dose to the collective dose from normal operations.

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ANNEX E

Doses from occupational exposure

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Introduction

1. In its 1962 report (116), the Committee discussed the contribution made to the population dose by occupational exposure. At that time it was concluded that the annual genetically significant dose (GSD) from this source was unlikely to exceed a value of 0.5 mrad. The subject was considered again in the 1972 report of the Committee (117), and it was noted that the annual GSD had been estimated in two countries as 0.07 mrad, with a corresponding *per caput* dose of about twice this value. Other estimates of the annual *per caput* dose ranged from 0.01 to 0.8 mrad. Both reports presented information on the number of workers in various countries which appeared to remain constant at about one or two per thousand of total population.

2. The 1972 report, in particular, presented a considerable body of data which showed that the majority of radiation workers (or the majority of those monitored) receive very low exposures. The occupational collective dose due to the production of electricity by nuclear power was estimated in 1972 as about 2-3 man rad per MW y; most of this dose was thought to have been incurred during the reprocessing of nuclear fuel. It was anticipated that improved technology would result in lower collective doses per unit of electrical energy produced. Doses over the recommended limits and injuries were found to be extremely rare in most kinds of radiation work with a few notable exceptions (e.g. industrial radiography, x-ray crystallography, mining and luminizing).

3. The purpose of this Annex to the current report is to provide some data to enable the conclusions of the two previous reports to be verified or modified if necessary. The main objectives are twofold, however. First, it is the intention of the Committee to examine particular occupations, and even particular job categories within occupational groups, which consistently give rise to the highest average doses and high collective doses. It is hoped in this way to identify the areas towards which a greater proportion of the available effort should be directed to reduce the levels of occupational doses; as a corollary to this, data on selected groups of individuals have been examined in an attempt to predict the likely values of lifetime doses to which occupationally exposed workers may be subjected.

4. In view of the burgeoning nuclear power industry, the second main objective is to concentrate on trying to obtain an overall view of the individual and collective doses associated with each operation in the nuclear fuel cycle. In particular, any trend of doses with time is of interest to see whether the prediction of a gradual decrease in collective dose per unit of electrical energy produced that was made in the 1972 report is being fulfilled.

I. BASIC INFORMATION

A. SOURCES OF DATA

5. It was noted in the 1972 report that much of the data supplied to the Committee was unpublished. In the intervening period, some data have been published, but these have tended to be mainly from countries with large or growing nuclear power programmes and have not filled in many of the gaps in the data available in 1972.

B. LIMITATIONS OF THE DATA

6. Most of the limitations of the data were identified in the 1972 report, but for the sake of completeness they are briefly summarized here again. Data on occupational exposure are generally obtained from personnel-monitoring programmes set up to satisfy legal or operational requirements. These data are not always suitable for interpretation as dose estimates in the form required by the Committee.

7. Accurate assessment of dose at the lower exposure levels is severely limited by a number of factors. The proportion of workers issued personal monitoring devices varies greatly from place to place. In some establishments virtually all staff are routinely issued individual monitoring devices, while in others only those workers whose exposures might exceed 0.3 of the annual dose limit are so monitored (51).

8. Another practical difficulty is the recording of doses which fall below the minimum detectable level of the monitoring device. These may be recorded either as the minimum detectable level or as zero. Since records usually do not indicate the procedures used for deriving the doses, it is not, in general, possible to correct for any instrumental or natural radiation background which may have been included. Because of these problems and in view of the large number of doses falling in this category, the collective dose contribution from the lowest dose interval is often not well known. The Committee has therefore used an analytical procedure based on the distribution of doses at higher levels to extract mathematically the average dose and the proportion of the collective dose above and below a certain datum. This method is described in chapter III.

9. The problem of the relationship between the response of the personal monitoring device and the dose received by the person wearing it was discussed in depth in the 1972 report. It is almost always the reading from the dosimetric device which is reported, without consideration of the relationship between this reading and the whole-body or organ dose actually received by the wearer. Since most of the data relate to external whole-body exposure to directly ionizing radiation, the Committee, while recognizing the problem, has decided once again to adopt a convention that all numerical results reported by monitoring services represent the average whole-body absorbed dose in tissue. In view of the lack of available information on calibration and analysis procedures from personnel dosimetry services, the Committee was unable to apply any more rigorous procedure. Other results, such as those in which specific organ doses are reported or where a substantial proportion of the dose is due to high-LET radiation, are treated as special cases.

10. It is likely that the direct use of data from personnel-monitoring programmes in this way will tend

to overestimate doses in the various tissues of interest. For example, even in the case of the exposure of radiologists to x rays during fluoroscopy, the results of an investigation (56) in Poland showed that the film badge gave a reasonable estimate of the surface dose to the trunk but an overestimate of the gonad dose. High doses to the extremities did, however, result in the chest film badge underestimating the average whole-body surface dose by a factor of two. In many cases, such extremity doses are separately monitored and reported.

11. It is even more difficult to group and compare the results of personal monitoring for internal exposure. In some cases, routine monitoring of individuals is carried out, e.g., tritium-in-urine monitoring of luminizers and monitoring of plutonium incorporation in nuclear-fuel processing workers by various techniques. In other cases, surveys of the working environment together with relatively small numbers of individual measurements are used to deduce doses, as in the case of lung doses received by uranium and other miners. In most other work places, the ambient levels of radioactivity are usually maintained at low levels, and therefore significant internal exposures of workers seldom occur. In these situations, internal monitoring procedures tend to be carried out as a consequence of incidents or as part of an experimental study, rather than as a routine practice.

II. REASONS FOR PRESENTING OCCUPATIONAL DOSE STATISTICS

12. The primary purpose for which almost all of the data on occupational doses presented here were collected was to demonstrate compliance with statutory or regulatory obligations regarding doses to individuals. The data are therefore in general not reported in a form which lends itself to further interpretation. The Committee wishes to emphasise that data collection and reporting in excess of these obligations must be justified and therefore sets out in this section the reasons for so doing. Given these reasons, the Committee recommends that, where possible, further uses of data reported should be borne in mind by the compiler so that the format and quantity of data can be made more suitable for these purposes.

13. The purposes of such further data compilation and analysis may be source justification, relative cost-benefit assessment, evaluation of trends, and indication of the worker's risk level. Each of these purposes is examined in turn.

A. SOURCE JUSTIFICATION

14. In order to judge the justification of practices which cause radiation exposures, the levels of individual doses and the collective dose or collective dose commitment are relevant quantities in respect of presumed radiation detriment. The detriment indicated by the collective occupational dose should be added to any other detriment caused by the practice. It is often convenient to express the collective dose relative to a unit of practice. This unit of practice should be chosen to represent the benefit from the practice and not something which may well represent the size of the practice but have no close correlation to its benefit. For example, the number of workers may be proportional to the magnitude of a practice, but is not necessarily a measure of results. For this reason the average dose, i.e., the collective dose divided by the number of workers, is often not useful in considerations of justification.

15. In some circumstances it may also be relevant to compare the collective dose to occupationally exposed workers and the collective dose to the general public or to recipients of the practice. This may be the case when evaluating the detriment from discharges of radioactive effluents from waste treatment plants or in some medical situations. In general, these two situations are characterized by quite different relationships between occupational and public doses. Effluent discharges, particularly from reactors and other nuclear establishments, generally give rise to public collective doses that are almost insignificant compared with the collective doses to the plant personnel.

B. RELATIVE COST-BENEFIT ASSESSMENT

16. The purpose of relative cost-benefit assessment is to explore whether it is reasonable to attempt to achieve a further reduction of radiation doses from a practice which has been found justifiable even at existing dose levels. It is therefore the mechanism for finding the dose level at which the overall cost of further dose reduction is equal to the cost of the presumed detriment which would be eliminated by the dose reduction.

17. For this purpose the collective dose is the relevant quantity in so far as it can be assumed to represent the radiation detriment (see Annex A). It may not be sufficient, however, to give information only on the total collective dose or collective dose per unit practice. It would often be helpful to have additional information on particular sources of substantial fractions of the collective dose. This may help to direct attention to particular practices or jobs for which alternatives can be sought.

18. One way of obtaining information on available means of dose reduction is to compare the dose levels at which the same practice is carried out in different establishments or in different countries. For this purpose the collective dose per unit practice would suffice to give the crude primary comparison and is better for this purpose than the average dose.

C. EVALUATION OF TRENDS

19. There are at least two reasons for following trends in occupational doses. One is to be aware of changes in the total radiation burden from a given practice. The most direct measure of the radiation burden from

occupational doses associated with a given practice is the collective dose, so this should be continually reassessed as a function of time to detect overall trends. The collective dose at any time will not necessarily be simply related to the size of the practice because changes in radiation protection techniques are likely and the methods employed in the practice will be affected by the size of the practice.

20. The other reason for assessing trends is to determine whether radiation protection efficiency is being maintained at acceptable levels. Any quantity used for this purpose must be handled with caution. The total collective dose will reflect both the protection efficiency and the magnitude of the practice. The collective dose per unit practice will react to changes in the practice efficiency as well as the protection efficiency. The average dose is dependent on the number of people considered. For these reasons any deductions from apparent trends should be based not only on the *prima facie* evidence but also where possible on an investigation of the underlying reason for the trend.

D. INDICATION OF THE LEVEL OF RISK IN PARTICULAR OCCUPATIONS

21. It is difficult to describe precisely in advance the risk situation of an individual worker before his doses over a reasonable period have been measured or assessed. Once the doses he has received are known, however, his individual risk of harmful effects could, in principle, be assessed. The following two types of information are of use in assessing the risk situation in different occupations: *(a)* the general level of risk in a particular occupation; *(b)* the identification of subgroups with a higher level of risk than the average for that occupation or for work in general.

22. In order to assess the general level of risk it is necessary to relate this to some measure of the dose distribution. If the average annual probability of inducing harm in a working population of N persons in a particular occupation is P_H, the expectation of harmed persons is $P_H N$.

23. Conceptually, P_H is obtained from the product of the probability of receiving a dose between D and $D + dD$, which could be called $P(D)dD$, and the probability of harm given the dose D which could be called $P(H \mid D)$. Therefore

$$P_H = \int_0^\infty P(D)\, P(H \mid D)\, dD$$

If we further assume, given the discussion in Annex A, that the risk of harm at a given dose D is proportional to D, the above expression becomes

$$P_H = k \int_0^\infty P(D)\, D\, dD = k\bar{D}$$

which shows that the average dose is the proper quantity to indicate the general level of risk in a particular occupation, given the assumption of proportionality between dose and risk of harm. It is also the proper quantity to determine an individual's *a priori* risk.

24. In practice, doses are monitored and information on the dose distribution for the occupation will be available. The distribution may include doses approaching or exceeding the recommended maximum permissible doses. These high doses may be delivered to different individuals each year or to the same individuals year after year. In the second case these individuals will be in a higher risk class than the average for the occupation as a whole. It is therefore of interest to identify such subgroups. It may also be of interest to detect an occupation giving rise to high doses even if these are to different individuals each year, since the doses may still be due to causes which might be eliminated. The mathematical formulation of the portion of the distribution defined as including high doses is developed in the next chapter.

III. ANALYSIS OF DOSE DISTRIBUTIONS

25. In the 1972 report of the Committee it was noted that surprisingly little information had been published on occupational exposure in the scientific literature, although there was a considerable body of data in sources of limited availability, such as annual reports. That body of data is steadily growing, but, in addition to being of limited availability, it consists of information that is not presented in a standardized form. This makes intercomparison difficult, and compilations of data tend to be rather complex and unclear.

A. THE LOG-NORMAL DISTRIBUTION

26. On the basis of preliminary results in analysing data on occupational exposure, there is reason to expect that individual doses would follow a log-normal distribution. It is usually difficult to verify that they do, since doses tend to be grouped within wide bands and the lowest band includes non-exposed persons. However, detailed analysis of personal film dosimeters from a thousand persons working in diagnostic radiology has been carried out by Bäuml *et al.* (11) in the Federal Republic of Germany. Taking advantage of the increased film sensitivity for low-energy x rays, annual doses as low as 12 mrad were estimated with sufficient precision. The results of this analysis plotted as a log-probability curve are shown as curve A in figure I; it approximates a straight line, indicating that the actual dose distribution is well fitted by a log-normal distribution.

27. The data given by Bäuml *et al.* are very detailed. However, most of the data received by the Committee are given in only three or four ranges of dose. Curve B in figure I is plotted using the data from Bäuml *et al.* for annual doses in the ranges 0-0.5, 0-1.5, and 0-5 rad. The geometric mean doses read from these curves are 12 mrad (curve A) and 20 mrad (curve B). The proportion of people receiving less than 10 mrad (unirradiated) is estimated as 46 per cent from curve A and 36 per cent from curve B. Therefore, it appears that data from only a few dose ranges can be used for estimating the geometric mean dose and frequency of low doses with a reasonable degree of accuracy and also for assessing the average dose by means of the relationship given in

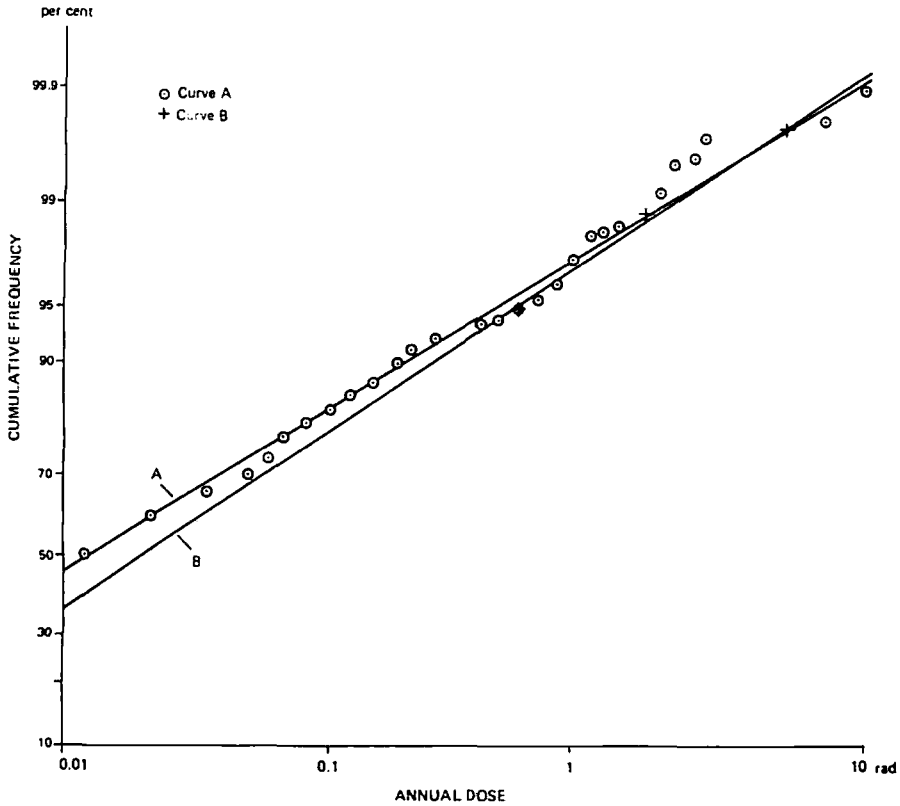

Figure I. Log-probability plot of annual doses to diagnostic x-ray workers in the Federal Republic of Germany

section C of this chapter. For example, the average dose $\overline{D}$ is estimated to be 120 mrad from curve A and 130 mrad from curve B.

28. Brodsky (16) has analysed a number of samples of dose distributions from occupations in medicine and industry and found that, in general, they followed a log-normal distribution. All distributions observed were of this form up to a level of about 1 rad, and for some it was true into the higher region. The deviation from log-normal above 1 rad, showing that fewer people were exposed to high doses than would be expected, was attributed to the effect of occupational exposure limits and was particularly noticeable for distributions with annual doses exceeding 5 rad. Examples of this deviation are shown in figures IX and X (para. 75).

29. On the basis of this evidence and after examining many of the actual dose distributions for different occupations used in later sections of this report, the Committee has decided to make the assumption that annual dose distributions are log-normal, except possibly for annual doses approaching or exceeding 5 rad. This assumption enables different types of data tabulation to be treated consistently in order to extract parameters which can be compared with those of the reference distribution to be discussed next.

B. THE REFERENCE DISTRIBUTION

30. In order to characterize those aspects of a dose distribution which contain relevant information for the objectives outlined in chapter II, it is helpful to define a reference distribution with the following clear properties:

(a) The distribution of annual doses is log-normal;

(b) The mean of the annual dose distribution is 0.5 rad (one tenth of the ICRP maximum permissible annual whole-body dose);

(c) The proportion of workers exceeding the maximum permissible annual dose of 5 rad is 0.1 per cent.

It appears to the Committee that a distribution with these properties would comply well with the intent of the ICRP dose limitation system for persons exposed to radiation in the course of their work. The mathematical construction of this reference distribution is described in appendix I. Some important parameters of the reference distribution which follow from the above definition are given below:

Annual dose range (rad)	*Probability of an annual dose in the range*	*Fraction of the total collective dose contributed by doses in the range*
0-0.5	0.668	0.253
0-1.5	0.956	0.690
0-5.0	0.999	0.941

31. In order to compare dose distributions with each other and the reference distribution, some comparison parameters must be identified. These should be related to the requirements of chapter II. The collective dose has already been recognized as useful for some purposes, but it is not a function of the dose distribution and is not considered further here. The average dose (arithmetic mean) is another relevant parameter, and, as already pointed out, the analysis of the data as log-normal should permit more consistent estimates of

the average dose. It is therefore considered to be a fundamental parameter of the distribution. The problems of defining the tail of a distribution were mentioned in chapter II. One possibility would be to use the relative numbers of persons receiving high doses; this, however, would give no information on the magnitude of the high doses. Another possibility would be to use the average dose for those individuals who receive doses above a certain level; this has the disadvantage that a few persons receiving high doses would carry too much statistical weight. It would therefore seem better to combine the two approaches and use the fraction of the collective dose in the high-dose tail. The annual dose level above which the tail is defined is obviously a somewhat arbitrary choice, but 1.5 rad seems a reasonable choice as it is the dose above which ICRP recommends special attention and is often used administratively as a dividing level in reporting readings. This measure is therefore defined as the fraction of the collective dose due to annual doses above 1.5 rad, i.e. $S_{1.5}/S$, and for the reference distribution it is $1 - 0.690 = 0.310$ (see table in paragraph 30 above). In order to normalize, we define a dimensionless quantity, Ω, as the ratio of the fraction of the collective dose due to annual doses above 1.5 rad for the observed distribution to the fraction for the reference distribution. For any observed distribution, therefore,

$$\Omega = (S_{1.5}/S)/0.310 = 3.23\, S_{1.5}/S$$

32. For the reasons referred to in chapter I, many persons who are issued a personal monitoring device will receive essentially no incremental dose due to their work. The number of such persons will be determined only by the policy of issuing dosimetric devices. In order to make a more realistic estimate of the collective dose associated with any given practice, it would be useful to be able either to calculate the average dose to those persons actually exposed, together with an estimate of their number, or to have a method of extracting the collective dose which is not sensitive to the number of essentially unirradiated people included in the sample. A further advantage of the use of a log-normal distribution analysis technique is that it enables the average dose to be calculated from the entire distribution without attaching too much importance to the lowest dose interval. It could be thought necessary to draw a distinction between this average dose calculated assuming the dose distribution to be log-normal (α) and the average dose obtained by dividing the total collective dose by the total number of individuals included in the distribution ($\bar{D}$). For distributions which are exactly log-normal, α and $\bar{D}$ will be the same and, in practical cases, as shown below, the difference is too small for the distinction to be worth making.

33. The effect of the addition or subtraction of large numbers of unirradiated individuals may be seen from the following example, which uses the data for United States agreement state licensees reported by Klement *et al.* (64). These data were chosen because they are an example of a set of data for which the annual dose distribution is available down to 0.1 rad. The procedure adopted was arbitrarily to add to, and then subtract from, the number in the lower annual dose range (0-0.1 rad), assuming 10 000 workers to have been unirradiated. This is a significant number compared with the 17 041 workers in this range in the original distribution and the original total of 24 519 workers. The resulting log-probability plots are shown in figure II, where curve A represents the original data, curve B shows the result of adding 10 000 workers in the 0-0.1 rad range, and curve C shows the result of subtracting 10 000 workers from the original number in this range.

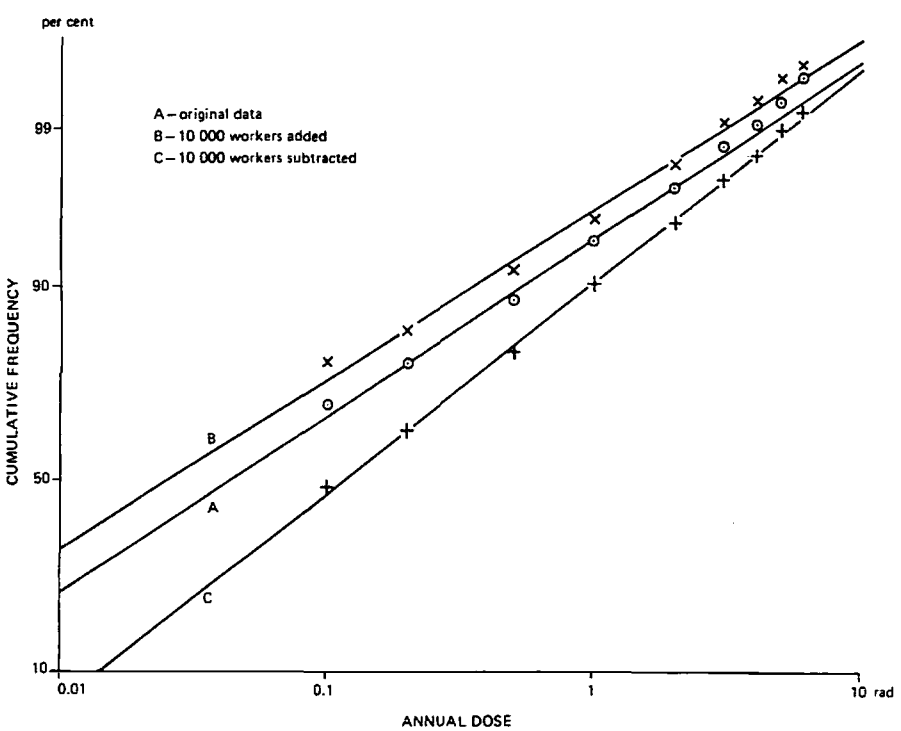

Figure II. Log-probability plot of annual doses to United States agreement state licensees, with addition and subtraction of 10 000 workers in the lowest dose range

34. Several observations can be made about these curves. The fit to a log-normal distribution is reasonably good for all three curves, indicating that arbitrary administrative decisions on issuing dosimeters do not greatly affect the conclusions. The collective doses calculated from the two extreme curves are 6890 and 6350 man rad for curves B and C, compared with 6660 man rad from curve A. The average annual doses calculated from the log-normal plot (α) are 0.1996 and 0.4371 rad for curves B and C, compared with 0.2718 rad from curve A (shown to four decimal places for comparison), demonstrating the dependence of this parameter on the number of workers considered. For comparison, the average annual doses calculated by dividing the collective dose by the number of workers ($\bar{D}$) are 0.1996 and 0.4374 rad for curves B and C and 0.2716 rad from curve A. For all practical purposes, α and $\bar{D}$ are therefore the same.

35. In order rapidly to compare dose distributions without the need to evaluate masses of raw data, it is sufficient therefore to extract from the distributions the collective dose S, the average dose $\bar{D}$ and the ratio Ω. It may also be of use to have the variation of these quantities with time. The collective dose S should be related to the benefit derived from the practice giving rise to the doses—it is not directly useful in itself. The average dose $\bar{D}$ represents the average level of risk in a given occupation or subgroup; in comparison with the reference distribution, occupations with high values of $\bar{D}$ would merit special attention. Similarly, occupations with high values of Ω should receive closer study. Occupations for which $\bar{D}$ or Ω are relatively small are probably those in which very little personnel monitoring need be carried out to meet the requirements of individual protection (see also chapter VII).

C. EXTRACTION OF THE PARAMETERS OF A DISTRIBUTION

36. A variable x is said to be distributed log-normally if the values of $y = \ln x$ are normally distributed. The mean, median and mode of the distribution of y is μ. The variance of the distribution of y is σ^2. The probability of a value of y lying between y and $y + dy$ is

$$dp = P(y)\,dy = \frac{1}{\sigma\sqrt{2\pi}}\, e^{-\frac{(y-\mu)^2}{2\sigma^2}}\, dy$$

The probability of a value of x lying between x and $x + dx$ is therefore

$$dp = P(x)\,dx = \frac{1}{\sigma\sqrt{2\pi}}\,\frac{1}{x}\, e^{-\frac{(\ln x-\mu)^2}{2\sigma^2}}\, dx$$

The arithmetic mean of the distribution of x is given by

$$\alpha = \int_0^\infty x P(x)\,dx = e^{\mu+\frac{\sigma^2}{2}}$$

Therefore, a simplified form of "probit analysis" can be used to assess the parameters of the distribution. A probit is a transformation which, when applied to the variate, will transform it to a straight line. A probit value is assigned to each probability value so that a plot of probit versus the logarithm of dose will also give a straight line. Some parameters can be readily estimated using a line fitted to the distribution by the method of least squares. The median, which is at a cumulative frequency of 50 per cent, is e^{μ}. In addition, the value of $y(= \ln x)$ is $\mu - \sigma$ at a cumulative frequency of 15.87 per cent and $\mu + \sigma$ at a cumulative frequency of 84.13 per cent. This procedure therefore enables μ, σ and α to be determined simply.

37. In some cases, a procedure was used which involved fitting a log-normal function to the data up to an annual dose value determined by inspection and using actual data points above this value. This procedure was used, for example, in analysing the dose distribution shown in figure VIII. A similar procedure, but with a different upper limit for the log-normal fit, was used for the dose distribution shown in figure X. In the few cases where the data did not fit a log-normal distribution sufficiently well to justify curve fitting, the values of the parameters for comparison with the reference distribution were obtained directly from the dose distribution, using the mid-point doses in the various dose ranges mutliplied by the number of workers in the range to obtain the collective dose.

IV. NUMBER OF WORKERS EXPOSED TO RADIATION

38. In 1966, the ICRP introduced (51) the concept of a single category of occupational exposure, namely the radiation exposure of any worker in the course of his work. The accompanying recommendation by the ICRP, that two conditions under which workers are exposed could be considered for administrative purposes, seems not to have been fully realized in practice. Under this recommendation, only people working in conditions such that their resulting doses might exceed 0.3 the annual maximum permissible dose require individual personal monitoring and health supervision. The expected result of this recommendation was that a considerable number of workers, employed under conditions such that their exposures were most unlikely to exceed 0.3 the annual maximum permissible doses, would no longer be subject to personal monitoring, but, as far as can be ascertained, no such change has occurred. The vast majority of persons routinely issued with personal monitoring devices still record annual doses less than 0.3 the maximum permissible doses.

39. Most of the data received relates to those persons potentially exposed to radiation who have been issued with individual monitoring devices or whose environment has been sufficiently closely monitored that good estimates of individual exposures can be made. There are in addition substantial numbers of people potentially or actually exposed to radiation who are not monitored in these ways and whose doses can only be inferred by modelling techniques similar to those used to estimate the doses to members of the public.

40. In practice, it is difficult to identify all occupational exposures. It is generally agreed that the term applies both to workers actually handling radioactive materials or radiation generators and to those employed on the same site (by the same or other employer) who may be exposed to radiation only

because of their physical presence there, e.g., typists and bricklayers. Less obvious is the situation of an employee of a different organization who, as a result of proximity or through discharge of wastes, is irradiated at his work. His doses, even if monitored, may not always be reported anywhere as "occupational". Since in principle any use of radiation gives rise to a very wide distribution of very small doses, it seems reasonable in practice to ignore doses that are sufficiently small. If protection of people directly connected with the radiation or on the same site is to be ensured, then doses to people unconnected with the work will generally be negligible from the point of view of individual risk. It would therefore seem more reasonable to include these people with the general public in assessing their levels of protection and the effects of doses to them. This would also avoid the anomalous situation of a man working in an office at home being permitted an annual dose of 1.5 rad, while his wife in the next room would only be permitted 0.5 rad, even through they are exposed to the same (extraneous) source.

41. Since the Committee had expressed an interest in doses to particular subgroups of workers in larger occupational groups,* a number of countries have submitted information on the type of work and the category of worker as well as the overall statistics. In order to overcome the objections above to defining workers involved with radiation in a general way, one alternative would be to attempt to define subgroups of workers and types of work in such a way that the dose distribution of each subgroup is relatively well characterized and the subgroups are mutually exclusive. Then by combining the subgroups it would be possible to survey any given category of worker. For such a system to work, considerably more thought will have to be given to defining the categories than has been given in those systems of which the Committee has knowledge.

42. In the 1972 report, data derived from personnel-monitoring programmes were used to estimate the number of persons exposed to radiation in the course of their work. For comparison, similar data (1, 19, 38, 44, 49, 64, 97, 98, 122) are presented in table 1. In many cases the figures are from the same sources as those represented in the 1972 report. Country totals are given only if it appears that the estimates are reasonably comprehensive. Although these may be of interest, they are not used as such for any of the purposes of chapter II.

V. OCCUPATIONAL EXPOSURE IN THE NUCLEAR FUEL CYCLE

43. As shown in the 1972 report, occupational exposure accounts for a substantial part of the collective dose due to the nuclear fuel cycle. It is therefore important to assess, in addition to the individual doses, the collective dose associated with each operation of the fuel cycle and, where possible, to relate, for each operation, the collective doses to the production of electrical energy. It is also of interest to analyse the temporal trend of the doses and, in particular, to see if the collective dose per unit electrical energy generated has decreased, as was thought likely in the 1972 report.

44. In this chapter, the most recent information on the distribution of doses in different dose ranges is used to obtain the parameters defined in chapter III. Where the data can be fitted by a log-normal distribution, the parameters are calculated on the basis of a least-squares fit. In those cases where there are insufficient data or for some reason the fit deviates significantly from log-normal, the parameters can often still be estimated by direct calculation from the raw data. This is done where possible. In order to clarify the interpretation of the data, the information as supplied to the Committee is presented in tabular form in appendix II (tables 46-96), and ordinarily only summaries or the extracted parameters are given in this Annex. The various stages of the nuclear fuel cycle are discussed in turn.

A. URANIUM MINING

45. One of the main radiological protection problems highlighted during the 1960s and early 1970s was the exposure of underground mine workers to high concentrations of radon and its daughter products. It was noted in the 1972 report that during the previous years there had been a marked improvement in working conditions in mines, with a subsequent lowering of the exposure to radon and its daughter products. French data (54) indicate that this improvement has continued. A discussion of the relationship between radon daughter exposure and dose to respiratory tissue can be found in Annex B (paras. 152-209). Measurements of radon concentrations in a Yugoslav mine (68) range form 90 pCi l^{-1} in the tunnels to 800 pCi l^{-1} in stopes with bad ventilation. The mean concentration of radon in French mines is only 130 pCi l^{-1}, because of greatly improved ventilation systems.

46. In South African gold-and-uranium mines, radon daughter concentrations in excess of 1 WL (see Annex B for definitions and discussion of the units WL and WLM) are found in places where uranium is the major mineral and gold is of secondary importance (36). An average of 0.9 WL was recorded for the uranium section of one such mine (9). The average of the annual reported exposures to radon daughters in 1974 in underground mines in the United States is 1.4 WLM (34). Table 46 (appendix II) shows the results of monitoring of French underground mines for exposure to radon daughters (54). It can be seen that the average exposure level had decreased from about 0.18 WL in the period 1971-1973 to 0.11 WL in 1975, by which time the proportion of workers exposed to 0.3 WL had dropped from 22 per cent to nearly 5 per cent.

47. Some information is available on the external gamma irradiation in uranium mines (68, 91, 93). In French uranium mines (91) the dose rates are of the order of 0.5 mrad h^{-1} in the centres of galleries where the ore is of low concentration, but can reach 100 mrad h^{-1} in the few places where the ore concentration is exceptionally rich. Dose rates in Yugoslav mines (68) can be up to 5 mrad h^{-1} near the ore. The average annual external dose to a small group of underground uranium miners in Japan is 122 mrad (41). The average of many measurements of dose rates in underground mines in the United States is 1.3 mrad h^{-1}

TABLE 1. NUMBER OF OCCUPATIONALLY EXPOSED PERSONS AND THEIR PROPORTION IN THE POPULATION OF VARIOUS COUNTRIES

Data derived from personnel monitoring records

(Absolute number n *and number per 1000 of population (10^{-3}))*

	Type of occupation															*Total*		
	Extractive industries		*Atomic industries*		*Non-atomic industries*		*Medical*		*Research and education*		*Other*		*Armed forces*			*Best estimates*		*From 1972 report*
Country	n	*(10^{-3})*	n	*(10^{-3})*	n	*(10^{-3})*	n	*(10^{-3})*	n	*(10^{-3})*	n	*(10^{-3})*	n	*(10^{-3})*	*Year*	n	*(10^{-3})*	*(10^{-3})*[a]
Argentina	150	<0.01	1 300	0.05	220	0.01	9 850	0.42	29	<0.01	40	<0.01			1971	11 000	0.5	0.1
Australia			1 007	0.08	1 782	0.14	12 219	0.96	3 233	0.25	420	0.03			1971	19 000	1.5	1.5
Austria	170	0.02			800	0.11	1 800	0.24							1971	3 000	0.4	
Barbados							40	0.17							1971	100	0.2	
Belgium			2 140		2 485		4 656		6 100							15 000		
Burma					15	<0.01	165	<0.01	5	<0.01	4	<0.01			1971	200	<0.01	
Canada			2 000	0.01				31 000	1.45						1971	33 000	1.5	
China			60	<0.01	10	<0.01	700	<0.01	500	<0.01	100	<0.01			1971			
Colombia			100	<0.01	37	<0.01	12 000	0.57							1971	12 000	0.6	
Cyprus					4	0.01	65[a]	0.01	4	0.01					1971			
Democratic Kampuchea							240	0.04							1971	300	<0.1	
Denmark					406	0.08	4 808	0.96	2 067	0.41					1973	7 000	1.5	1.9
Finland			5	<0.01	350	0.07	4 700	1.00	40	0.01	400	0.09			1971	6 000	1.2	0.9
France			15 000	0.30	15 000	0.30	60 000	1.20	10 000	0.20					1975	100 000	2.0	2.1
German Democratic Republic															1972	34 000	2.0	1.5
Germany, Fed. Rep. of							87 056	3.35		24 069	0.93				1975	111 000	4.3	
Ghana					46	0.01	196	0.02	32	<0.01	1	<0.01			1971	300	<0.1	
Greece	10	<0.01			40	<0.01	2 500	0.28	500	0.06					1971	3 000	0.3	
Guyana							46	0.06							1971	100	0.1	
Hungary					1 647	0.16	5 183	0.50	126	0.01	334	0.03			1971	7 000	0.7	
Iceland					15	0.07	400	1.90	15	0.07					1971	400	2.0	
India	2 561	<0.01	7 887	0.01	2 580	<0.01	10 913	0.02	2 450	<0.01					1971	26 000	0.5	
			5 578	–	1 760	–	7 739	–	1 562	–					1973	16 000		
Indonesia	92	<0.01	100	<0.01					18	<0.01	9	<0.01			1971			
Iraq							450	0.05	250	0.03	90	0.01			1971	1 000	0.1	
			267	0.03	6	<0.01	624	0.07							1972	1 000	0.1	
Ireland	4	<0.01			45	0.02	580	0.20	55	0.02					1971	700	0.2	
Israel			907	0.30	231	0.08	2 794	0.94	646	0.22					1971	4 500	1.5	
Italy			4 600	0.09	2 300	0.04	18 000	0.34	120	<0.01	800	0.01			1971	26 000	0.5	0.7
Jamaica							62	0.03	2	<0.01					1971	100	<0.1	
Luxembourg					255	0.75	265	0.78							1971	600	1.5	

TABLE 1 *(continued)*

Country	Type of occupation: Extractive industries n	Extractive industries (10^{-3})	Atomic industries n	Atomic industries (10^{-3})	Non-atomic industries n	Non-atomic industries (10^{-3})	Medical n	Medical (10^{-3})	Research and education n	Research and education (10^{-3})	Other n	Other (10^{-3})	Armed forces n	Armed forces (10^{-3})	Year	Total: Best estimates n	Best estimates (10^{-3})	From 1972 report (10^{-3})[a]
Madagascar							215	0.03			5	<0.01			1971	300	<0.1	
Malawi							23	0.01							1971	100	<0.1	
Malaysia							460	0.04			40	0.01			1971	500	<0.1	
Mali							26	0.01							1971	100	<0.1	
Malta							<100	<0.31							1971	100	<0.3	
Mauritius							73	0.09							1971	100	0.1	
Mexico	148	<0.01	56	<0.01	271	0.01	488	0.01	93	<0.01	33	<0.01			1971	1 000	<0.1	
New Zealand					137	0.05	2 735	0.97	300	0.11	364	0.13			1971	4 000	1.3	1.3
Netherlands			260	0.02	1 100	0.08	9 000	0.69							1971	10 000	0.8	0.8
Nigeria	>5 000	>0.08			2 000	0.03	4 000	0.06	200	<0.01					1971	11 000	>0.2	
Norway			598	0.15	326	0.08	7 460	1.92			15	<0.01			1971	8 000	2.2	2.7
Peru															1971	8 000	0.6	
Philippines	6	<0.01	180	<0.01	164	<0.01	405	0.01	6	<0.01	11	<0.01			1971	800	<0.1	
Poland			1 253	0.04			1 298	0.04			2 786	0.09			1971			
					14 600	0.45									1971	20 000	0.6	0.5
Rwanda	2	<0.01			52	0.01	2	<0.01							1971	100	<0.1	
Sierra Leone	<20	<0.01					<100	<0.04							1971	100	<0.1	
Singapore					40	0.02	85	0.04	35	0.02					1971	200	0.1	
Socialist Rep. of Viet Nam					100	<0.01	439[b]	0.01	20	<0.01	3	<0.01			1971	600	<0.1	
Spain	500	0.02	2 300	0.07	100	<0.01	200	0.01	300	0.01					1971	4 000	0.1	
Sudan					26	<0.01	196	0.01	50	<0.01					1971	300	<0.1	
Sweden	5 136	0.64	1 188	0.15	1 000	0.12	12 000	1.49	1 300	0.16					1971	21 000	2.6	2.0
Switzerland															1974	15 000	2.4	
Thailand							878	0.03	90	<0.01	12	<0.01			1971	1 000	<0.1	<0.1
Tunisia							100	0.02			6	<0.01			1971	100	<0.1	
Turkey	65	0.02			60	0.02	2 000	0.56	250	0.07	70	0.02			1971	2 500	0.7	
United Kingdom			19 700	0.36	22 250	0.40	24 200	0.44	12 000	0.22					1974	78 000	1.4	
			22 787	0.41							2 798	0.05			1971			
United States			125 000[b]	0.61	90 000[b]	0.44	453 700	2.21	23 000[b]	0.12			80 087	0.39	1970	772 000	3.8	3.7
Venezuela	25	<0.01	40	<0.01	121	0.01	3 200	0.31	410	0.04	8	<0.01			1971	4 000	0.4	
Zambia	30	0.01			5	<0.01	250	0.06	15	<0.01					1971	300	0.1	

[a] Government establishments only.

[b] Estimated number of workers in these groups.

(93). Since a miner in a tunnel is exposed to something between a plane (2π) and a completely surrounding (4π) source, the conversion procedures given in Annex A for the assessment of tissue doses in a 3π geometry can be used. On this basis, and assuming 2000 h of work per year and a dose rate of 1.3 mrad h^{-1}, the annual average absorbed dose (in the gonads or bone marrow) is estimated to be 1.6 rad. However, as shown in table 47 (appendix II), measurements of the external doses to French underground miners show a decrease in the annual average dose from about 1 rad in the period 1971-1972 to 0.5 rad in 1975. It therefore seems reasonable to assume an annual average dose of 1 rad for current conditions in uranium mines throughout the world.

48. The assessment of the collective dose per unit electricity for the mining operation requires an estimation of the number of miners involved in the extraction of the amount of ore needed to produce 1 MW y of electrical energy. Assuming that one miner produces 3 t of U_3O_8 in one year and that 160 t of U_3O_8 are required to fuel one 1000-MW(e) light-water reactor for a year (114), it is estimated that the fraction of a man year required to produce 1 MW y of electrical energy is $5.3\ 10^{-2}$. This value, combined with the annual dose calculated above, gives a collective dose per unit electrical energy for uranium mining of approximately 0.05 man rad per MW y.

49. Similar calculations can be performed to assess the collective dose contribution to the lung. The average of the annual reported exposures to radon daughters in 1974 in underground mines in the United States is 1.4 WLM (34). Omitting the exposures reported as zero, under the assumption that they are not really the result of underground work, the annual average becomes 1.9 WLM. The annual average for French miners is 1.3 WLM. As estimated in Annex B, this exposure corresponds to an annual bronchial dose of 1.5-2 rad. The collective dose to the lung per unit electrical energy is therefore about 0.1 man rad per MW y. It should be pointed out, however, that this collective dose to the lung is due to alpha irradiation and cannot be added to that from other steps of the fuel cycle.

B. MILLING AND FUEL FABRICATION

50. The contribution of occupational exposure in milling and fuel fabrication steps of the cycle to the collective dose is minimal. The Committee has received detailed data only from the United Kingdom on fuel enrichment and fabrication carried out at two establishments (47, 53). Table 2 shows these data in summary form. It is difficult to correlate these doses with any particular level of power generation, but if it were assumed that the average annual collective dose over the four years 1972-1975 could be related to the average annual United Kingdom nuclear electrical output over those four years, which was relatively stable at 2612 MW(e) y (39, 85), then the normalized collective dose would be 0.15 man rad per MW(e) y.

TABLE 2. OCCUPATIONAL DOSES TO FUEL ENRICHMENT AND FABRICATION WORKERS IN THE UNITED KINGDOM, 1972-1975

	Annual average dose (rad)				*Annual collective dose[a] (man rad)*			
Occupational description	*1972*	*1973*	*1974*	*1975*	*1972*	*1973*	*1974*	*1975*
Fuel enrichment		0.07	0.04			29 (0)	19 (0)	
Fuel manufacture – chemical processes	0.41	0.61	0.58	0.45	90 (0.7)	134 (1.0)	128 (1.1)	99 (0.6)
Fuel manufacture – fabrication	0.47	0.53	0.58	0.58	56 (0.7)	64 (0.8)	70 (1.0)	70 (0.9)
Fuel manufacture – canning and assembly	0.23	0.28	0.35	0.33	14 (0.4)	17 (0.3)	21 (0.9)	20 (0.5)
Fuel manufacture – maintenance[b]	0.30	0.40	0.40	0.35	150	200	200	175
Total[c]	–	–	–	–	330	440	440	390

[a] The numbers in parentheses are the values of Ω.
[b] Assuming that the dose to maintenance workers is 75% of the dose to production workers.
[c] Assuming annual collective doses from fuel enrichment of 25 man rad in 1972 and 1975.

51. A category for fuel reprocessing and fabrication appears in the occupational exposure summary report of the United States Nuclear Regulatory Commission (18). Since no reprocessing of commercial reactor fuel was carried out in the United States for the years in question (1973-1974), it could be assumed, as an upper limit, that the doses were attributable to fuel fabrication. The data are shown in table 3. A log-probability plot of the dose distribution is shown in figure III. It is a good example of the presumed effect of regulations on the part of the distribution with annual doses exceeding a few rads. If

TABLE 3. COLLECTIVE DOSES TO FUEL REPROCESSING AND FABRICATION WORKERS IN THE UNITED STATES, NRC LICENSEES 1973-1974

Year	*Total number of individuals monitored*	*Number of individuals with measurable exposure*	*Collective dose (man rad)*
1973	10 610	5 056	2 400
1974	10 921	4 617	2 740

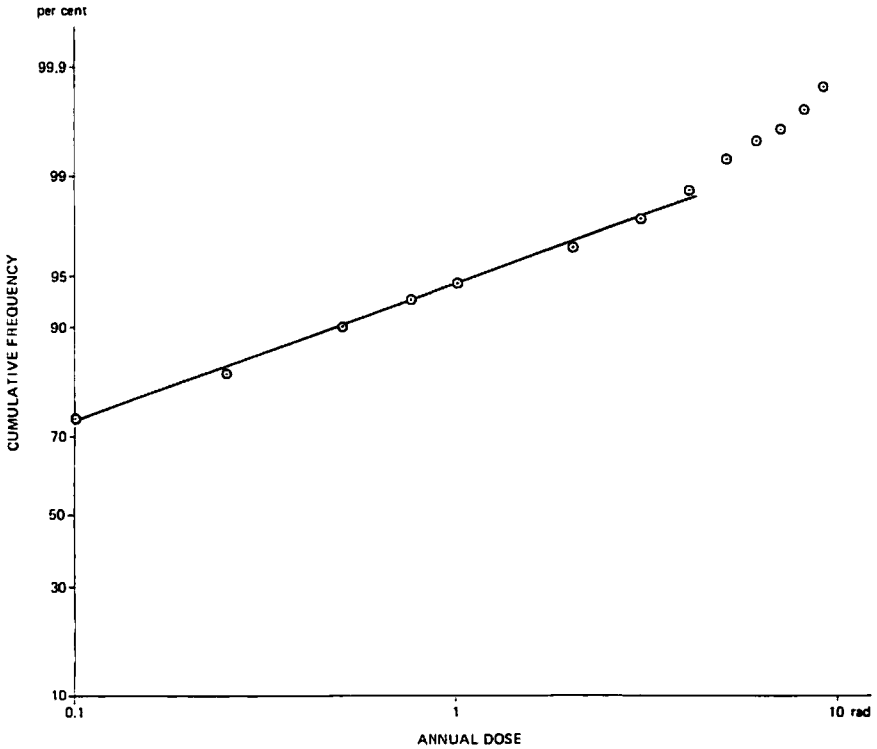

Figure III. Log-probability plot of annual doses to fuel reprocessing and fabrication workers in the United States, 1974

these doses are correlated with the total electricity generated in the same two years (77), then a normalized collective dose of approximately 0.25 man rad per MW(e) y is obtained. Since the United States power reactor industry is rapidly expanding, however, a considerable amount of the fuel fabricated will have been used to fuel reactors that did not contribute significantly to power production in the same year. If this proportion approached 30-40 per cent, as seems likely, then the resulting figure is in reasonable agreement with that for the United Kingdom.

52. In the future, since plutonium will be used in the fabrication of fast reactor fuels, radiological protection of workers at this stage in the fuel cycle will have to adapt itself to the difference of techniques connected to this modification of the fuel nature. The increased handling of plutonium will increase the potential for plutonium intakes. It is not possible for the Committee to judge the importance of this increased potential since it has received no information on doses directly attributable to plutonium fuel fabrication.

C. NUCLEAR POWER REACTORS

53. In contrast to the other stages of the fuel cycle, a reasonable amount of information is now available on doses to personnel at civil nuclear power reactor sites. Most of the information relates to operation of light-water reactors, especially in the United States, but comprehensive data on United Kingdom gas-cooled reactors have also been supplied.

54. A comprehensive summary of occupational radiation exposures in United States light-water cooled reactors has been recently published by the United States Nuclear Regulatory Commission (78). Some data on dose distributions were quoted in the report, but it was indicated that collective doses were obtained either by multiplying the number of people in a range by the mid-point dose in that range and summing the result or, in a small number of cases, by summing the actual doses to all individuals. The collective doses were obtained by including doses to all individuals at the site whether they were plant personnel, utility personnel brought in on a temporary basis, contractor personnel or visitors. The results are summarized in table 4, which shows the annual average collective doses per plant for boiling water reactors (BWRs) and pressurized water reactors (PWRs) from 1969-1975 and the cumulative average collective doses. Although it appeared from the 1973 figure for PWRs that these reactors were starting to experience problems leading to larger personnel doses than anticipated, the considerably reduced figures for 1974 and 1975 lend support to the idea that this may have been transient rather than a trend. The annual average collective doses for BWRs have increased over the same years, but no firm conclusions can be drawn from the figures. The cumulative annual average collective dose per plant for all reactors for the years 1969-1975 is 420 man rad (78). This figure is tending to become stable. Table 48 (appendix II) gives the detailed figures on which these summaries are based.

55. Annual average doses to individuals decreased again in 1974 from the peak in 1972 and remained steady in 1975. The mean number of personnel per plant also showed a decrease in 1974 from the very high figure for 1973, but showed a rise again in 1975. Table 5 shows the annual average doses from 1969-1975 at all United States light-water reactors (78), and figure IV is a log-probability plot of the annual doses (78) for the years 1973, 1974 and 1975. The agreement with a log-normal distribution is not very good, presumably due to a tendency to reduce annual doses approaching or exceeding 5 rad.

TABLE 4. SUMMARY OF COLLECTIVE DOSES AT 32 LIGHT-WATER REACTORS IN THE UNITED STATES, 1969-1975

Year	*Boiling water reactors*				*Pressurized water reactors*			
	Number of plants	*Average rated electrical power capacity (MW)*	*Annual average collective dose (man rad)*	*Cumulative average collective dose (man rad)*[a]	*Number of plants*	*Average rated electrical power capacity (MW)*	*Annual average collective dose (man rad)*	*Cumulative average collective dose (man rad)*[a]
1969	3	116	195	195	4	381	165	165
1970	5	322	130	154	5	403	599	406
1971	7	351	255	200	6	459	340	380
1972	10	450	286	235	8	500	463	409
1973	14	521	330	269	12	575	772	533
1974	14	521	507	332	18	625	364	476
1975	18	626	670	418	26	650	309	421

[a]Collective dose from current year and previous years after 1969 divided by cumulative reactor operating years.

TABLE 5. ANNUAL AVERAGE INDIVIDUAL DOSES AT LIGHT-WATER REACTORS IN THE UNITED STATES, 1969-1975

Year	*Average number of employees per plant*	*Annual average individual dose (rad)*
1969	141	1.06
1970	305	0.98
1971	302	0.96
1972	344	1.20
1973	584	0.85
1974	514	0.74
1975	578	0.80

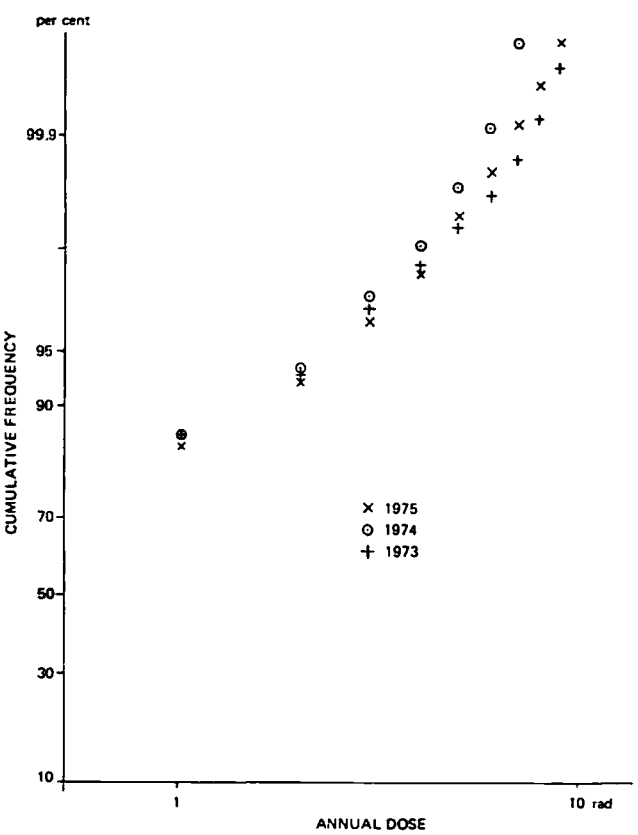

Figure IV. Log-probability plot of annual doses to workers at light-water reactors in the United States, 1973, 1974 and 1975

56. The collective dose per unit electrical energy generated for each station is also given in table 48 (appendix II). These data are summarized in table 6. Murphy *et al.* (78), in quoting these figures, caution that until more experience with light-water reactors (LWRs) is accumulated it will be difficult to draw any conclusions from the data presented. An attempt to relate the collective dose per unit electricity generated with the rated capacity of the units showed no significant correlation. It was found, however, that the collective dose generally increased after the first years of operation.

TABLE 6. ANNUAL NORMALIZED COLLECTIVE DOSE AT LIGHT-WATER REACTORS IN THE UNITED STATES, 1969-1975

(man rad per MW(e) y)

Year	*BWRs*	*PWRs*	*All*
1969	1.75	0.66	0.94
1970	0.63	2.39	1.59
1971	1.36	1.12	1.22
1972	0.81	1.44	1.07
1973	1.00	2.13	1.55
1974	1.75	0.99	1.28
1975	2.03	0.67	0.89

57. The causes of the doses have been carefully analysed in other reports (71, 89). It is apparent that most occupational exposure at reactors is incurred during maintenance rather than routine operation of the reactor. Table 7 shows the percentage of annual exposures received during outages for a number of LWRs (89). This conclusion agrees with the United States Nuclear Regulatory Commission study (78), which lists the following causes of exposure with the percentage of the total collective dose attributable to each:

Routine reactor operation and surveillance	11
Routine maintenance	52
Special maintenance	19
Refuelling	8
In-service inspection	3
Waste processing	7

TABLE 7. PROPORTION OF ANNUAL EXPOSURE RECEIVED DURING OUTAGE AT CERTAIN LIGHT-WATER REACTORS IN THE UNITED STATES

Plant No.	*Year since start-up*	*Outage time (h)*	*Proportion of annual exposure (%)*
1	9	1 406	71
	10	1 257	83
	11	139	27
	12	3 873	67
3	3	1 567	70
	4	1 548	54
	5	2 263	71
4	3	1 432	79
	4	479	74
	5	1 835	69
5	1	4 481	61
	2	2 798	58
	3	2 618	36
	4	2 079	61
10	3	2 131	52
11	1	4 633	97
	2	1 429	81
	3	1 261	84

Source: Reference 89.

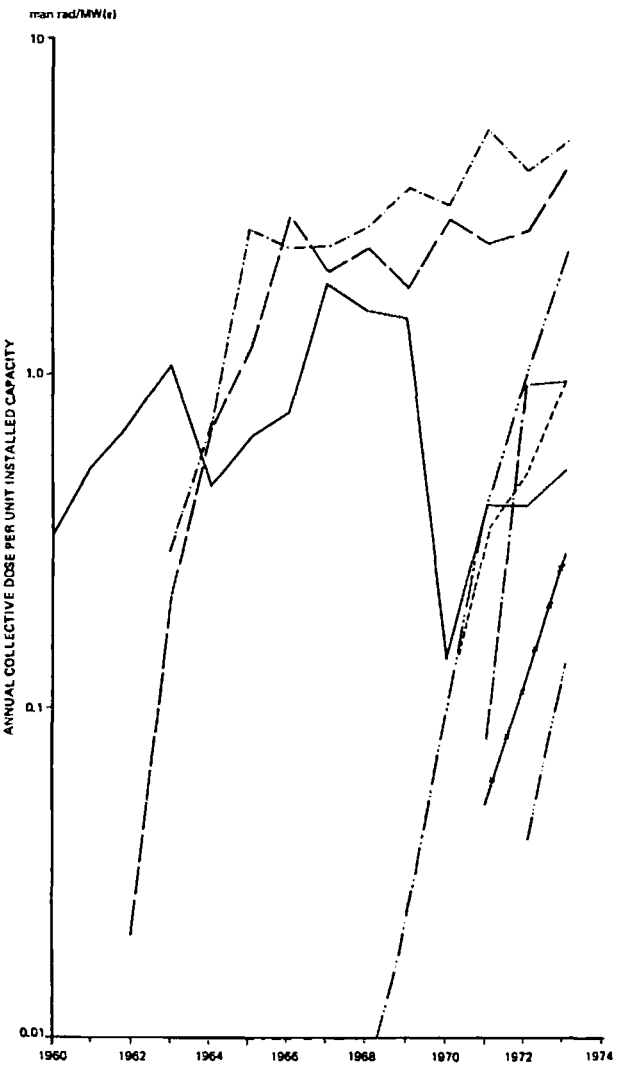

Figure V. Variation of the annual collective dose per unit installed electric power capacity for different boiling water reactors in the United States (89). The plant represented by the solid curve had different capacities during the period, as follows [MW(e)]: 1960-1969, 200; 1970, 200 + 800; 1971-1973, 200 + 2 X 800

58. In the study by Pelletier *et al.* (89), the effect of plant age on annual collective dose was examined (figures V and VI). All the BWR plants showed a marked increase in doses by a factor of two or three each year for the first three to four years, after which the rate of increase dropped considerably. It is suggested that this rapid increase is due to the increasing dose rate encountered for maintenance jobs; these increasing dose rates are due to crud accumulation in pipes, pumps, valves etc. Any change in dose with plant age is not so marked with PWRs as with BWRs after the first year. The annual collective dose at most of the PWRs was dominated by doses received during the inspection and repair of steam generators.

59. The trend in doses and the electricity generated in France is shown in table 8 for the period 1964-1974 (12, 88). The results of individual dosimetry on approximately 2000 workers show good stability of the annual average dose between 1970 and 1975. Figure VII shows the variation of the frequency of annual doses $\geq$0.5 rad over the period 1964-1975 (12, 88). The collective dose has been within the range 0.5-1.0 man rad per MW(e) y from 1966 to 1974. Detailed dose distributions to workers at French nuclear power stations for 1970 (28) and 1971 (29) are shown in table 49 (appendix II),

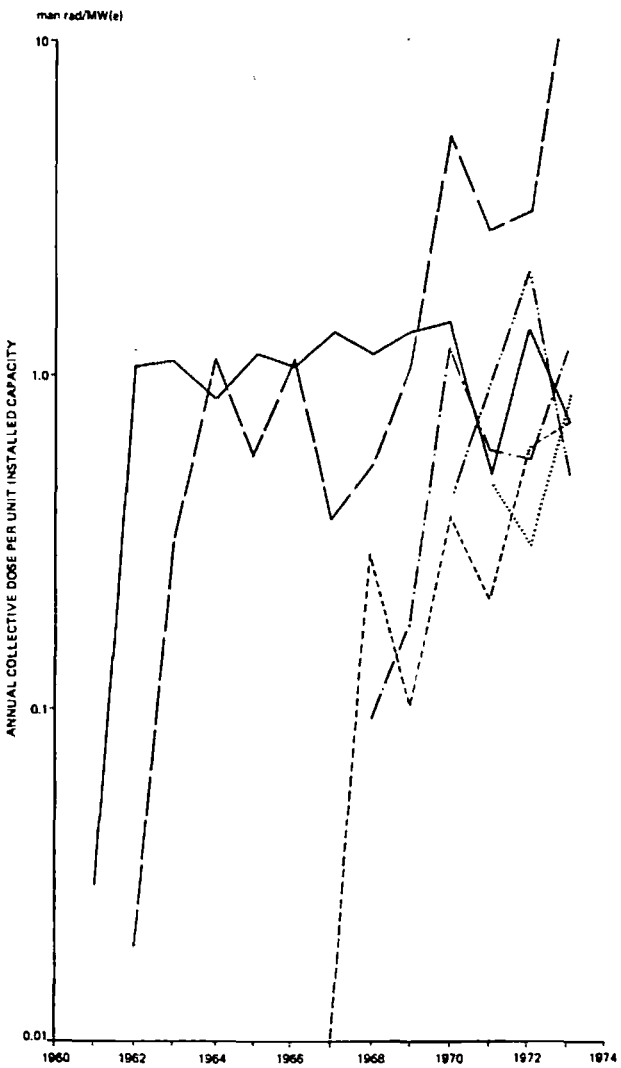

Figure VI. Variation of the annual collective dose per unit installed electric power capacity for different pressurized water reactors in the United States (89)

TABLE 8. DATA RELATING TO OCCUPATIONAL DOSES AT NUCLEAR POWER PLANTS IN FRANCE, 1964-1974

	1964	*1965*	*1966*	*1967*	*1968*	*1969*	*1970*	*1971*	*1972*	*1973*	*1974*
Number of workers with film badges	333	434	495	578	758	1 167	1 509	1 644	1 593	1 560	1 598
Installed electrical capacity (MW)	80	270	270	820	820	1 546	1 546	2 085	2 625	2 565	2 565
Net electrical energy produced (MW y)	17	40	103	229	282	440	522	823	1 500	1 512	1 444
Annual average dose (rad)	0.16	0.16	0.18	0.30	0.28	0.30	0.34	0.39	0.48	0.47	0.55
Annual collective dose (man rad)	53	72	89	173	212	350	513	648	776	733	883
Collective dose per unit energy produced (man rad per MW(e) y)	3.1	1.8	0.87	0.76	0.75	0.80	1.02	0.79	0.52	0.48	0.61

Sources: References 12, 88.

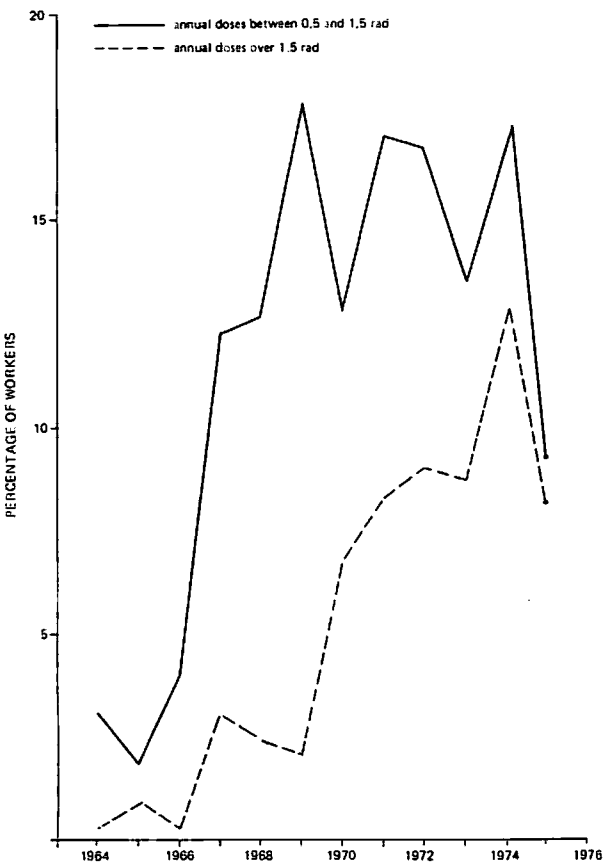

Figure VII. Variation of the frequency of individual annual doses ≥0.5 rad at reactors in France (12, 88)

together with the dose distribution for 1974 (12). The Ω values calculated by fitting a log-normal curve to these distributions are 1.5, 1.2 and 1.7 for 1970, 1971 and 1974, respectively.

60. Many other countries have reactors of a type similar to those in the United States. They have less experience and fewer operating plants than the United States, but the data reported support, for the most part, the United States figures for doses associated with the operation and maintenance of LWRs.

61. Data from the Federal Republic of Germany for the period 1973-1975 are given in table 50 (appendix II) (72a). The reported collective doses are obtained by summation from the measured individual doses; the mean values are arithmetical mean values. The average individual doses and collective doses are quoted separately for the plant personnel employed permanently in the nuclear power plant and for the external personnel working in the plant temporarily and during fixed periods. The information covers all commercial nuclear power plants currently in operation in the Federal Republic of Germany. The average individual doses for all nuclear power plants in the Federal Republic of Germany are summarized in table 9. For all personnel, doses are of the same order of magnitude as for light-water reactors in the United States. The indicated average doses to external personnel are always less than those to plant personnel. The reason is that some of the external personnel work in several plants and are therefore quoted several times when the total for all plants is made up. The annual average dose to external personnel shown in the table is therefore an underestimate.

62. Some data have been provided on doses in Swedish power plants (69a). These are shown in detail in table 51 (appendix II). It is apparent that most of the collective dose is received by contractors' employees rather than direct employees of the utility; however, the annual

TABLE 9. SUMMARY OF DOSES TO WORKERS AT NUCLEAR POWER PLANTS IN THE FEDERAL REPUBLIC OF GERMANY, 1973-1975

	Plant personnel			*External personnel*			*All personnel*		
Year	*Number of persons*	*Annual collective dose (man rad)*	*Annual average dose (rad)*	*Number of persons*	*Annual collective dose (man rad)*	*Annual average dose (rad)*	*Number of persons*	*Annual collective dose (man rad)*	*Annual average dose (rad)*
1973	1 108	1 270	1.15	2 586	1 240	0,48	3 694	2 520	0.68
1974	1 471	1 300	0.89	3 251	1 650	0.51	4 722	2 950	0.62
1975	1 549	1 380	0.89	3 225	2 120	0.66	4 774	3 500	0.73

TABLE 10. ANNUAL COLLECTIVE DOSE AND COLLECTIVE DOSE PER UNIT ELECTRICAL ENERGY GENERATED AT THREE ITALIAN POWER PLANTS

	Latina		*Trino*		*Garigliano*	
Year	*Annual collective dose (man rad)*	*Collective dose per unit nergy generated (man rad per MW(e) y)*	*Annual collective dose (man rad)*	*Collective dose per unit energy generated (man rad per MW(e) y)*	*Annual collective dose (man rad)*	*Collective dose per unit energy generated (man rad per MW(e) y)*
1963	57	1.56	–	–	27	[a]
1964	78	0.45	7.4	0.54	75	0.89
1965	88	0.51	27	0.23	102	0.92
1966	77	0.46	28	0.16	108	1.16
1967	100	0.55	51	0.69	146	1.39
1968	85	0.48	31	[a]	148	1.26
1969	87	1.52	109	[a]	144	1.07
1970	80	0.59	53	0.38	202	2.42

[a] No electricity generated.

average doses to the two groups are comparable and quite low, rarely exceeding 0.20 rad. There is as yet insufficient operating experience on these reactors to establish any trends, but the overall annual collective doses for the two larger operational stations in 1975 were 84 and 166 man rad, comparable with the lower end of the range covered by United States reactors.

63. There are some data on occupational doses for three Italian power plants (24). It is apparent that radiation protection staff in general received the highest doses; however, they are fewer in number than the maintenance staff. There was a considerable amount of maintenance work done at Trino Vercellese during 1967 and 1970. The annual collective dose from 1963 to 1970 at the plants is shown in table 10. The variation in collective dose per unit electrical energy generated is rather large, but the values cover the range of the United States figures.

64. Data on doses to contract workers at two Swiss nuclear power stations are shown in table 52 (appendix II) (60). The annual collective doses at the two stations were 110 and 82 man rad, respectively, in 1975 for 194 and 175 workers on each station, and the values for Ω were 1.4 and 1.3.

65. Data have been supplied by Argentina on the occupational doses received at the nuclear power plant at Atucha in 1974 and 1975 (21, 25). These are shown in detail in tables 53 and 54 (appendix II). The annual collective doses due to external exposure in the two years 1974 and 1975 were 83 and 138 man rad, with average annual doses of 0.31 and 0.44 rad. The Ω values for the two years were 0.4 and 0.8. The installed generating capacity of the station is 320 MW(e) and the energy generated in the two years was 118 and 287 MW(e) y. Doses from exposure to tritium were in general small and, since these are likely to be overestimates, are only thought to add about 20 per cent to the above collective dose estimates. The normalized collective dose for this station is therefore 0.6-0.8 man rad per MW(e) y.

66. Canadian reactors of the CANDU type have now been operating for 12 years. Sufficient experience has been accumulated at Pickering, where four units were brought into service between 1971 and 1973, to enable some conclusions to be drawn on occupational doses at stations of this type. Table 11 summarizes the information on annual collective doses at Pickering from commissioning up to 1974 (125). It may be seen that with this type of reactor some 20-30 per cent of the collective dose is a result of internal doses from tritium. The overall figures are again comparable with those for United States light-water reactors (see tables 4 and 6).

TABLE 11. COLLECTIVE DOSES AT THE NUCLEAR POWER PLANTS AT PICKERING, CANADA, 1971-1974

Year	*Annual collective doses (internal and external) (man rad)*	*Fraction due to internal doses from tritium (%)*	*Collective dose per unit energy generated (man rad per MW(e) y)*
1971	198	24	0.60
1972	993	18	1.70
1973	899	30	0.55
1974	1 613	30	1.10
Average	926	26	0.90

67. The United Kingdom commercial nuclear power stations are of the gas-cooled graphite-moderated reactor type (GCR). Complete data on occupational exposures are shown in table 55 (appendix II) and in summary form in table 12 (39, 85). It can be seen that the annual average doses, collective doses and collective doses per unit energy supplied to the grid are considerably less at the newer stations (Oldbury, Sizewell, Wylfa) than at the older ones (Berkeley, Hinkley Point, Hunterston). The high collective doses at Trawsfynydd and Hinkley Point during this period were due to cooling-pond problems. The normalized collective dose due to electricity supplied to grid by all United Kingdom reactors over the three years considered was 0.73 man rad per MW(e) y. This should be regarded as representative of the current situation rather than indicative of future expectations. Data on eye doses at five United Kingdom reactors from 1971-1973 have been supplied. The detailed figures are shown in table 56 (appendix II).

68. A gas-cooled reactor of a type similar to the older United Kingdom reactors is installed at Tokai in Japan.

TABLE 12. SUMMARY OF OCCUPATIONAL DOSES AT UNITED KINGDOM GAS-COOLED NUCLEAR POWER PLANTS, 1972-1974

	Annual average dose (rad)			*Annual collective dose[a] (man rad)*			*Collective dose per unit electrical energy supplied to grid (man rad per MW y)*		
Plant	*1972*	*1973*	*1974*	*1972*	*1973*	*1974*	*1972*	*1973*	*1974*
Berkeley	0.69	0.72	0.70	271 (0.8)	302 (1.3)	284 (1.0)	1.21	1.27	1.27
Bradwell	0.40	0.29	0.32	164 (0.1)	146 (0.1)	129 (0.1)	0.79	0.80	0.63
Hinkley Point	0.35	0.32	0.31	253 (0.8)	410 (1.0)	514 (0.01)	0.74	1.53	1.47
Trawsfynydd	1.12	0.72	0.43	575 (2.3)	430 (2.1)	260 (1.0)	2.12	1.85	0.70
Dungeness	0.25	0.20	0.20	135 (0)	129 (0)	135 (0)	0.37	0.35	0.35
Sizewell	0.11	0.13	0.16	53 (0)	84 (0.3)	82 (0.5)	0.17	0.25	0.23
Oldbury	0.17	0.17	0.17	75 (0)	73 (0)	71 (0)	0.25	0.25	0.22
Wylfa	0.12	0.10	0.12	37 (0)	62 (0)	72 (0)	0.13	0.21	0.17
Hunterston	0.54	0.40	0.50	364 (0.1)	277 (0.1)	360 (0.4)	1.61	1.25	1.48

[a]The number in parentheses is the Ω value.

The annual collective doses at this reactor in 1973 and 1974 were 131 and 65 man rad, leading to values for the collective dose per unit electrical energy produced of 1.11 and 1.16 man rad per MW y (41).

D. FUEL REPROCESSING

69. The major commercial fuel-reprocessing installation which has been in operation over recent years is in the United Kingdom at Windscale, Cumbria. Table 13 shows the annual average individual doses and the annual collective doses from 1971-1975 (48). The dose distributions for these years are shown in table 57 (appendix II); the Ω values shown in table 13 were calculated from them. Figure VIII shows a typical distribution indicating the effect of dose limits. The procedure used was therefore to fit a log-normal curve to the distribution up to 1.5 rad but to use the actual results above that value.

TABLE 13. OCCUPATIONAL DOSES TO FUEL-REPROCESSING WORKERS AT WINDSCALE, UNITED KINGDOM, 1971-1975

Year	*Annual collective dose (man rad)*	Ω	*Annual average dose (rad)*
1971	3 050	2.2	1.20
1972	3 380	2.3	1,27
1973	3 250	2.3	1.25
1974	3 440	2.3	1.23
1975	4 030	2.2	1.19

70. It is very difficult to correlate the collective doses with a particular rate of electricity generation, but assuming again that the doses incurred at Windscale over the years 1972-1975 could be related to the average electrical output over those years, as in paragraphs 50-51, and making an allowance for the 8-per-cent fuel throughput from overseas (83), then the collective dose

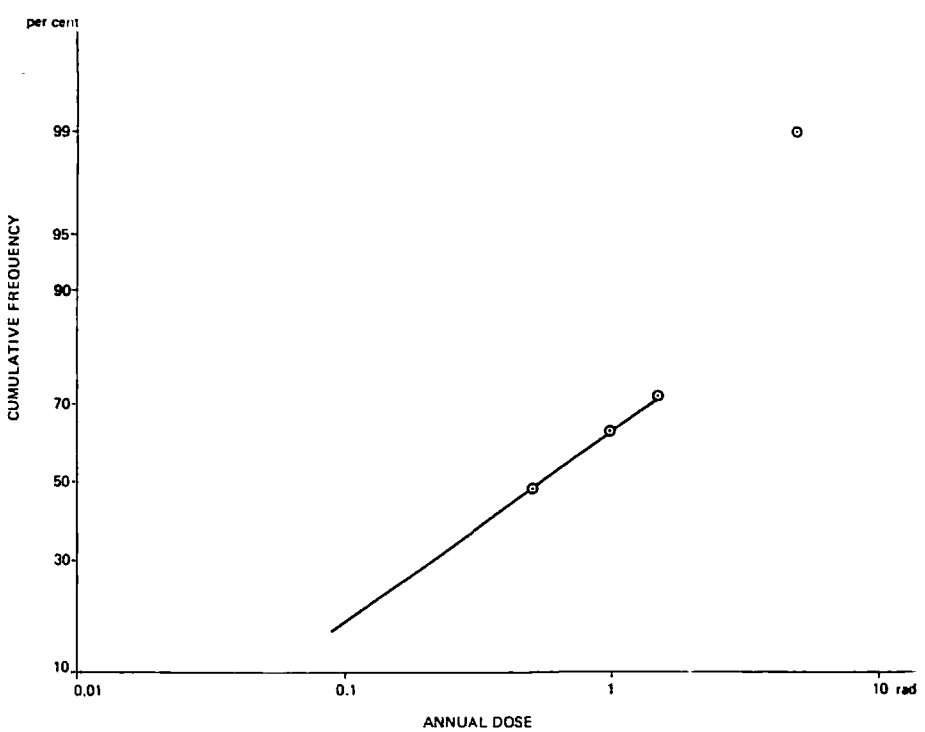

Figure VIII. Log-probability plot of annual doses to fuel-reprocessing workers at Windscale, United Kingdom, 1975

per unit energy produced would be 1.2 man rad per MWI(e) y. It cannot be sufficiently emphasized that this figure is historical and refers to past practices in the reprocessing of natural uranium, Magnox fuel elements. It is unlikely to be indicative of future collective doses per unit energy produced, particularly for oxide fuel reprocessing.

71. Some information has been provided by Belgium (73) on the dose distribution of workers in fuel fabrication, reprocessing and research for 1973. These data are shown in table 58 (appendix II), where the relevant category is "producers". The annual collective dose is 690 man rad with an Ω value of 1.8, and the annual average dose is 0.32 rad. Unfortunately, no indication of fuel throughput was available so no estimate can be made of collective dose per unit energy produced.

E. TRANSPORTATION

72. Occupational exposures of workers involved in transportation cannot be obtained directly, as many of these workers are not subject to individual monitoring and those who are may also be involved in other jobs within the industry. Dose calculations are, therefore, based on assumptions as to the dose rates at different distances from the packages and the times spent by workers in various operations. As an example, the doses to truck drivers from the transportation of unirradiated fuel have been estimated, using the following assumptions (115): the external dose rate at 1 m from the truck and in the vehicle cab are unlikely to exceed 0.1 and 0.01 mrad/h, respectively; the average distance of a journey is 1600 km; two drivers spend about 20 h in the cab and about 1 h outside the truck at a distance of 1 m during a journey.

73. With reasonable assumptions such as those given above, it can be estimated that each driver could receive about 0.3 mrem per shipment. Under normal conditions the estimated collective doses to transport workers for light-water reactors in the United States are as follows (man rad per MW(e) y): transport of unirradiated fuel, 10^{-5}; transport of spent fuel, $2\ 10^{-3}$; transport of solid waste, 10^{-3} (115). For GCRs in the United Kingdom, values of about $3\ 10^{-4}$ for the transport of unirradiated fuel and $2\ 10^{-3}$ for spent fuel have been estimated (123).

F. RESEARCH AND DEVELOPMENT

74. If the nuclear fuel cycle is to be considered as a whole, then some account must be taken of exposures in the research and development organizations devoted wholly or largely to servicing the industry. It is difficult to separate that part of the work of, for example, the United Kingdom Atomic Energy Authority or the United States Energy Research and Development Administration directly connected with the nuclear power industry from that part connected with other aspects of radioactivity. However, it seems likely that the bulk of the occupational exposures are connected with the nuclear power support work.

75. Overall dose distributions for United States Atomic Energy Commission employees and contractors are shown in table 59 (appendix II) for the years 1971-1973. These were obtained from the reports of the United States Atomic Energy Commission Central Repository of Industrial Radiation Exposure Information (111, 112, 113). Because of the very large percentage of doses in the 0-1 rad category and the large number of visitors included in the "contractor" category, it is unusually difficult to estimate average doses. A breakdown of the doses below 1 rad was attempted by Klement *et al.* (64) for the 1969 data relating to 102 918 employees, on the basis that the percentage in each division below 1 rad was the same as that reported for the Atomic Energy Commission and some agreement state licensees. A log-probability plot of these data is shown in figure IX, in which the points have been fitted by a straight line up to a dose of 2 rad. The annual average dose has been estimated from this line as 0.17 rad. Using the same technique on the 1973 data, with the visitors discounted on the basis that they rarely receive any dose, the log-probability plot of figure X is obtained, again with a straight-line fit up to a dose of 2 rad, from which an annual average dose of 0.14 rad is obtained. The annual collective dose is therefore 13 300 man rad with a value for Ω of 1.1.

76. Most of the nuclear research establishments in the United Kingdom are operated by the United Kingdom Atomic Energy Authority. Table 14 summarizes the doses from 1972 to 1974 (33). The collective dose recorded includes the estimated dose added for lost badges and is used to calculate the average dose. In addition, the Central Electricity Generating Board runs a research laboratory at Berkeley to support the commercial exploitation of nuclear power. The annual doses at this establishment are also summarized in table 14 (85). The detailed dose statistics from each organization are shown in tables 60 and 61 (appendix II). Since these data did not approximate a log-normal distribution very closely, the value of Ω was calculated directly from the dose distribution assuming mid-point doses for ranges above 1.5 rad. For the Central Electricity Generating Board values, only a small number of persons receive annual doses exceeding 1.5 rad, so changes in the Ω value are not necessarily indicative of a trend.

TABLE 14. OCCUPATIONAL DOSE AT RESEARCH AND DEVELOPMENT ORGANIZATIONS IN THE UNITED KINGDOM CONNECTED WITH THE NUCLEAR POWER INDUSTRY, 1972-1974

Organization	*Year*	*Annual collective dose (man rad)*	Ω	*Annual average dose (rad)*
United Kingdom	1972	5 020	2.1	0.71
Atomic Energy	1973	4 450	1.9	0.66
Authority	1974	3 960	1.9	0.57
Central				
Electricity	1972	126	0.5	0.24
Generating	1973	109	0.3	0.18
Board	1974	99	0.1	0.15

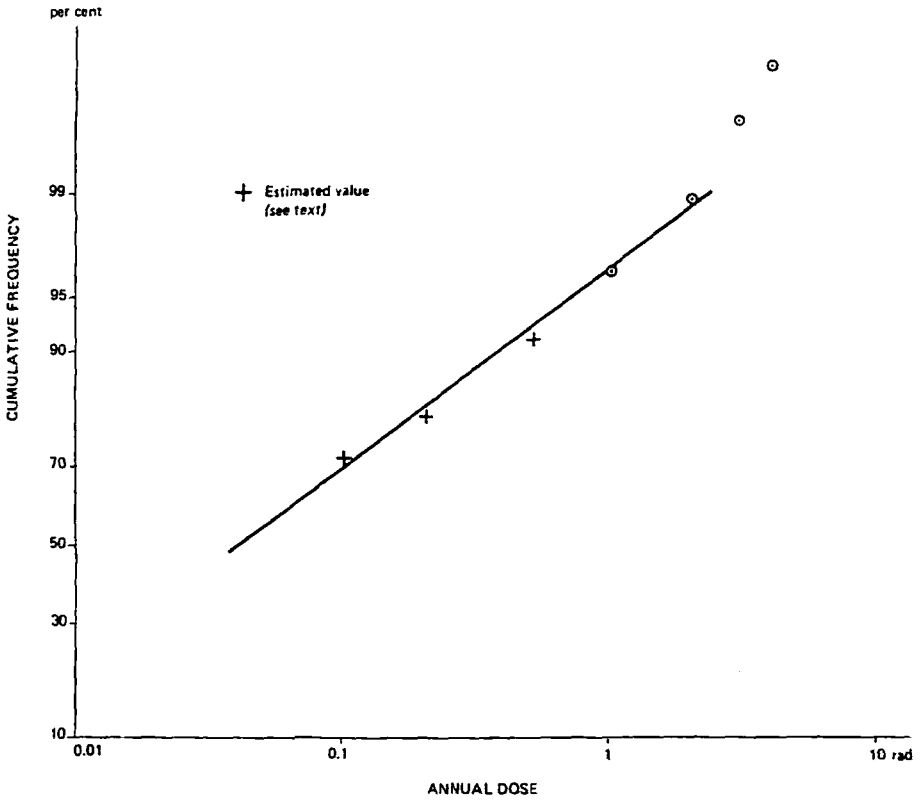

Figure IX. Log-probability plot of annual doses to radiation workers at United States Atomic Energy Commission sites, 1969

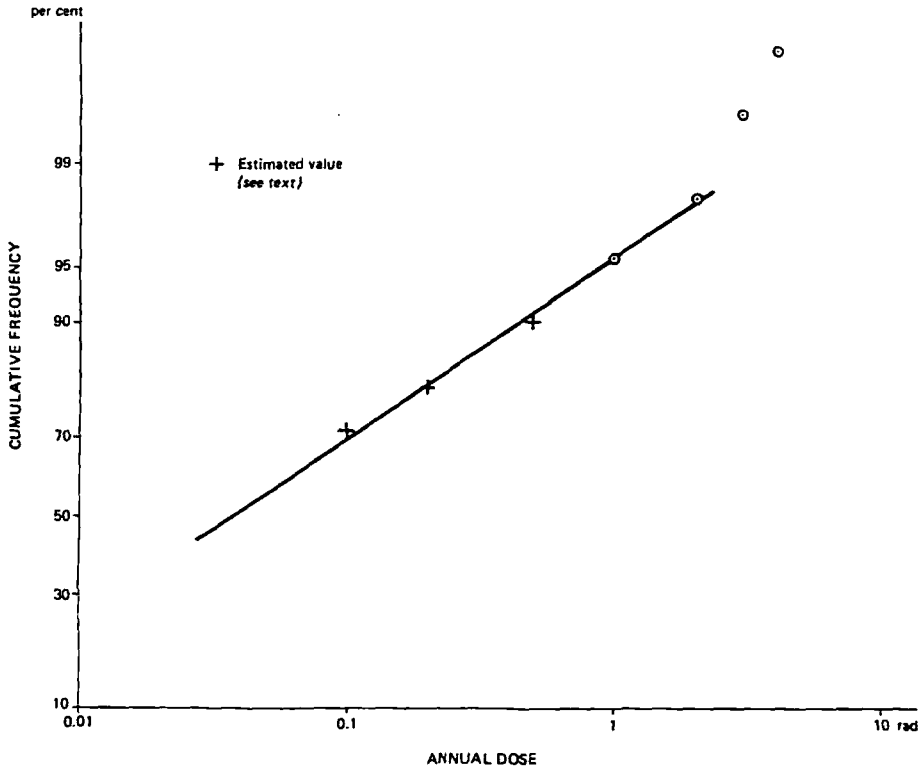

Figure X. Log-probability plot of annual doses to radiation workers at United States Atomic Energy Commission sites (excluding visitors), 1973

77. Data have been supplied by Argentina (21, 25) on the occupational dose received by personnel of the Comisión Nacional de Energía Atómica (CNEA) for the years 1968-1974. These are shown in detail in table 53 (appendix II) and the extracted parameters are given in table 15.

78. Data on average doses for the years 1970-1973 have been supplied for the Indian Department of Atomic Energy (50). These are shown in table 62 (appendix II). The annual average doses in 1972 and 1973 were approximately 0.75 rad and the annual collective doses in those two years about 4000 man rad.

TABLE 15. OCCUPATIONAL DOSES AT CNEA, ARGENTINA, 1968-1974

Year	Annual collective dose (man rad)	Ω	Annual average dose (rad)
1968	122	1.0	0.17
1969	87	0.4	0.10
1970	85	0.7	0.09
1971	116	0.9	0.12
1972	93	0.8	0.10
1973	200	1.7	0.22
1974	135	1.1	0.16

79. In Thailand, the annual average doses in 1974 at a research reactor and in general research were 0.58 rad. These data led to a value for the annual collective dose of 70 man rad (94). The complete data are shown in table 63 (appendix II).

80. The doses to atomic energy research workers in Israel are shown in table 64 (appendix II) (7). The average annual dose over the years 1970-1972 was about 0.1 rad, leading to an annual collective dose of 80-90 man rad.

G. SUMMARY OF COLLECTIVE DOSES FROM THE NUCLEAR POWER INDUSTRY

81. On the basis of the data supplied to the Committee and the analyses performed on these data, the portions of the nuclear fuel cycle which contribute the majority of the collective dose per unit energy generated are reactors, fuel reprocessing and the associated research and development. Uranium mining, milling and fuel fabrication together with transportation of both irradiated and unirradiated fuel give rise to a collective dose to the whole body per unit energy generated of only 0.2 man rad per MW(e) y. An additional collective dose to the lungs of uranium miners per unit energy generated of 0.1 man rad per MW(e) y is also delivered. Annual average doses and collective doses vary considerably both between different reactors in the same year and at the same reactor in different years. In general these variations are greater than those between different reactor types, e.g., light-water reactors and gas-cooled reactors. Nonetheless, a sufficient number of reactors are now in operation and have been operating long enough for an overall average figure for collective dose per unit energy generated to be derived, one that will not be susceptible to rapid change. It appears from all the information supplied that a value of 1.0 man rad per MW(e) y is a reasonable general figure. Fuel reprocessing undoubtedly will contribute significantly to the overall occupational dose, but so far it is not practised commercially on a wide scale. Based solely on the United Kingdom data, a value of 1.2 man rad per MW(e) y may be taken. This figure is only representative of past experience with the reprocessing of Magnox fuel and is unlikely to be appropriate for future reprocessing, particularly of oxide fuels. Making the assumption that all the doses received in such diverse organizations as the United Kingdom Atomic Energy Authority or the United States Energy Research and Development Administration are all received in support of the nuclear power industry, research and development emerges as the largest single contributor to the collective dose per unit energy generated with an average value for this quantity of 1.4 man rad per MW(e) y. This assumption is also cautious; even if it is true, the proportion of research and development required would be expected to decrease as the industry matures.

VI. DOSES IN OCCUPATIONS OTHER THAN THE NUCLEAR POWER INDUSTRY

82. As in chapter V, summaries or extracted parameters are presented in this chapter with more detailed information given in appendix II. It is also the intention to present in this chapter overall summaries of the situations; more detailed information on particular types of workers, especially those receiving higher than average doses, is presented in chapter VII.

83. In the case of the nuclear power industry, the beneficial output could readily be defined as electricity supplied to the grid. In this section, however, the beneficial output cannot be so easily identified, and even where it could be identified, data on the magnitude of the output and its relation to doses are normally not supplied.

A. MEDICAL USES OF RADIATION AND RADIOACTIVITY

84. It is perhaps in the process of assessing doses to medical workers that the difficulties noted in paragraphs 9 and 10 become most acute. The doses received by different parts of the body will often be quite different, and it is not always clear to what organ or organs the reported dose corresponds. The Committee has perforce had to assume that reported doses with no other indication were average whole-body doses. In all countries which reported, monitoring of doses to workers involved with medical uses of radiation or radioactivity is carried out by a number of establishments ranging from individual hospitals to large commercial or governmental specialized personnel-monitoring services. Usually, the results are reported to the employer but are not collated nationally. That, and the fact that medical workers are employed in small numbers in each of a large number of establishments rather than concentrated in a few easily identified centres as in the nuclear power industry, means that the collection of dose information is difficult. Ensuring that the data is comprehensive and representative is almost impossible. Hence, in this section the Committee can only present that information which is available, and it is hoped that the picture it forms is not too distorted.

85. The problem is exemplified in the information supplied by the United Kingdom, which does at least provide an estimate of the magnitude of the total problem (110). Medical workers in the United Kingdom are monitored by a number of different laboratories and individual hospitals. Data were obtained from some of these. It was estimated that there were at least

18 000 medical workers involved with radiation: there could be several thousand more. The annual dose distribution for 6552 of these workers in 1974 is shown in figure XI (23, 27, 31, 43, 69, 81, 105, 109, 110). The annual collective dose to these workers is 1370 man rad with a Ω value of 0.90 and an annual average dose of 0.21 rad. If it is assumed that these parameters are representative and that the total number of workers is 20 000, then the total annual collective dose to medical workers in the United Kingdom in 1974 was about 4000 man rad.

86. Some local or sample surveys have been reported for the United States. Figure XII shows the dose distributions of monitored individuals in the state of Illinois, both in hospitals and clinics and in the surgeries of doctors or dentists (16). The hospital and clinic population has enough people in the higher dose range for the presumed effect of the maximum permissible dose limit to be seen above annual doses of 1 rad. The annual average dose reported for these hospitals and clinics in 1973 was 0.074 rad; however, reporting is required in Illinois only for those employees whose quarterly doses may exceed 0.312 rad (64). Thus, the actual distribution of all monitored workers would probably be on a line lying to the left of that in figure XII. Figure XIII shows a sample of three annual recorded dose distributions for the smaller population of Mercy Hospital, Pittsburgh. All the dose distributions at this hospital from 1965 to 1974 were consistent with log-normal functions (103).

87. In the survey of ionizing radiation doses in the United States (64), it was recognized that "the most tenuous estimate developed in this study is the mean annual dose of non-federal employees exposed during the use of radiation in diagnostic and therapeutic medical and dental radiology". The data available to the authors consisted of information from three states, including the data from Illinois cited above. A survey in 1969 of 663 medical x-ray workers in the state of Wisconsin indicated an average collective dose rate of 4.15 man rad per week (64). Assuming that each individual worked for 50 weeks per year, the annual average dose would be 0.313 rad. The data for Illinois in 1970 shown in table 65 (appendix II) give an estimated annual average dose of 0.324 rad to medical workers. In the state of Maine in 1965, the average monthly dose for all categories of radiation workers was 0.020 rad. Using the foregoing data, Klement *et al.* assigned an annual average dose of 0.32 rad per non-federal medical x-ray worker (64); this mean was applied to 194 541 medical x-ray workers.

88. A survey of personnel occupationally exposed in radium therapy was conducted by the state government of Wisconsin and made available to the United States Public Health Service. From this study it was estimated (64) that there may be in the United States up to 38 000 individuals occupationally exposed in radium treatment who are not otherwise reported. The estimated number of radium treatments in Wisconsin was 800 per year. From 37 treatments monitored, the average dose was 0.5 rad per treatment or 400 man rad y^{-1} from all treatments. This resulted in an annual average dose of 0.54 rad for the 740 medical workers in Wisconsin. This average was assumed to apply nationally.

89. A more recent survey of occupational doses to personnel in United States nuclear medicine departments

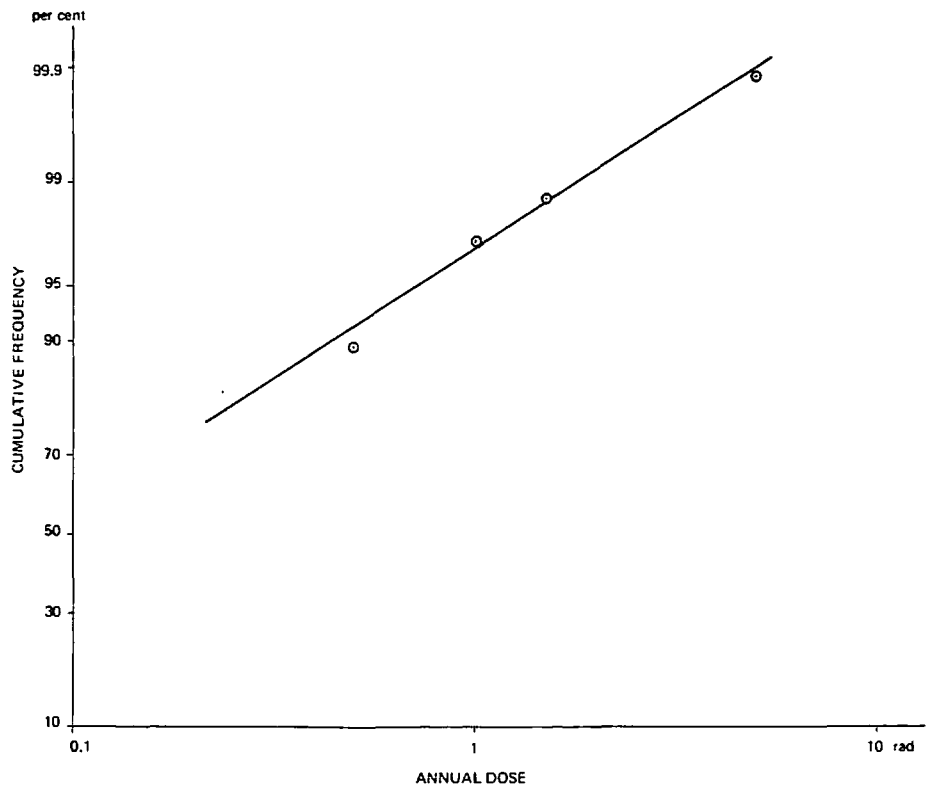

Figure XI. Log-probability plot of the annual doses to a sample of 6552 medical workers in the United Kingdom, 1974

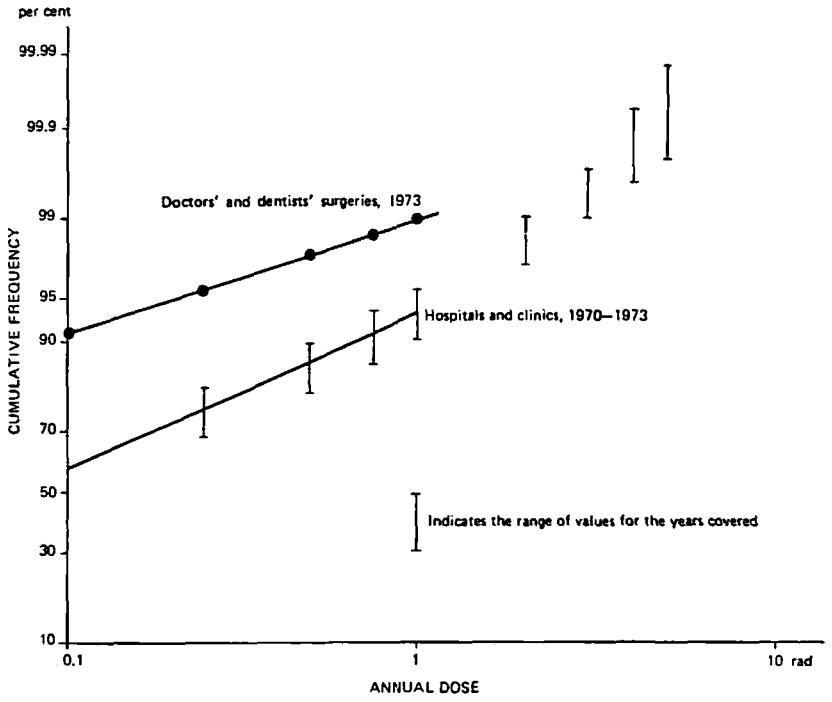

Figure XII. Log-probability plot of annual doses to workers at medical and dental institutions in the state of Illinois, United States, 1970-1973

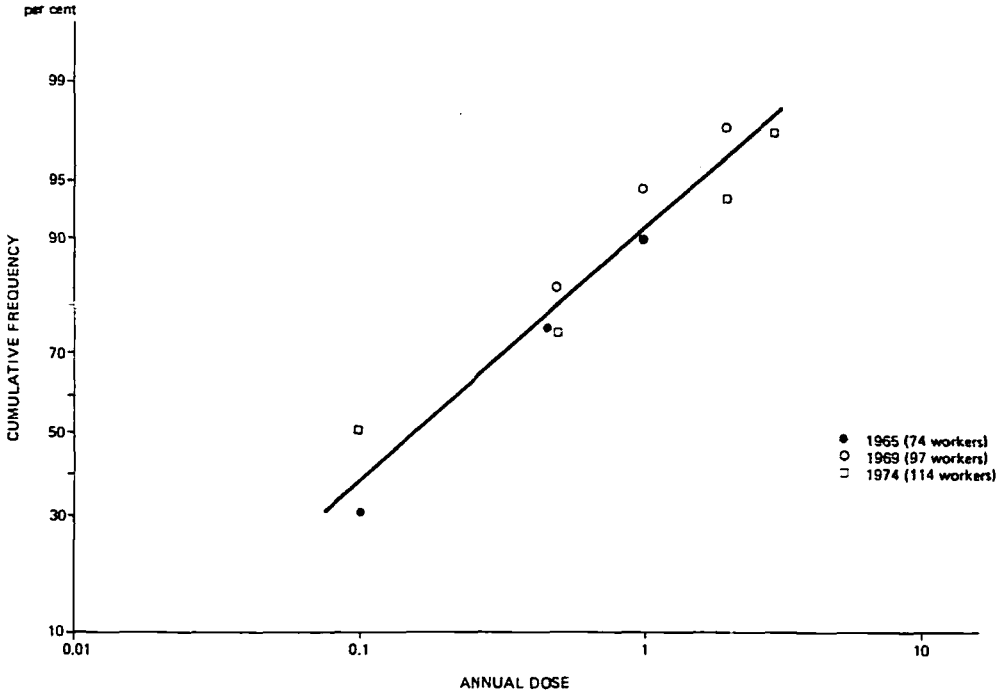

Figure XIII. Log-probability plot of annual doses to workers at Mercy Hospital, Pittsburgh, Pennsylvania, United States, 1965, 1969 and 1974

has been carried out by the Scientific Committee on Radiation Protection of the American Association of Physicists in Medicine (8). Forty-seven hospitals were included in the study; both teaching and non-teaching institutions were included in varied geographical locations, although no attempt was made to obtain a representative sample of the whole country. The method was to send a questionnaire and analyze the results. One outstanding feature of this survey was that an attempt was made to relate the doses to some measure of the workload. The measure selected was the total amount of ^{99m}Tc injected. It was assumed tha the total work of the department results in the total collective dose to the workers, regardless of the distribution of work and dose among the personnel. As part of the questionnaire, it was established that in most institutions ^{99m}Tc accounted for more than 90 per cent of the total activity of radionuclides administered, so the use of this as a measure seemed reasonable. Some results of the survey are shown in table 16; each figure in this table is an independent average of the values reported for that quantity. The total amount of ^{99m}Tc injected and therefore the amount injected per employee increased by a factor of four from 1968 to 1973. The collective

TABLE 16. SOME RESULTS OF A SURVEY OF NUCLEAR MEDICINE DEPARTMENTS OF 47 HOSPITALS IN THE UNITED STATES, 1968-1973

	1968	*1969*	*1970*	*1971*	*1972*	*1973*
Average number of full-time employees in nuclear medicine	7.52	8.23	6.52	6.48	7.06	7.38
Annual average collective dose (man rad)	1.68	1.89	2.39	2.47	2.70	2.77
Annual average individual dose (rad)	0.38	0.37	0.45	0.45	0.49	0.48
Annual average activity of ^{99m}Tc injected (Ci)	6.6	8.2	11.0	13.4	16.5	25.8
Annual average collective dose per unit ^{99m}Tc injected (man rad Ci^{-1})	0.47	0.34	0.35	0.27	0.30	0.11

dose did not increase proportionately, with the result that the average dose per unit workload decreased by about 70 per cent from 1970 to 1973. The results for 1968 and 1969 may be biassed, as only a small number of hospitals responded for these years. Tentative correlations were established between higher doses per unit workload and overcrowding (laboratories with less than 14 m^2 per person) and small numbers of employees (less than five). It was also noted that over the 47 hospitals the collective dose per unit workload varied by more than a factor of 60. The higher values could be reduced significantly if more care were taken and more attention paid to the details of shielding and patient positioning. It was concluded that with proper attention to good radiation protection practices, it appears feasible to reduce collective doses to nuclear medicine personnel per unit quantity of ^{99m}Tc injected to an annual average of less than 0.05 man rad Ci^{-1}. Despite the usefulness of this survey, it did not give a figure for the overall doses in the United States. However, Brodsky has estimated the average annual dose to nuclear medicine workers as 0.5-0.6 rad, leading to a total annual collective dose of 7000 man rad (17).

90. The Committee has received a great deal of information from the Health Protection Branch of the Health and Welfare Department in Canada (4). The data are grouped according to job classification and provide comprehensive information for 1974. They are summarized in table 17, which is based on a log-probability analysis of each set of figures. From this it can be seen that the largest annual collective dose, over 500 man rad, is due to diagnostic radiology, with a further 73 man rad from therapeutic radiology. A collective dose of 160 man rad is received by nurses, ward aides and orderlies. Physicians received 80 man rad and technicians 87. All other contributions to the collective dose were relatively low. The average annual doses were relatively low in all cases (<0.2 rad) and none of the Ω values were very much greater than 1.0, indicating that the collective dose was received at annual doses roughly similar to those of the reference distribution. The total annual collective dose for human medical work (excluding dentistry) in Canada in 1974 is about 1000 man rad.

91. Some information has been supplied on film badge doses in Denmark in 1974 (118). This is reproduced in table 66 (appendix II); the part relative to medical workers is summarized in table 18. Since the data related to the distribution of doses among the film badges rather than among the people, it was not possible to calculate a value for Ω for individual groups. The highest collective doses were to workers in hospital x-ray departments and radium centres, who received 165 and 114 man rad, respectively. The highest annual average dose, 0.3 rad, was recorded at the radium centres. The total annual collective dose to all medical workers (excluding dentistry) was 355 man rad.

TABLE 17. SUMMARY OF OCCUPATIONAL DOSES TO MEDICAL AND ALLIED WORKERS IN CANADA FOR 1974

Occupational classification	*Annual collective dose (man rad)*	Ω	*Annual average dose (rad)*
Physician	81	1.1	0.05
Radiological technician (diagnostic)	398	0.5	0.06
Radiological technician (therapeutic)	49	1.1	0.14
Radiologist (diagnostic)	111	0.7	0.09
Radiologist (therapeutic)	24	1.3	0.19
Medical physicist	10	1.3	0.09
Laboratory technician	31	0.6	0.02
Isotope technician	56	1.0	0.15
Nurse	128	1.2	0.05
Ward aide or orderly	32	0.5	0.03
Gynaecologist	1	0.7	0.04
Dentist	37	0.3	0.01
Dental hygienist[a]	14	1.0	0.10
Chiropractor	11	0.4	0.02
Veterinarian	13	0.4	0.02
Other[a]	74	1.3	0.03

[a] Data for this classification do not fit well a log-normal.

TABLE 18. SUMMARY OF OCCUPATIONAL DOSES TO MEDICAL AND ALLIED WORKERS IN DENMARK FOR 1974 (EXCLUDING TWO ESTABLISHMENTS)

Category	*Number of departments*	*Annual collective dose (man rad)*	*Annual average dose (rad)*
X-ray departments (hospitals)	127	165	0.07
Surgical departments (hospitals)	14	8	0.04
Other departments (hospitals)	11	7	0.05
Hospitals in Greenland	19	1	0.01
Medical practitioners	21	3	0.03
Lung clinics	40	7	0.03
Isotope laboratories	122	30	0.02
Radium centres	21	114	0.29
Dermatologists	30	15	0.14
Chiropractors	63	0	0.00
Public dental clinics	10	1	0.01
Veterinary x-ray personnel	72	2	0.02

92. A general survey of doses in the personnel monitoring service provided by the SCPRI in France has been received by the Committee (88). The complete data are shown in tables 67 and 68 (appendix II). It should be noted that a reading of less than 10 mrad is recorded as zero (98). A summary of the medical doses for 1975 is given in table 19. From these results for 20 000 workers, it can be seen that the major part of the collective dose is due to radiodiagnosis. The annual average dose attributable to all radiodiagnostic practices (including dentistry) is of the order of 0.13 rad. All the establishments practising radiodiagnosis or radiotherapy in France were not included in the survey; an extended survey of 32 000 workers in 1973 is mentioned as giving almost the same overall annual average dose, although it contained a higher proportion of industrial workers (98). The Ω values for most groups are below 1.0; only four groups have a value appreciably greater than 1.0, showing that some high doses, due generally to isolated incidents, can make an excessive contribution to the collective dose when the great majority of individual doses are low. Some data were also supplied on internal doses from tritium to French medical workers (88). Annual average doses from 1968 to 1976 were all less than 0.02 rad, and no annual doses exceeding 1.5 rad were recorded. The data are shown in table 69 (appendix II).

TABLE 19. SUMMARY OF OCCUPATIONAL DOSES TO 20 517 MEDICAL WORKERS IN FRANCE, 1975

Type of establishment	*Number of workers*	*Annual collective dose (man rad)*	Ω	*Annual average dose (rad)*
Radiodiagnostic				
Hospitals	6 787	1 220	0.9	0.18
Private specialized medicine, clinics	1 378	300	0.8	0.22
Private radiology	1 101	240	1.4	0.22
Private general medicine	625	90	1.0	0.15
Industrial medicine, dispensaries	4 194	210	0.6	0.05
Dental surgeries, stomatology	2 661	110	0.2	0.04
Total	16 746	2 170	0.8	0.13
Radiotherapeutic				
Conventional	713	260	0.7	0.36
Curie	484	100	1.3	0.20
Cobalt	797	130	1.2	0.17
High-energy	456	60	0.5	0.14
Nuclear medicine	1 321	210	0.2	0.16

93. The total number of persons in New Zealand whose exposures are monitored are shown in table 70 (appendix II) (127). The largest numbers are engaged in medical work, principally diagnostic radiology, dentistry and therapy. There are in addition other users, but when these have been monitored the doses have been found to be consistently low. The annual average dose for all categories of users was estimated to be 0.11 rad. This leads to an annual collective dose from human medical procedures of about 300 man rad. For certain categories, notably medical diagnosis and therapy, the mean doses are greater than 0.1 rad.

94. As part of an exercise to establish lifetime doses, a considerable amount of data have been received from Australia (106). These data on medical and allied workers are shown in table 20. All the annual average doses are well below 0.5 rad, with many groups less than 0.1 rad. For workers occupied in medical and dental procedures including radiology, dermatology and nuclear medicine, the weighted mean annual dose for the samples tabulated is 0.11 rad; multiplying this value by the number of Australian workers in these occupations (table 1) gives an annual collective dose of 1400 man rad.

95. Some information on dose to workers with x rays and isotopes has been received from South Africa (9). These data are summarized in table 21. The parameters were derived by a log-normal fit to the dose distribution.

96. A breakdown of annual doses in 1974 according to occupation has been provided by Switzerland (30). These are shown in table 71 (appendix II), and the doses relevant to medical work are summarized in table 22.

97. Data from Thailand are shown in table 63 (appendix II) (94). The annual collective doses in 1974 due to radiography, radium use and nuclear medicine were 200, 77 and 69 man rad, respectively. The highest annual average dose was 0.46 rad, to radium workers.

98. Annual average doses have been supplied for persons employed in the medical field in West Berlin, and in the states of Niedersachsen, Hamburg, and Schleswig-Holstein in the Federal Republic of Germany from 1969 to 1974. The data are shown in table 74 (appendix II) (10a). The mean values were not determined by the Committee from a log-normal plot, but were reported to have been calculated by arithmetical mean value formation, omitting the two extreme ends of the dose distribution. The mean values are quoted separately for workers with radioactive substances and radiation, and workers with x rays only. The fluctuation of the average with time and place is considerable; however, a tendency to decrease over the years can be observed. The mean values for workers with x rays are lower than for those workers using radioactivity and radiation.

99. A very comprehensive set of information on occupational doses in the German Democratic Republic is available for the years 1970-1972 (65, 66, 67). Some of these data are shown in table 72 (a, b and c) in appendix II. A typical analysis of the doses to medical workers in 1972 is shown in table 23.

B. INDUSTRIAL USES OF RADIATION AND RADIOACTIVITY

100. Very few countries provided comprehensive summaries or estimates of doses due to all industrial uses of radiation or radioactivity. It is generally recognized that industrial radiography gives rise to some of the highest average individual doses and to a large proportion of the overexposures. This particular occupational group and some others are covered in more detail in chapter VII.

TABLE 20. AVERAGE OCCUPATIONAL DOSES TO MEDICAL AND ALLIED WORKERS IN AUSTRALIA

Occupational classification	*Number of workers in sample*		*Annual average dose (rad)*	*Fraction of dose from sealed gamma sources*[a] *(%)*
	Male	*Female*		
Radiology				
Hospital radiologists, including trainees and medical practitioners	184	15	0.16	
Radiologists in clinics and private practices	59	1	0.31	
Radiographers, hospital and private practices	500	633	0.14	
Assistants, nurses, porters etc.	53	359	0.09	
Dermatology, gynaecology and radiotherapy				
Dermatologists	19	–	0.10	30
Assistants, including therapy radiographers	–	9	0.18	70
Radiotherapists and gynaecologists including trainees	29	7	0.16	90
Therapy radiographers, physicists	57	94	0.10	80
Assistants	16	37	0.08	90
Nurses of patients with sealed sources *in situ*	1	228	0.44	100
Nuclear medicine				
Nuclear radiographers and assistants, including trainees	247	234	0.08	35
Dentistry				
Dentists	343	74	0.01	
Dental nurses and assistants	66	505	0.01	
Chiropractic				
Chiropractors	96	7	0.03	
Veterinary				
Veterinary surgeons	111	16	0.02	
Assistants	16	89	0.01	

[a]Except for last entry, which pertains to gamma sources of energy >160 keV.

TABLE 21. OCCUPATIONAL DOSES TO X-RAY WORKERS AND ISOTOPE USERS IN SOUTH AFRICA, 1974

Category	*Number of workers*	*Annual collective dose (man rad)*	Ω	*Annual average dose (rad)*
X-ray workers	5 090	336	0.6	0.07
Isotope users	1 832	167	0.8	0.09

TABLE 22. OCCUPATIONAL DOSE TO MEDICAL WORKERS IN SWITZERLAND, 1974

Type of establishment	*Annual collective dose (man rad)*	Ω	*Annual average dose (rad)*
Hospital	249	1.0	0.14
Clinic	35	1.4	0.05
Medical private practice	132	1.0	0.05
Dental private practice	284	0.5	0.09
Chiropractic	1	–	0.02
Other	36	0.3	0.04

TABLE 23. OCCUPATIONAL DOSES TO MEDICAL WORKERS IN THE GERMAN DEMOCRATIC REPUBLIC, 1972

Category	*Number of workers*	*Annual average dose (rad)*	Ω	*Annual collective dose (man rad)*
X ray	17 028	0.02	0.9	331
Brachytherapy	551	0.54	1.5	298
Radionuclides (excluding brachytherapy)	440	0.20	0.4	86
Accelerator	13	0.02[a]	0	0.3[a]
Deep therapy	132	0.42	2.7	55
Total	18 164	0.06	0.7	1 131

[a]Estimated by comparison of the distribution with x-ray workers, since there were insufficient data to fit a log-normal distribution.

101. For the United Kingdom, it has been estimated (109) that there are approximately 18 000 industrial workers occupationally exposed to radiation, of whom 7000 are industrial radiographers (5). The annual dose distribution is available for a sample of approximately

10 per cent of these 18 000 workers (81, 109); it is given in table 73 (appendix II). It was noted, however, that the proportion of industrial radiographers in the sample was probably less than the overall proportion. With this reservation, the annual average dose to industrial workers in the United Kingdom can be estimated from figure XIV, which is a log-probability plot of the data, as 0.43 rad, and the annual collective dose to all 18 000 workers as 7700 man rad, with value for Ω of 1.1.

102. Log-probability plots of the data for all categories of United States Atomic Energy Commission and agreement state licensees are shown in figures XV and XVI (64). Curve A in figure XV represents the data for those licensees who report (62 090 individuals), and Curve B (155 090 individuals) includes the estimated number who do not report, assuming that the annual doses are less than 2 rad. Good agreement with a log-normal distribution is obtained for these large samples. Log-probability plots of the annual dose to two categories of United States Atomic Energy Commission licensees are shown in figures XVII and XVIII (16). Figure XVII shows the results for by-product material licensees in manufacturing and distribution from 1971 to 1974 and figure XVIII, for industrial radiographers over the same period. Those included were the licensees who reported all monitored personnel, not only those receiving annual doses greater than 1.25 rad. Since this is only a partial sample, no analysis has been performed on the values, but Brodsky estimated that the data fitted a log-normal distribution up to annual doses of 1 rad (16). Klement *et al.* (64) estimated the doses to the reporting United States Atomic Energy Commission licensees and agreement state licensees shown in table 24 for 1969/70. If these are added, the total annual collective dose from industry, radiography and "unspecified" is estimated as 5925 man rad delivered at an average dose of 0.19 rad. More recent estimates for 1974 have been made by the United States Nuclear Regulatory Commission (18). The dose distributions for the two categories of covered licensees, industrial radiography and manufacturing and distribution are shown in table 75 (appendix II).

TABLE 24. SUMMARY OF ESTIMATED DOSES TO INDUSTRIAL WORKERS IN THE UNITED STATES, 1969/70

Category	*Number of workers*	*Annual collective dose (man rad)*	*Annual average dose (rad)*
Reporting Atomic Energy Commission licensees			
Industrial	13 331	2 140	0.16
Radiography	1 894	752	0.40
Not specified	7 815	1 020	0.13
Reporting agreement state licensees			
Industrial	6 479	1 490	0.23
Radiography	1 174	294	0.25
Not specified	731	226	0.31
Total	31 424	5 920	0.19

103. Some information has been supplied on average doses to industrial workers in Australia (106); it is summarized in table 25. The average doses are in all cases rather low, even for the group which included industrial radiographers.

104. A considerable body of data has been supplied from Canada (4) on doses to non-medical industrial workers. The dose distributions have been fitted by log-normal distributions and the resultant parameters are shown in table 26.

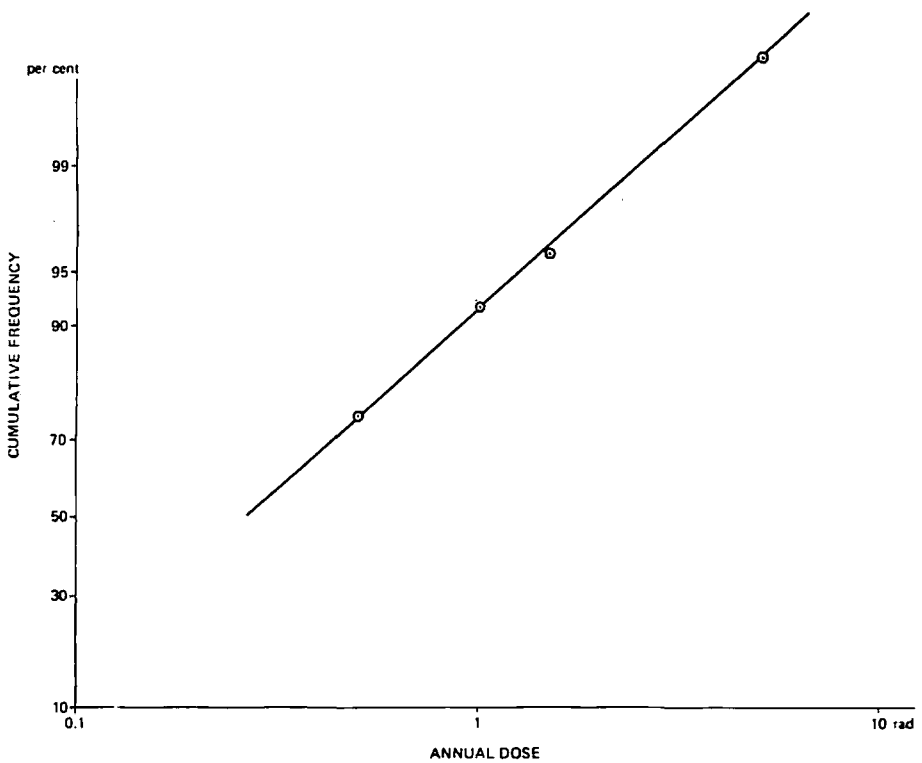

Figure XIV. Log-probability plot of the annual doses to a sample of industrial workers in the United Kingdom, 1974

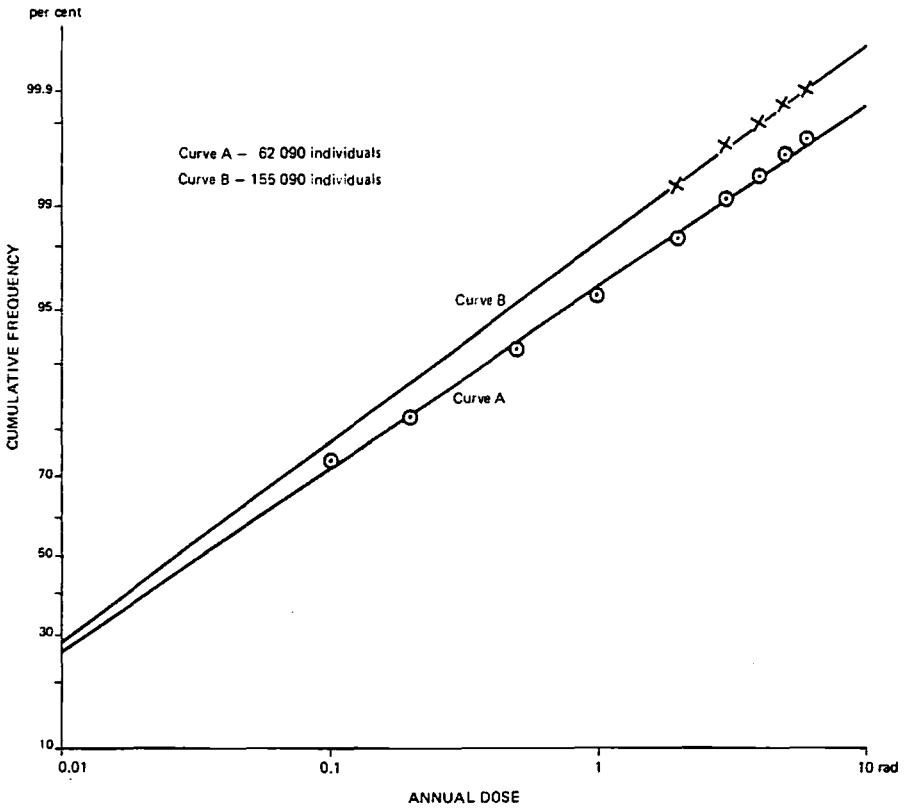

Figure XV. Log-probability plot of annual doses to radiation workers employed by United States Atomic Energy Commission licensees, 1969

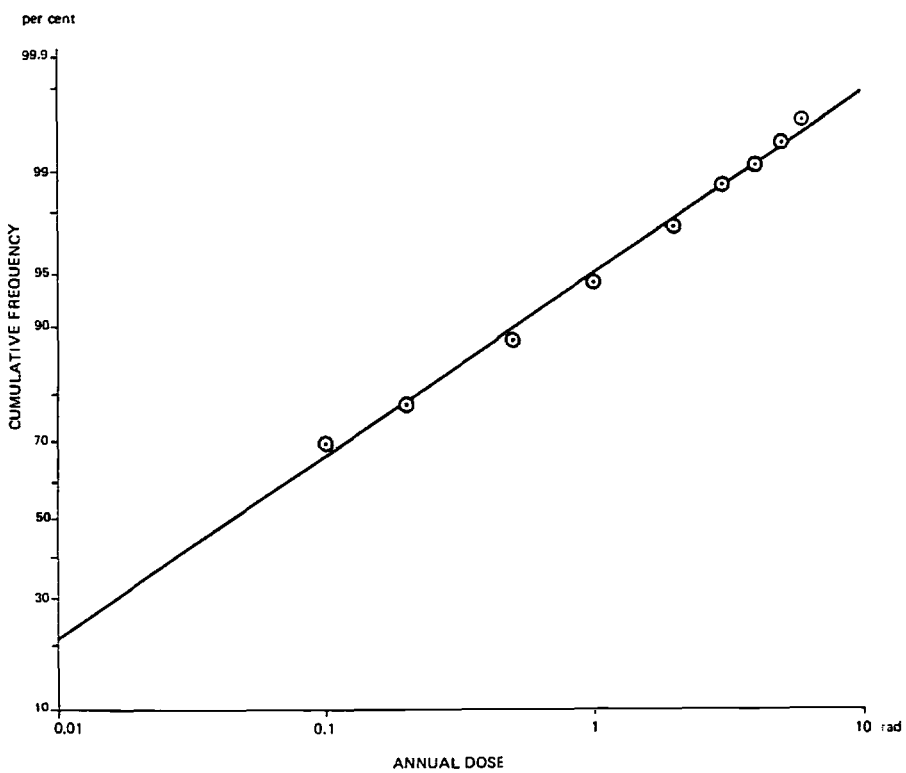

Figure XVI. Log-probability plot of annual doses to radiation workers employed by United States agreement state licensees, 1969

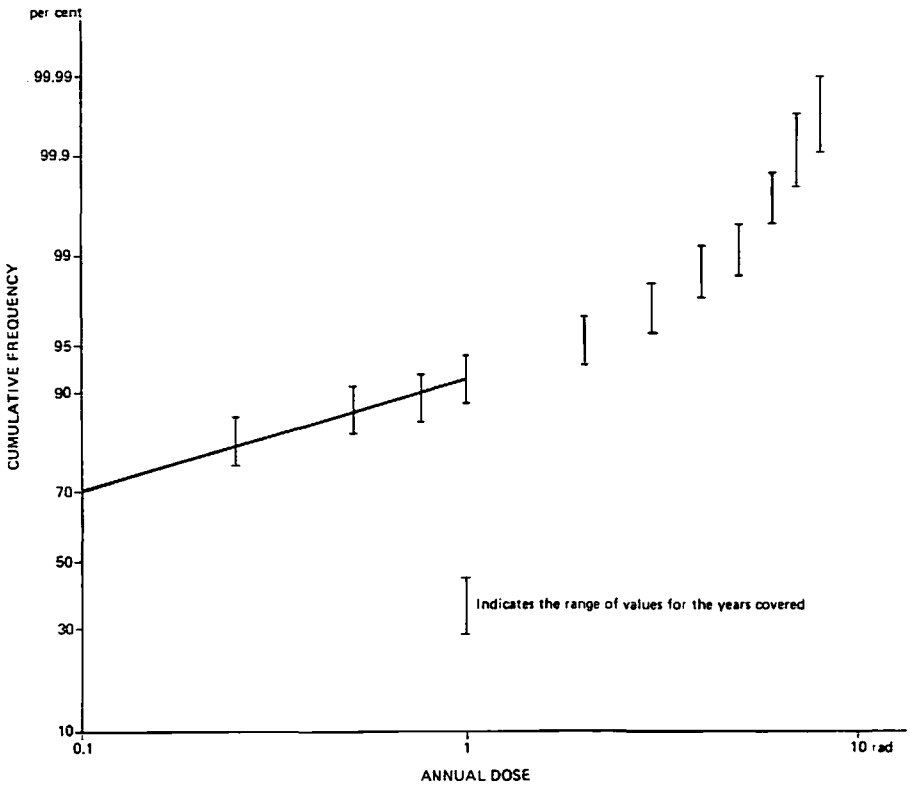

Figure XVII. Log-probability plot of annual doses to by-product licensees in manufacturing or distribution, United States, 1971-1974

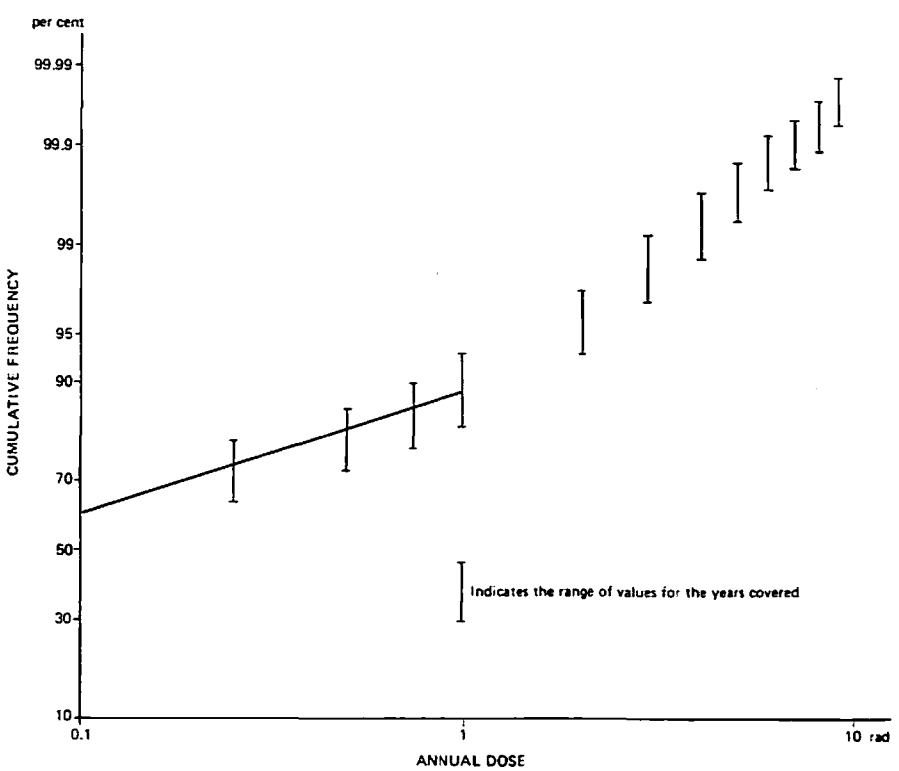

Figure XVIII. Log-probability plot of annual doses to industrial radiographers, United States, 1971-1974

TABLE 25. AVERAGE OCCUPATIONAL DOSES TO INDUSTRIAL AND RESEARCH WORKERS IN AUSTRALIA

Occupational classification	*Number of workers in the sample*		*Annual average dose (rad)*	*Fraction of dose from specified sources (%)*
	Male	*Female*		
Research				
Users of x-ray analysis units, electron microscopes, etc.	341	26	0.01	
Industry				
Users of enclosed installations[a] or "quality control" sources, e.g., package monitors, thickness gauges etc.	341	92	0.01	
Users of open installations,[a] including industrial radiographers	413	12	0.24	Sealed gamma >160 keV, 80
Users of tracers	265	85	0.06	Gamma >160 keV, 95
Installation and maintenance engineers	147	–	0.02	

[a]As defined in ICRP Publication 15 (52a).

TABLE 26. SUMMARY OF OCCUPATIONAL DOSES TO INDUSTRIAL WORKERS IN CANADA, 1974

Occupational classification	*Annual collective dose (man rad)*	Ω	*Annual average dose (rad)*
Dial painter[a]	4	2.8	0.40
Instructor	1	0.2	0.01
Instrument technician	62	2.1	0.10
Laboratory technician	97	1.9	0.07
Oil logger	14	1.5	0.09
Radiography	369	2.0	0.43
Scientist and engineer (field)	61	2.0	0.17
Scientist and engineer (laboratory)	26	1.2	0.02
Other technician[a]	1 230		0.53
Office staff[a]	24	1.8	0.02

[a]Data for this classification did not fit well a log-normal.

105. Some information on industrial workers in Denmark is included in table 66 (appendix II). The results are summarized in table 27 (118).

106. The data supplied on the German Democratic Republic and shown in table 72 (a, b and c) in appendix II includes some information on doses to industrial workers. These workers are divided into those using x rays and those using radionuclides, with a small number using accelerators. None of those using accelerators received annual doses exceeding 0.5 rad in the years 1970-1972. The results for the other workers are summarized in table 28 (65, 66, 67).

107. Information on occupational doses in France has been provided by SCPRI (88), and is given in tables 67 and 68 (appendix II). A summary is given in table 29. The average doses and Ω values are low; this is true both for radiography installations and for work with unsealed sources. In general, industrial and research workers do not incur high doses and the low Ω values demonstrate the rarity of incidence. For all other non-medical

TABLE 27. SUMMARY OF OCCUPATIONAL DOSES TO INDUSTRIAL WORKERS IN DENMARK, 1974

Type of establishment	*Number of departments*	*Annual collective dose (man rad)*	*Annual average dose (rad)*
Industrial x-ray and gamma	44	26	0.11
X-ray firm	15	14	0.07
X-ray analysis	30	1	0.00

TABLE 28. SUMMARY OF DOSES TO INDUSTRIAL WORKERS IN THE GERMAN DEMOCRATIC REPUBLIC, 1970-1972

Year	*Category*	*Number of workers*	*Annual average dose (rad)*	Ω	*Annual collective dose (man rad)*
1970	X-ray	1 725	0.03	1.1	57
	Radionuclide	1 697	0.08	1.0	128
1971	X-ray	1 790	0.02[a]	0.0	36[a]
	Radionuclide	1 864	0.05	1.4	102
1972	X-ray	1 619	0.03	0.7	48
	Radionuclide	1 740	0.08	0.5	131

[a]Mean dose estimated by comparison with other years, since there were insufficient data to fit a log-normal distribution.

TABLE 29. SUMMARY OF OCCUPATIONAL DOSES TO 2579 INDUSTRIAL AND RESEARCH WORKERS IN FRANCE, 1975

Type of work	*Number of workers*	*Annual collective dose (man rad)*	Ω	*Annual average dose (rad)*
Industrial radiography (x and gamma)	839	33	0.3	0.04
Research and industrial application of unsealed sources	752	26	0.4	0.03
Other non-medical	988	86	1.6	0.09

applications (e.g., crystallography, neutron sources, particle accelerators) the average dose is also low but with a relatively higher Ω value because of a small number of incidents.

108. Information on the doses to radiography workers using x rays and gamma sources has also been supplied by Hungary (15). The data are summarized in table 76 (appendix II). Log-probability analysis shows annual average doses of 0.35 rad for gamma radiographers and only 0.06 rad for the x radiographers. The Ω value of the distributions were 1.9 for gamma radiographers and 1.3 for x radiographers. The annual collective dose from all radiography was 480 man rad.

109. A summary of doses to industrial workers in Switzerland in 1974 is included in table 71 (appendix II) (30). The annual average dose is given as 0.23 rad, with an annual collective dose of 60 man rad. The Ω value is 0.6. A more detailed set of data for 1969-1975 is shown in table 77 (appendix II) (60, 61). Typical annual collective doses in recent years are about 100 man rad at an Ω value of 0.1-0.3.

110. Data are available for the states of Niedersachsen, Hamburg and Schleswig-Holstein in the Federal Republic of Germany, and for West Berlin for the years 1969 to 1974. They are shown in table 74 (appendix II) (10a). The reported average dose values are mean values which were determined from the dose distribution by arithmetical mean value formation, omitting the two extreme ends of the dose distribution. The mean values refer to all technical applications of radioactivity and radiation, including the nuclear industry. The doses are quoted separately for workers with radioactivity and radiation and for workers with x rays only. For the medical field, as was noted in paragraph 98, the doses show considerable fluctuations with time and place; the average dose values to workers from x rays are nearly always lower than those to workers from radiation sources.

C. USES OF RADIATION AND RADIOACTIVITY BY MILITARY PERSONNEL

111. The majority of involvement with radiation and radioactivity by military personnel is concerned with the same activities as civilian personnel: operation and maintenance of nuclear reactors, medical treatment and procedures, radiography etc. It is of interest to compare the doses to these categories of military workers with the doses to their civilian equivalents, where they can be made available.

112. Klement *et al.* (64) give data from the United States for different occupational groups. The distribution of doses varies with the group. Although in all cases the majority of workers receive low doses, the percentage receiving very low doses is higher for the army and air force personnel. Log-probability plots of these data for the army and the air force are shown in figures XIX and XX, in which the lines are the result of least-squares fitting to the data points. The number of workers who might be exposed to ionizing radiation is high, 22 790 and 34 975 for the army and air force, respectively, but the number of workers receiving annual doses more than 100 mrad is given as 298 and 330 in the

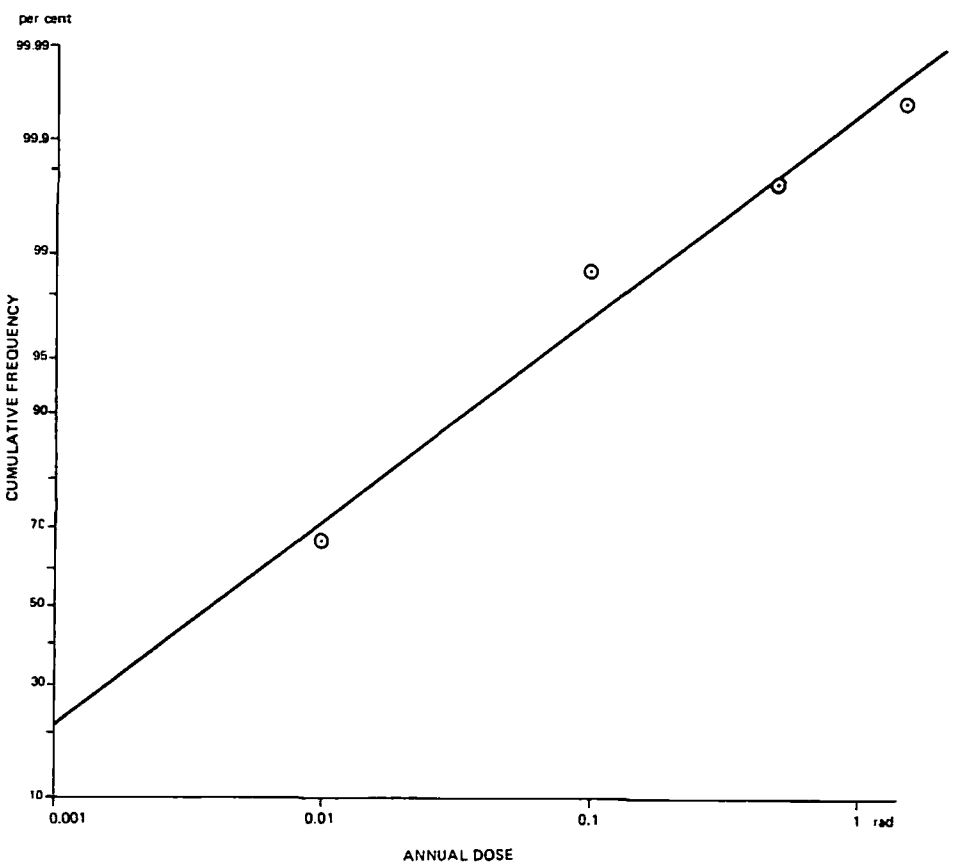

Figure XIX. Log-probability plot of annual doses to radiation workers in the United States Army, 1969-1970

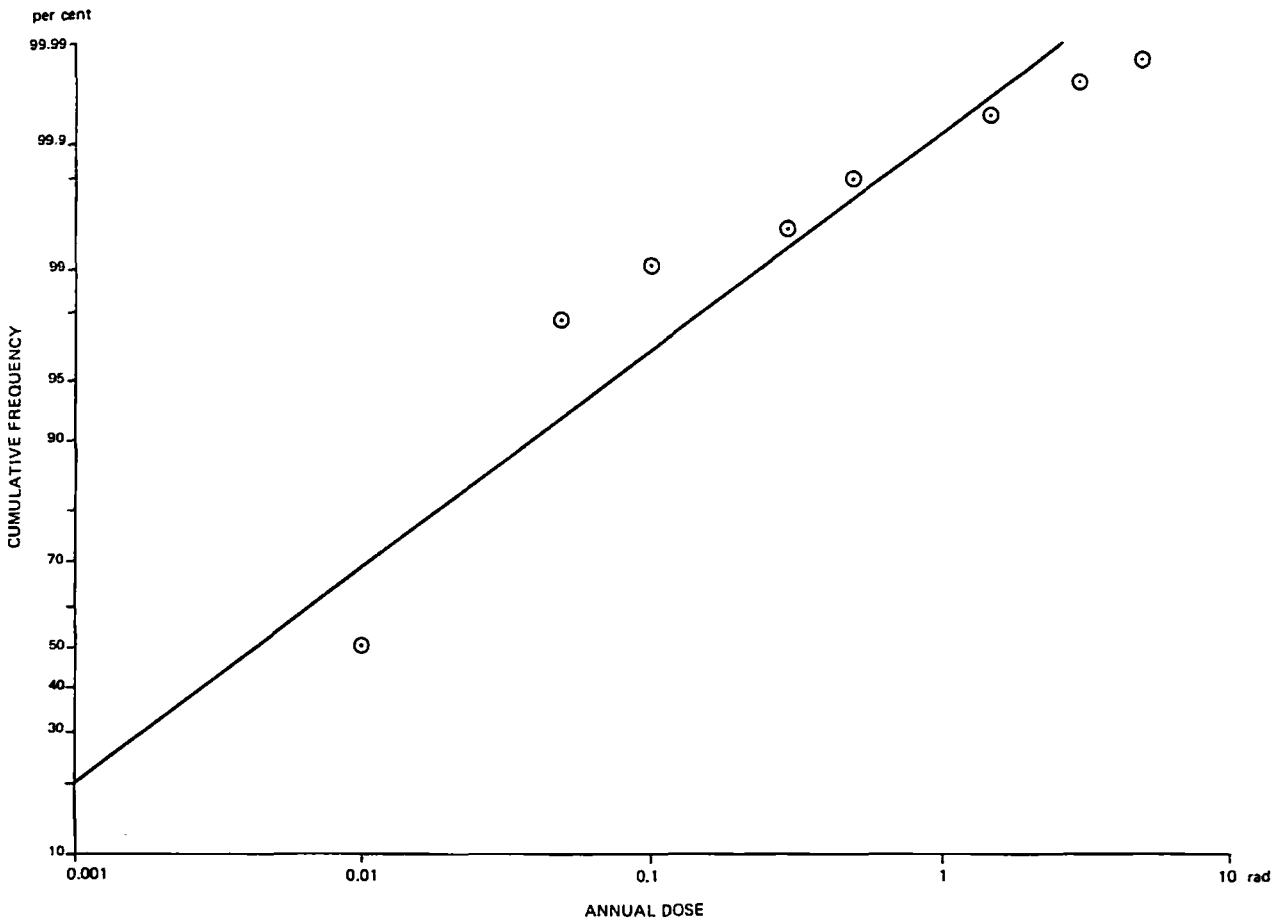

Figure XX. Log-probability plot of annual doses to radiation workers in the United States Air Force, 1969-1970

original data and is estimated as 296 and 329 from the log-normal plot. The values of the annual average dose, as estimated from the log-normal plots, are 15 and 18 mrad for the army and air force, respectively, compared with the published values of 100 and 88 mrad, but these published values were calculated for those workers receiving annual doses above 10 mrad.

113. The collective dose can be estimated from both sets of data, using either the total number of workers and the average dose as obtained from the log-probability plot, or the number of workers receiving annual doses over 10 mrad and the published annual average dose. The collective doses calculated from the log-probability plots are 360 and 650 man rad for the army and air force respectively, whereas those calculated using the published average doses are 740 and 1550 man rad. The discrepancy of a factor of about two for the collective dose is due to the different methods of including the large number of low doses. The extrapolation of the log-probability plot assumes a log-normal distribution of doses, whereas the other method probably assigns a nominal dose value to the low-dose group; it is not clear from the text whether this assignment was actually made.

114. In the United Kingdom Ministry of Defence, radiation dose records are analysed to obtain the number of films received from each establishment and a breakdown of the distribution of readings as a function of occupation (95). The distribution is reduced to two blocks, those films reading 0.025 rad or less and those reading greater than 0.025 rad. The overall average dose is then calculated using individual results above 0.025 rad and an estimate of the average below 0.025 assuming that the results follow an exponential distribution (95). The results for 1971-1974 are shown in table 30.

TABLE 30. ANNUAL AVERAGE DOSE BY OCCUPATIONAL GROUP FOR WORKERS IN THE UNITED KINGDOM MINISTRY OF DEFENCE, 1971-1974

(rad)

Occupational group	*1971*	*1972*	*1973*	*1974*
Supervisors	0.58	0.47	0.21	0.20
Medical	0.22	0.21	0.10	0.21
Dental	0.15	0.16	0.17	0.16
Industrial	0.46	0.59	0.62	0.50
Laboratory	0.15	0.14	0.14	0.18
Operators	0.33	0.31	0.36	0.48
Instructors	0.11	0.12	0.16	0.17
Students	0.37	0.40	0.45	0.41
Health physics	0.13	1.33	0.76	0.94
Procurement executive	0.24	0.20	0.21	0.19
Other	0.58	0.55	0.45	0.53

D. NON-URANIUM MINING

115. The doses to uranium miners have been considered in paragraphs 45-49. Radon also occurs in relatively high concentrations in many non-uranium mines. An excess

TABLE 31. DISTRIBUTION OF RADON-DAUGHTER EXPOSURE IN NON-URANIUM MINES IN VARIOUS COUNTRIES

Country		Year	Radon-daughter concentration range (WL)				All	Weighted average annual exposure[a] (WLM)
			< 0.1	0.1-0.3	0.3-1.0	> 1.0		
			(Number and, in parentheses, percentage of miners or mines)					
Finland	Miners	1973	469 (35)	246 (18)	247 (19)	369 (28)	1 331	8.8
		1974	898 (68)	310 (23)	119 (9)	0	1 327	1.7
	Mines	1973	8 (36)	4 (18)	4 (18)	6 (28)	22	
		1974	13 (65)	5 (25)	2 (10)	0	20	
Italy	Mines	1973	8 (50)	4 (25)	4 (25)	0	16	–
Norway	Miners	1972	1 608 (86)	264 (14)	0	0	1 872	0.9
	Mines	1972	20 (83)	4 (17)	0	0	24	
South Africa	Miners	1973	227 000 (71)	69 000 (21)	21 000 (7)	3 000 (1)	320 000	1.7
Sweden	Miners	1970	1 110 (22)	1 560 (33)	2 000 (42)	130 (3)	4 800	4.8
		1974	1 860 (40)	2 390 (52)	360 (8)	0	4 610	2.1
		1976	2 730 (51)	2 345 (44)	225 (4)	0	5 300	1.7
	Mines	1970	25 (45)	8 (15)	18 (33)	4 (7)	55	
		1974	28 (56)	14 (28)	8 (16)	0	50	
		1976	29 (63)	12 (26)	5 (11)	0	46	
United Kingdom	Miners	1973	1 073 (60)	49 (3)	223 (12)	443 (25)	1 788	4.2
		1975						3.4
	Mines	1973	25 (61)	3 (7)	9 (22)	4 (10)	41	

[a] The weighted average annual exposures are calculated by multiplying the number of miners in each group by the mean values of the radon concentration (0.05, 0.2, 0.65 or 2 WL) and by 12 months, obtaining the sum of the products and dividing by the total number of miners. See paragraph 116 for treatment of British data.

of lung cancer has been found among some non-uranium miners in a number of countries (14, 87, 92, 119), and the excess has been attributed to radon-daughter exposure (100).

116. The number of miners and mines in different concentration categories are presented in table 31 for six countries (10, 13, 59, 79, 101, 108). The corresponding weighted annual exposure is also presented for each country. The United Kingdom miners included in table 31 represent 70 per cent of all non-coal miners, and the United Kingdom mines, mostly metalliferous, represent 41 per cent of all non-coal mines. The annual exposure is calculated directly from the original data (108). For comparison, the annual exposure would be calculated as 7 WLM using the same method as for the other entries in the table. The data from Finland are based on the maximum values of radon-daughter concentration in working areas (59). The sixteen Italian mines were selected by Bottino *et al.* (13) to give a general picture of the situation. The radon-daughter concentrations have been calculated by multiplying the radon concentrations by 0.2, which was the average equilibrium factor (13). In the conversion of the Norwegian values an average equilibrium factor of 0.6 was used (79). Since the temporal variations in radon and daughter concentrations can be considerable, and since measurements tend to be relatively infrequent, the data in table 31 should be treated with caution. Nevertheless, it is clear that some miners are exposed to more than 4 WLM in a year. This value or its equivalent has been adopted by several national authorities as the occupational exposure limit for miners. The results that a determined programme of corrective action can achieve in a relatively few years can be seen, for example, from the Swedish data in table 31.

VII. DOSES TO SPECIFIC OCCUPATIONAL GROUPS

117. It is the intention in this chapter to review selected occupational groups which appear to be of special interest because they fall well outside the anticipated dose distribution defined in chapter III as the reference distribution. The characteristics used to define whether any particular occupational group receives doses that are consistent with the reference distribution are the average annual dose $\overline{D}$ and the relative proportion Ω of the annual collective dose due to annual doses exceeding 1.5 rad. For the reference distribution, $\overline{D} = 0.5$ rad and $\Omega = 1$. In selecting a range of values for $\overline{D}$ and Ω which appear appropriate for judging actual distributions, note is taken of the actual and theoretical extremes of the two parameters. In principle, $\overline{D}$ has a range from zero to a very large number, but in practice it has a range from almost zero to a few rads. It appears that a suitable criterion for selecting distributions for study may be that $\overline{D}$ is outside the range 0.1-1.0 rad. The theoretical range of Ω is from zero to 3.23, and in practice values from zero to nearly 3.0 are found. It therefore appears that a suitable range of values for this parameter outside which the distribution is unusual is 0.1-2.0. There will, of course, be a dependence on country and year, so that the assignment to a particular category is not definite, but merely indicative.

A. GROUPS FOR WHICH $\bar{D} \geq 1.0$ rad OR $\Omega \geq 2.0$

1. Industrial radiographers

118. This is an occupation in which large sources capable of giving substantial doses in a short time are used, usually under adverse conditions, with a minimum of direct radiation protection control. An extensive survey of doses to industrial radiographers was carried out in the United Kingdom (6). Tables 78 and 79 (appendix II) show the quarterly doses for a sample of individual firms concerned mainly with factory and site radiography. It is not possible to calculate annual average doses from these data, but it appears likely that $\bar{D} > 1$ rad, for site radiographers at least. No correlation with size of firm is apparent, but site radiographers, in general, received higher doses than factory radiographers, probably because of adverse working conditions or lack of direct supervision. The United Kingdom study was initiated as a result of a number of workers receiving excess radiation doses. Table 80 (appendix II) summarizes these occurrences of excess dosage for a number of years (121). This experience is reflected in other countries; for example, analysis of the more significant radiation exposure incidents occurring among United States Atomic Energy Commission contractors and licensees in the United States during 1971 shows that of 14 incidents, 8 involved industrial radiographers (111). Many other incidents of overexposure involving industrial radiographers have been reported (20, 40, 57, 74, 75, 96).

119. On the other hand, although the United States has experienced a substantial number of incidents of overexposures involving radiographers, table 75 (appendix II) shows that the average doses and the Ω value are well within the normal range (18). The same is true for the Canadian radiographers represented in table 26 (4), which displays values very similar to those in the United States.

120. Average doses to industrial x-ray workers and gamma-ray workers in Denmark are comparatively low, as shown in table 27. Information from the German Democratic Republic and Hungary, already noted in paragraphs 106 and 108, tends to show a considerable difference between x radiography and gamma radiography with radionuclide sources, with the highest average doses being received by gamma radiographers. This difference could also be the reason for the difference between the average doses received by site and factory radiographers in the United Kingdom, assuming that site radiographers were more likely to use radionuclide sources.

121. It appears that industrial radiographers, particularly those using gamma-ray rather than x-ray sources, may still be among the highest exposed groups with a particular tendency to incidents involving overexposure.

2. Luminizers

122. Luminizers have traditionally been among the workers receiving higher-than-average doses. The marked improvement which could be brought about by an energetic programme of radiation protection was demonstrated in the 1972 report. Mean annual doses to tritium luminizers in 1969-1970 were around 0.5 rad in France, the Federal Republic of Germany and the United Kingdom (omitting two highly exposed individuals). Data have been supplied (46) for workers producing luminous paint and gaseous tritium light sources in the United Kingdom, who are regularly monitored for tritium in urine. The results for 1974 are shown in table 81 (appendix II). The first group of workers provided no samples above the derived investigation level (DIL), which corresponds to a committed dose[1] of 0.050 rad in two weeks; the doses to this group were therefore not recorded. The second group provided some samples below the DIL which are not included in the value for the committed dose. The collective dose was re-estimated, taking this into account, as 115 man rad. In addition, there were 87 luminizers who were not monitored regularly; an estimate was made of the contribution of these luminizers to the collective dose, which resulted in an overall estimate of 157 man rad for the annual collective dose to the 223 luminizers, corresponding to an annual average dose of 0.7 rad. Using these figures with the data from table 81 (appendix II), the Ω value can be estimated as 1.2.

123. A detailed breakdown of annual doses for 1969-1975 is available for Switzerland. These data are shown in table 82 (appendix II) and summarized in table 32 (60, 61). A similar set of data for French luminizers over essentially the same period is shown in table 83 (appendix II) and summarized in table 33 (88). Possibly because of the small number of workers in France, many of these dose distributions were not a good fit to a log-normal curve, whereas the Swiss data in general were. Values for Ω for the Swiss data were therefore estimated using a log-probability plot, but those for the French data were obtained directly from the numbers in each dose range. Both sets of data show the same improvement over the years, in terms of the values for Ω. A similar downward trend in annual average dose is apparent in the Swiss data but not the French; all of the annual average doses to French luminizers are, however, less than 1 rad, the recent average for Swiss luminizers.

124. Doses to dial painters in Canada are summarized in table 26 (4). The high Ω value may be due to the small

TABLE 32. DOSES TO TRITIUM LUMINIZERS IN SWITZERLAND, 1969-1975

Year	*Number of workers monitored*	*Annual collective dose (man rad)*	*Annual average dose (rad)*	Ω
1969	333	618	1.85	2.5
1970	313	478	1.53	1.9
1971	226	276	1.22	2.0
1972	228	268	1.18	2.0
1973	221	231	1.05	1.7
1974	290	316	1.09	1.8
1975	235	239	1.02	1.7

[1] The term "committed dose" is used here to mean the time-integral of the dose rate in an individual over his lifetime from an intake of radioactivity during a specified period of time.

TABLE 33. DOSES TO TRITIUM LUMINIZERS IN FRANCE, 1968-1975

Year	Number of workers monitored	Annual collective dose (man rad)	Annual average dose (rad)	Ω
1968	30	16	0.52	3.0
1969	24	11	0.47	2.3
1970	15	13	0.86	2.8
1971	35	6	0.17	0
1972	33	10	0.29	1.8
1973	67	44	0.66	1.7
1974	84	46	0.55	1.6
1975	90	44	0.49	1.5

number of workers involved (only 11). All of the contribution to the collective dose from annual doses above 1.5 rad is due to one individual who received 3.8 rad in the year.

125. Some information on monitoring of luminizing workers exposed to ^{147}Pm in the German Democratic Republic has been reported (3). The maximum annual dose was estimated from excretion monitoring to be 6 rad, to either the lung or gastro-intestinal tract, but the annual doses to these organs were in the range 1-3 rad for the 10 other individuals with measurable ^{147}Pm levels.

126. In view of the increasing use of tritium in the watch industry, supervision of workers using tritium in the Federal Republic of Germany has continued. Table 84 (appendix II) shows the mean annual dose per person from 1966 to 1975 (19). When the values are broken down into specified ranges, it can be seen that in different years, 40-70 per cent of workers received doses exceeding 0.1 rad, and 5-40 per cent received doses in the range 1.5-5 rem. While in the 1960s up to 13 per cent of the workers received doses exceeding 5 rad, no such doses were recorded from 1970 to 1972. In 1973-1975, one or two workers received annual doses in excess of 5 rad. The average annual dose has varied from 0.4 to 1.4 rad.

127. Luminizing is an occupation in which high doses can be received by a few individuals, but improvements in the practice of radiological supervision over the last decade have resulted in the achievement of an adequate level of protection.

3. Medical workers in radiotherapy

128. Undoubtedly the highest doses from the use of radiation in radiotherapy have been from the use of radium sources for interstitial and intracavitary therapy. This was illustrated in the 1972 report with data from the German Democratic Republic and Sweden. In recent years the trend has been to replace radium sources by other nuclides (35, 126). Conventional radium tubes and needles can be replaced directly with ^{137}Cs tubes and needles, which have the advantage, for radiation protection, of a lower gamma energy. In addition, "afterloading" techniques have been developed for both the treatment of cancer of the uterine cervix and interstitial radiotherapy. In these techniques, a hollow tube is positioned first and the source then introduced into the tube; the result is a reduction in the occupational dose.

129. A survey of techniques used in the treatment of cancer of the cervix was given by Snelling (99); ^{192}Ir, ^{137}Cs and ^{60}Co are used in various afterloading systems (22, 42, 58). Iridium-192 and ^{182}Ta wires are used in afterloading techniques in interstitial radiotherapy (86, 90).

130. From the German Democratic Republic, for example, the Committee has had data showing that in the mid-1960s the highest monthly doses and most overexposures were due to medical radium applications. From the mid-1960s to 1970, all sealed radium sources for medical purposes were replaced by other radionuclide sources: since then the number of overexposures has considerably decreased (97). The French results reported in table 19 show that interstitial and intracavitary therapy (Curie therapy) gave values for Ω slightly greater than 1.0, accompanied by low values of the annual average doses. This is explained by the new techniques using ^{192}Ir and ^{137}Cs in afterloading, causing hardly any exposure of the operators to radiation: however there still remain a small number of radium workers who are exposed to higher doses. The highest annual average doses for any medical workers in Denmark were for workers at radium centres. These were still low by comparison with most other countries, but not enough information was given to enable the Ω value to be calculated, so nothing can be deduced as to the reason. It is not clear from the Canadian results in table 17 which category would be expected to handle radium, but no categories had high values of either $\overline{D}$ or Ω.

131. The effect of the introduction of improved procedures and equipment on doses received in a single institution are exemplified in the results submitted by Bozoky (15) and shown in table 85 (appendix II). As is pointed out by Bozoky, although the reduction in annual dose is considerable, the reduction in the mean energy imparted (referred to as the integral dose), calculated on the basis of measurements at ten different parts of the body, is very much less. There is some doubt whether average dose is a valid measure of harm for a procedure in which the distribution of dose over the body is extremely non-uniform.

132. The use of external-beam therapy would be expected to result in much lower doses to workers compared with intracavitary and interstitial therapy. Provided that the treatment rooms are adequately shielded, the users of cobalt teletherapy sources might be expected to receive slightly higher doses than users of x-ray or electron-beam sources. The French results reported in table 19 show that indeed cobalt therapy gave a higher Ω value and average dose than high-energy therapy. However, the annual average dose from conventional radiotherapy with low-energy x rays was the highest reported in 1974. The comparable group in the Canadian data in table 17 is radiological technicians (therapeutic) with an Ω value of 1.0 and a low mean dose. The mean dose received by Australian therapy radiographers (table 20) is also low.

4. Workers at nuclear reactors

133. Most of the data reported in paragraphs 53-68 relate to the collective doses rather than the individual doses of workers at nuclear reactor sites. Some additional data have, however, been received on the annual dose to different occupational groups within the overall reactor staff. Doses at two United Kingdom reactors are shown in tables 86 and 87 (appendix II) (39, 85). The one group of workers consistently receiving the highest annual average doses at both reactors is the radiological protection workers. Operational workers at one station also received annual average doses exceeding 1 rad in two successive years, although in the latest year (1974) their average dose had been reduced to 0.8 rad.

134. Doses to three groups of workers in the Canadian Ontario Hydro nuclear power stations are shown in table 88 (appendix II) (125). The group receiving the highest annual dose is mechanical maintenance workers. Radiological protection workers are not specifically identified as, in general, all workers carry out their own radiological protection procedures. Annual average doses to all workers at some United States nuclear power stations are higher than 1 rad (see table 48 in appendix II). There is no indication of those groups receiving the highest doses, although it could be inferred that, as maintenance operations contribute most of the collective dose, maintenance workers probably receive the highest average doses. Radiological protection monitors would also be expected to be closely associated with maintenance work.

5. Nuclear fuel reprocessing workers

135. Information has been provided (48) on average doses to some selected groups of workers at Windscale in the United Kingdom. The detailed results for 1973-1975 are shown in table 89 (appendix II). It is apparent that, as with reactors, operations and maintenance workers receive the highest annual average doses. The average doses to these small groups of workers are among the highest reported to the Committee.

6. Manufacturers of radiopharmaceuticals and industrial sources

136. The only specific information on workers producing radiopharmaceuticals and industrial sources has been supplied by the United Kingdom (82). The Radiochemical Centre produces a variety of sealed and unsealed sources for use in industry and medicine. The distribution of annual dose is given in table 90 (appendix II). The average annual dose has decreased from 1.11 to 0.76 rad from 1972 to 1974, but the value for Ω in 1974 was 2.2, indicating that a substantial proportion of the workers received annual doses in excess of 1.5 rad.

7. Miners

137. The doses to workers in uranium, coal and metalliferous mines have been discussed in paragraphs 45-49 and 115-116. From these it can be seen that, even with the reservations on conversion of WLM to lung dose, many miners are exposed to radon-daughter concentrations considered excessive by some authorities. Improvements in ventilation are under way in many countries where this problem exists (52b). Such efforts should be vigorously pursued; as has been noted, significant improvements can result within relatively few years.

8. Aircrew and cabin staff of jet aircraft

138. The increase of cosmic-ray dose rate with altitude was discussed in the 1972 report and in chapter I, section A, of Annex B. At the normal cruising altitude of subsonic jet aircraft, about 10 000-12 000 m, the dose rate is in the range 0.15-0.35 mrad h^{-1}. This range includes the variation within the solar cycle and with latitude from 43°N to 50°N (84). Some components of the radiation field have a measured RBE considerably greater than unity, and it has been estimated that if a quality factor were to be assigned to the mixed field it would be of the order of 1.5. With this factor, the dose equivalent rates would be in the range 0.25-0.50 mrem h^{-1}. If the average crew member flies at this altitude for 1000 h per year, then the average annual dose equivalent received would be in the range 0.25-0.5 rem.

139. In the case of supersonic aircraft flying at altitudes of 20 000 m, the dose rate is appreciably greater than that in conventional jet aircraft, but the combination of the increase in dose rate with the reduction in travelling time means that the dose received in a given journey is of the same order, whichever type of aircraft is flown. It is not yet clear whether supersonic aircrew will fly the same number of hours as conventional aircrew. If they do, the annual dose equivalent that they will receive could be in the range 0.5-1.5 rem. The provision of in-flight radiation dose-rate monitors to provide direct warning of solar flares will prevent the occurrence of large doses, and it is expected that the average dose equivalent from solar flares will be a small proportion of the total.

B. GROUPS FOR WHICH 0.1 rad $< \bar{D} <$ 1.0 rad AND $0.1 < \Omega < 2.0$

140. If the general practice of radiological protection is satisfactory and the limits of the parameters have been correctly defined, the parameters for most groups of occupational workers should fall within the range 0.1-1.0 rad for $\bar{D}$ and 0.1-2.0 for Ω. In general, the results made available to the Committee suggest that that is the case. Examples of large groups of workers for which it is the case include:

Most workers at most unclear reactors

Fuel manufacture workers in the United Kingdom and the United States

All workers in nuclear power research in Argentina, the United Kingdom and the United States

All industrial workers in the United States

All military workers in the United Kingdom and the United States

All medical, industrial and atomic energy workers in India
All medical and research workers in Thailand
Most medical workers in Switzerland

1. Medical users of diagnostic x rays

141. Bearing in mind the cautions expressed in paragraph 84, it appears that the diagnostic use of x rays in medicine does not lead to high average doses or large proportions of workers receiving annual doses above 1.5 rad. The United Kingdom data for all medical workers, for example, gave values for Ω of 0.90 and for $\overline{D}$ of 0.21 rad. Since the data included radium workers, the average values for radiologists should be even lower. Data supplied for Canada, Denmark, South Africa, Switzerland and the United States would seem to support this conclusion (see paragraphs 84-99).

142. In France, a value for Ω of 0.8 was found together with an annual average dose of 0.13 rad, values close to those found in the United Kingdom. Among medical x-ray workers, only private radiology practitioners show an Ω value appreciably greater than 1.0, namely 1.4, although their annual average dose is 0.22 rad.

143. It has been suggested that, although diagnostic use of x rays does not in general lead to high average occupational doses (with the exception noted above), certain specialized x-ray examinations may well do so. Examples of doses from angiography procedures in Norway have been published (32). Doses were measured during 160 angiography examinations in 10 different hospitals; most doses were low (5 mrad per examination), but in a few cases, particularly of manual procedures, doses of 10-100 mrad were found. The highest doses were due to the use of too large a field and in some cases were associated with manual injection of the contrast medium. The annual number of angiography examinations in Norway were 14 600 in 1970 and 16 580 in 1971, out of a total number of x-ray examinations of about $3\ 10^6$.

144. The dose to the radiologist from cardiac catheterization has been extensively studied by many authors, but the evidence is somewhat conflicting. Some data (70) suggest that the dose to the principal physician may be about 50 mrad to the chest; however, other data (2) suggest that the dose to the trunk area is only 2 mrad. Stacey *et al.* (104) have measured doses to a number of cardiologists. The dose to the chest is low, less than 5 mrad when an undercouch tube is used, but is higher by approximately a factor of three when an overcouch tube is used. Doses of up to 200-300 mrad to the hands were measured. There is, however, a wide variation of dose received by the radiologist, depending on the technique used for each examination.

2. Workers in nuclear medicine

145. There have been some indications that the continual use in diagnosis of short-lived radioisotopes, such as ^{99m}Tc, may contribute considerably to the occupational doses to the staff, although the dose to the patient is less than with longer-lived isotopes. One of the hazards is the irradiation of the fingers from unshielded syringes, and under certain conditions the dose may be as high as 5-10 rad per week (26, 45, 80).

146. The only comprehensive survey known to the Committee is that of the American Association of Physicists in Medicine referred to in paragraph 89 (8). The main objective of this survey was to relate the collective dose to the unit practice, but it was also found that annual average doses were of the order of 0.5 rad (see table 16). On this basis, the occupational doses in nuclear medicine seem to be within the normal range. No value for Ω could be estimated from the survey.

147. The only other sets of data in which nuclear medicine was specifically identified were those from France (table 19) and Australia (table 20). In the French set, if the data for nuclear medicine are compared with those for conventional radiodiagnosis, the Ω value (0.2) is found to be lower, but the annual average dose (0.16 rad) is slightly higher, which shows that annual doses exceeding 1.5 rad are unusual. The Ω value for Australian nuclear medical workers could not be determined, but the average annual dose was very low, only 0.08 rad.

C. GROUPS FOR WHICH $\overline{D} \leqslant 0.1$ rad OR $\Omega \leqslant 0.1$

148. If a given group of workers falls into this category consistently over a number of years, these conclusions can be drawn:

1. Both $\overline{D} \leqslant 0.1$ rad and $\Omega \leqslant 0.1$

149. The workers in the group are most unlikely to receive annual doses exceeding 1.5 rad and the annual average dose is also very low. That implies that these workers may fall into the category defined by the ICRP (51) as not needing individual personal monitoring and health supervision. Examples of workers in this group include:

United Kingdom fuel-enrichment workers
Possibly some Danish medical and industrial workers (although Ω is not known for them)
Workers in chiropractic in Switzerland and possibly also Denmark
Some Canadian industrial workers, e.g. instructors

2. $\overline{D} \leqslant 0.1$ rad but $\Omega > 0.1$

150. The workers in the group may be more likely to receive annual doses exceeding 1.5 rad and therefore there is justification for individual monitoring. The extremely low average dose means, however, that probably more people are included in the monitored group than is justified by the need for protection. Examples of workers in this group include:

Some groups of Canadian medical workers
Dental workers in Canada, Denmark, France and Switzerland

Workers in chiropractic in Canada, Denmark and Switzerland
Veterinarians in Canada and Denmark
Some groups of hospital workers in Denmark
Industrial workers in South Africa
Some medical workers in Switzerland
Some industrial workers in Canada and Denmark
Some groups of workers in Israel

3. $\Omega \leqslant 0.1$ but $\bar{D} > 0.1$

151. The workers in the group would have very nearly the same annual dose. Very few workers would receive doses in excess of 1.5 rad, and the fraction receiving low doses would be less than in the reference distribution. No such distributions have been found in practice.

VIII. OCCUPATIONAL LIFETIME DOSE PREDICTIONS

152. In 1966 the ICRP noted (51) that "any worker who, for prolonged periods, receives doses annually at the maximum permissible levels, might accumulate lifetime doses of the order of hundreds of rems, or, for exposure at the extremities, thousands of rems". The ICRP considered that any limitation of the lifetime accumulated dose in addition to that implied by the maximum permissible dose was not justified, but indicated that the matter was being kept under review.

153. Since to comply with national and international requirements all reporting is of annual doses, data on lifetime cumulative doses have not been readily available. In particular, when high doses are reported for several years, it is not usually clear whether they are high doses to the same or different individuals in successive years. It is the Committee's aim to stimulate publication of figures for cumulative doses to highly exposed individuals from which extrapolations to lifetime doses can be made.

154. Various methods for assessing lifetime doses are available, mainly based on retrospective analysis of individuals or groups who have been employed in the same occupation for a number of years. Although more sophisticated mathematical techniques can be devised, such as that used by Jankowski (55), the Committee felt that the uncertainties introduced by assuming that past doses would be a guide to future doses were sufficiently large that only the simplest mathematical extrapolations were justified. On this basis cumulative lifetime doses have been calculated from the formula

$$D_{40} = (40/n) \sum_{i=1}^{n} \bar{D}_i$$

where $\bar{D}_i$ is the average annual dose for each of the n years over which records are available, and D_{40} is the predicted dose for a 40-year employment. If possible, n should be greater than 5.

155. Where information is available on the numbers of workers with predicted lifetime doses in certain ranges, then the probability of exceeding a given lifetime dose can be calculated for the sample (124) as:

$$P[D_{40} > D_j] = 1 - \frac{N_j}{N}$$

where $P[D_{40} > D_j]$ is the probability of receiving a lifetime dose exceeding D_j, N_j is the number of persons in the sample with an estimated lifetime dose less than D_j, and N is the total number of persons in the sample.

A. NUCLEAR POWER INDUSTRY

156. A most useful analysis of lifetime doses along the lines described above has been provided to the Committee (124). The average annual doses for a number of current work groups and for all nuclear station workers at Ontario Hydro in Canada were analyzed as a function of the length of time since the individual was hired as an "Ontario Hydro Radiation Worker". These data are summarized in table 91 (appendix II). Only those groups of workers who had been employed for 5-9 or 10-14 y were used in subsequent analysis. Table 34 shows the results of extrapolating to 40 years, using the average annual doses for these two groups. These are the average lifetime doses for relatively small groups of workers with long service and therefore are reasonably representative; however, it is reasonable to ask what is the probability of a small number of workers reaching higher lifetime doses. Using the method suggested above, the results in table 35 were obtained, showing that the probability of exceeding a lifetime dose of 180 rad is very small (<0.005) for all groups. Even for those in the most exposed group (mechanical maintenance), this probability is less than 0.05 based on the 5-9 y data, but drops to less than 0.01 for the 10-14 y group, as can be seen from figure XXI.

TABLE 34. ESTIMATES OF THE LIFETIME DOSE (D_{40}) FOR WORKERS AT ONTARIO HYDRO IN CANADA

	Lifetime dose estimate (rad)	
Current work group	*A*	*B*
All nuclear station workers	56	39
Operators	78	49
Mechanical maintainers	102	90
Control technicians	51	35

Notes: A—estimates based on workers employed for 5-9 years. B—estimates based on workers employed for 10-14 years.

157. Data have also been provided on termination reports for several categories of United States Nuclear Regulatory Commission licensees (74), two of which are relevant to the nuclear power industry. Termination reports are dose summaries prepared when a monitored individual terminates employment at United States Atomic Energy Commission offices, contractors or covered licensed facilities. These categories are "power reactor and testing facilities" and "fuel processors, fabricators or reprocessors". A summary of the data

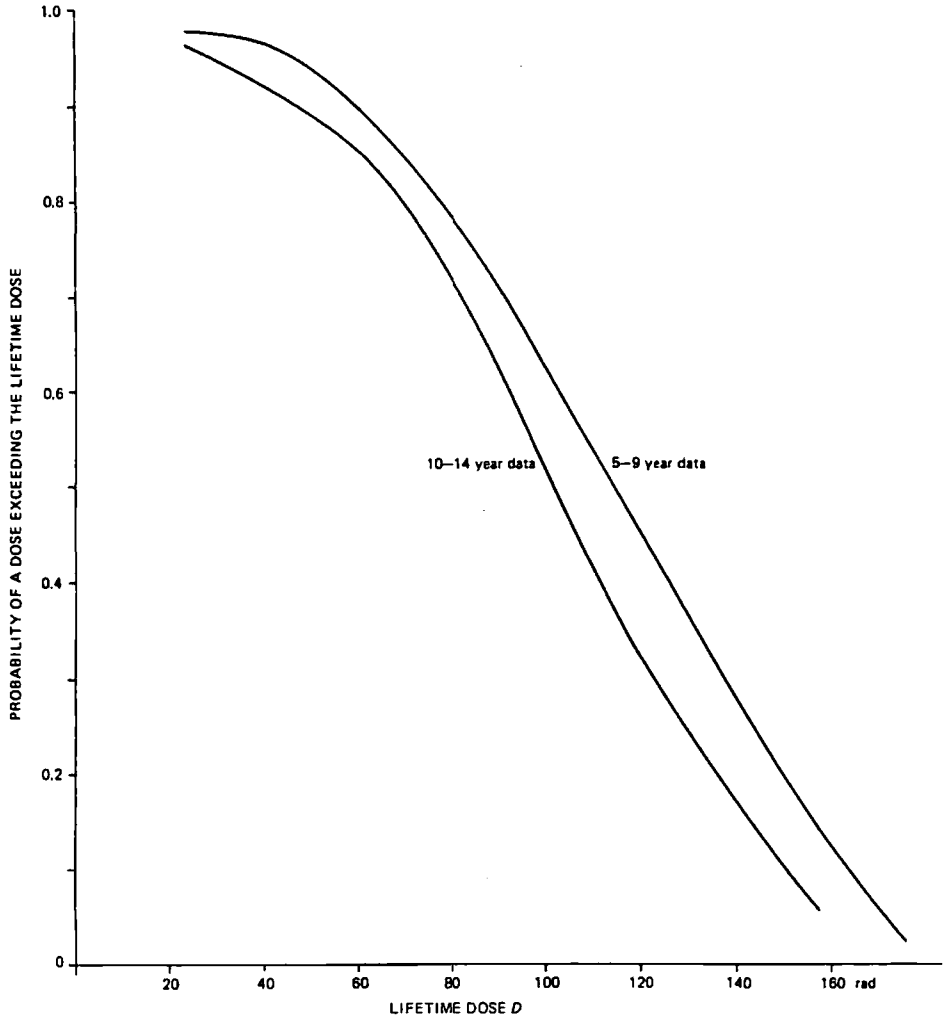

Figure XXI. Probability of exceeding a given lifetime dose for mechanical maintainers at Ontario Hydro, Canada

TABLE 35. ESTIMATES OF THE PROBABILITY OF RECEIVING A LIFETIME DOSE EXCEEDING A SPECIFIED LEVEL FOR WORKERS AT ONTARIO HYDRO, CANADA

Dose level	*All nuclear station workers*		*Operators*		*Mechanical maintainers*		*Control technicians*	
rad	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*
22.5	0.68	0.64	0.89	0.93	0.97	0.95	0.78	0.71
45	0.56	0.44	0.81	0.67	0.95	0.90	0.58	0.47
67.5	0.44	0.21	0.70	0.26	0.85	0.81	0.34	0.12
90	0.31	0.12	0.47	0.09	0.72	0.62	0.24	0
112.5	0.19	0.06	0.32	0.02	0.51	0.38	0.11	0
135	0.11	0.03	0.18	0	0.34	0.24	0.02	0
157.5	0.04	0.01	0.07	0	0.15	0.05	0	0
180	0	0	0	0	0.03	0	0	0
> 200	0	0	0	0	0	0	0	0

Notes: A—estimates based on workers employed for 5-9 years. B—estimates based on workers employed for 10-14 years.

supplied is given in tables 92, 93 and 94 (appendix II). The average annual dose was calculated by dividing the average cumulative dose, excluding those receiving zero or minimal doses, by the mean number of years of employment and is shown in table 36 with the corresponding estimate of the average lifetime dose. The estimated lifetime doses for power reactor workers are similar to the Canadian estimates. The lifetime doses estimated for workers in fuel reprocessing are very much higher, however, owing to the large percentage of terminating workers with high cumulative doses. This is demonstrated in table 37, showing the probability of a lifetime dose exceeding a given level, which indicates that for workers with 5-10 and 10-15 y of employment there is a 50-per-cent probability of a lifetime dose well in excess of 100 rad. Average doses to fuel fabricators and scrap-recovery workers were low and lifetime doses of only 10-15 rad are predicted (see tables 36 and 37).

158. Estimates have also been made of predicted lifetime doses at Windscale (48) to workers who have been employed for 10-15 y. For each individual, the 40-y extrapolated dose was calculated as above if the current cumulative dose divided by the number of years worked was less than 5 rad y^{-1}. Where it exceeded 5 rad y^{-1}, in view of current radiological protection standards at Windscale, which restrict individual doses to less than 5 rad y^{-1}, the lifetime dose was calculated by adding $5(40 - n)$ rad to the worker's current cumulative dose over n years. The results are shown in table 38.

159. Data have been received from the United Kingdom on workers at some Central Electricity Generating Board nuclear power stations whose current cumulative dose exceeded 15 rad (85). These workers had been employed in the nuclear industry for 8-15 y. Their cumulative doses have been extrapolated to 40 y and are shown in table 39. Data have also been received on nine workers at the Central Electricity Generating Board nuclear research laboratories who had cumulative doses exceeding 15 rad up to 1975 (85). The extrapolated lifetime doses are also shown in table 39. These workers had been employed for 10-15 years. The average annual dose to a random sample of 50 workers employed in fuel fabrication, each with over 20 y of occupational exposure, was 0.46 rad (47), leading to an average estimated lifetime dose of 20 rad.

TABLE 36. AVERAGE LIFETIME DOSE FOR WORKERS ASSOCIATED WITH THE NUCLEAR POWER INDUSTRY IN THE UNITED STATES

Based on workers employed for 5-10 or 10-15 years

(rad)

Length of employment (y)	*5-10*	*10-15*
Occupational group		
Power reactor workers	34 (0.85)	19 (0.46)
Fuel reprocessors	145 (3.62)	126 (3.15)
Fuel fabricators and scrap recoverers	15 (0.37)	10 (0.26)

Note: The number in parentheses is the average annual dose (rad) based on the actual doses for each group, omitting workers with zero or minimal doses.

TABLE 37. ESTIMATES OF THE PROBABILITY OF RECEIVING A LIFETIME DOSE EXCEEDING A SPECIFIED VALUE

United States nuclear power industry workers

Dose level (rad)	*Power reactor workers*		*Fuel reprocessors*		*Fuel fabricators and scrap recoverers*	
	A	*B*	*A*	*B*	*A*	*B*
10	0.49	0.39	0.99	1.00	0.28	0.26
20	0.37	0.29	0.93	0.86	0.17	0.15
50	0.22	0.08	0.83	0.71	0.07	0.06
80	0.12	0.05	0.72	0.71	0.05	0.02
100	0.06		0.65		0.03	
130	0.02		0.54		0.02	
> 130						

Notes: A—estimates based on workers employed for 5-10 years. B—estimates based on workers employed for 10-15 years.

TABLE 38. ESTIMATES OF THE LIFETIME DOSE FOR WORKERS AT WINDSCALE, UNITED KINGDOM

Based on workers employed for 10-15 years

Estimated lifetime dose range (rad)	*Number of workers in range*	*Probability of a lifetime dose exceeding the maximum of the range*
0-10	47	0.87
10-20	67	0.70
20-30	41	0.59
30-40	37	0.49
40-50	31	0.41
50-60	35	0.32
60-70	35	0.23
70-80	17	0.18
80-90	13	0.15
90-100	7	0.13
100-110	13	0.09
110-120	7	0.08
120-130	10	0.05
130-140	5	0.04
140-150	9	0.01
150-160	2	0.01
160-170	1	0.01
170-180	0	0.01
180-190	0	0.01
190-200	1	0
200-210	1	

TABLE 39. ESTIMATES OF THE LIFETIME DOSE FOR WORKERS AT UNITED KINGDOM CENTRAL ELECTRICITY GENERATING BOARD SITES

Workers with cumulative doses exceeding 15 rad in 1975

Estimated lifetime dose range (rad)	*Power station*	*Nuclear research laboratory*
	Number of workers	
40-50	11	1
50-60	11	2
60-70	4	3
70-80	2	2
80-90	4	0
90-100	0	1
100-110	1	0
> 110	0	0

B. MEDICAL USES OF RADIATION

160. The average annual doses to medical and allied workers in Australia shown in table 20 have been used to estimate lifetime doses by a rather different procedure, in which the predicted total number of years of occupational exposure is estimated for each category (106) for both male and female workers. The lifetime doses for females are often lower than for males, as their retiring age is generally lower, and in many cases women leave employment for a number of years. The estimate is based on the results of a survey to determine the age and sex distribution in specific occupational categories. The results of this survey are given in table 95 (appendix II). The estimated average lifetime doses for some occupational categories are given in table 40. As might be expected from the low reported dose levels in Australia, the predicted lifetime doses are all low. The highest values are 9-12 rad for clinical and private radiologists.

TABLE 40. ESTIMATES OF THE LIFETIME DOSE TO MEDICAL AND ALLIED WORKERS IN AUSTRALIA

Based on annual average doses[a] and predicted length of exposure

Occupational group[a]	*Predicted length of occupational exposure (y)*		*Estimated average lifetime dose (rad)*	
	Male	*Female*	*Male*	*Female*
Diagnostic radiology				
Hospital radiologists	40	30	7	5
Radiologists, clinics and private	40	30	12	9
Radiographers	40	30	6	4
Assistants	10	10	1	1
Dermatology, gynaecology and radiotherapy				
Dermatologists	40	–	4	–
Assistants	–	30	–	5
Radiographers and gynaecologists	40	30	6	5
Therapy radiographers	35	30	3	3
Assistants	10	10	1	1
Nurses	10	10	4	4
Nuclear medicine				
Radiographers and assistants	40	30	3	2
Dentistry				
Dentists	40	30	< 1	< 1
Nurses and assistants	30	10	< 1	< 1
Chiropractic				
Chiropractors	35	25	1	1
Veterinary				
Veterinary surgeons	35	30	1	1
Assistants	30	5	< 1	< 1

[a] See table 20.

161. Data were received from the United Kingdom on cumulative doses for workers with more than 10 y of employment in South Wales hospitals (27). These results have been extrapolated to give the lifetime doses shown in table 41. Considerably higher than the Australian results, they represent the doses to long-term workers who may have relatively high doses as compared with an overall average such as was used to obtain the Australian figures.

TABLE 41. ESTIMATES OF THE LIFETIME DOSE FOR HOSPITAL WORKERS EMPLOYED FOR MORE THAN 10 YEARS IN SOUTH WALES, UNITED KINGDOM

Estimated lifetime dose range (rad)	*Number of workers in range*	*Probability of a lifetime dose exceeding the maximum of the range*
0-5	32	0.74
5-10	45	0.38
10-15	16	0.25
15-20	6	0.20
20-30	13	0.10
30-40	8	0.03
40-50	1	0.03
50-60	1	0.02
60-70	0	0.02
70-80	1	0.01
> 80[a]	1	

[a] Cumulative dose 154 rad.

162. Estimates of the lifetime dose to broad categories of Japanese workers have been obtained from the average annual doses to personnel with more than 10 y of employment (41). The estimates also take into account the gradual reductions of annual dose during a person's working lifetime. The results are shown in table 42. They are higher than would be obtained by use of only the current average annual dose, as in the Australian study, but lower than extrapolation of the past cumulative dose experience would appear to give. This extrapolation could not be carried out since the average length of employment was not given; but if, for example, all the group B medical workers had been assumed to work for 12 y, the extrapolated 40-y lifetime dose would have been nearly 20 rad rather than 10 rad.

163. It was noted that in New Zealand lifetime doses would be unlikely to exceed a few rads if levels of dose continued as at present (72). Cardiologists and some specialized surgeons carrying out special theatre procedures could receive lifetime surface doses to regions of the head and neck of up to 40 rad assuming a working life of 40 y. It was felt, however, that it would be unusual for a cardiologist to be actively employed in specialized work for so long a period. This observation supports the more widespread use of the Australian technique of taking into account the likely working lifetime in the particular employment causing the dose.

164. In the data from Hungary (15) regarding the most highly exposed workers in a gynaecology department, a number of workers are indicated as having actually been in the institute for 40 y. Their actual estimated lifetime doses are (rad): one physician in gynaecology, 220; two physicians, 40 and 25; two physicians, 80 and 30; one assistant, 140. It is noted, however, that, on the basis of present practice and estimating for the next 40 y, the expected dose to a physician in gynaecology would only

TABLE 42. ESTIMATES OF THE LIFETIME DOSE FOR SOME OCCUPATIONAL CATEGORIES IN JAPAN

Occupational category	*Group*[a]	*Number of workers in group*	*Cumulative dose to 1973 (rad)*	*Annual average dose 1971-1973 (rad)*	*Estimated average lifetime dose (rad)*
Medical	A	32	9	0.28	13
	B	390	6	0.25	10
Atomic energy	A	390	1	0.08	2
	B	421	1	0.07	2
Research and education	A	98	2	0.03	2
	B	196	1	0.05	3
Industrial radiography	B	17	21	0.18	24

[a] A = monitored since 1956; B = monitored since 1961.

be 40 rad. The highest lifetime doses in the department are to a surgeon's assistant (280 rad) and a hospital porter (400 rad).

C. INDUSTRY AND RESEARCH

165. The Australian survey referred to in the previous section also covered industrial and research workers in the same way (106). The results are shown in table 43, and are again very low for the reasons cited above. In the report from New Zealand, it was stated that industrial radiographers would appear to be the group most likely to receive the highest cumulative doses, estimated over a 40-y working life as 20 rad with extreme values perhaps a factor of two greater (72). These estimates are closer to those for Japan shown in table 42, which predict lifetime doses of about 25 rad for industrial radiographers.

166. Analysis of termination reports for industrial radiographer licensees in the United States can be carried out as described in paragraph 157. The data are shown in table 96 (appendix II) (74) and lead to the predicted lifetime doses shown in table 44.

TABLE 43. ESTIMATES OF THE LIFETIME DOSE TO INDUSTRIAL AND RESEARCH WORKERS IN AUSTRALIA

Based on annual average doses[a] and predicted length of exposure

	Predicted length of occupational exposure (y)		*Estimated average lifetime dose (rad)*	
Occupational group[a]	*Male*	*Female*	*Male*	*Female*
Research				
Research workers	25	10	< 1	< 1
Users of enclosed installations	35	30	< 1	< 1
Users of open installations[b]	30	25	7	6
Users of tracers	25	20	2	1
Engineers	35	–	1	–

[a] See table 25.
[b] Including industrial radiographers.

TABLE 44. ANNUAL AND LIFETIME DOSES AND LIFETIME DOSE PROBABILITIES FOR INDUSTRIAL RADIOGRAPHY LICENSEES IN THE UNITED STATES

	Length of employment (y)		
	5-10	*10-15*	*15-20*
Average annual dose[a] (rad)	0.48	0.36	0.34
Estimated lifetime dose (rad)	19	14	14
Probability of a lifetime dose exceeding the rounded dose level (rad)			
10	0.39	0.30	0.39
20	0.27	0.15	0.15
50	0.13	0.08	0.06
80	0.06	0.03	
100	0.02		
130	0.01		

[a] Based on actual doses, omitting workers with zero or minimal doses.

IX. CONCLUSIONS

167. In this report the Committee has tried to identify more clearly the purposes of presenting information on occupational dose statistics other than to demonstrating compliance with regulations. It has also defined those parameters of a dose distribution which are useful for those purposes and for comparison with a reference distribution. The Committee recommends that when data on occupational doses are presented, they should be in such a form that these parameters can be readily extracted. The parameters of interest from a dose distribution are (a) the average dose $\bar{D}$, (b) the fraction of the collective dose received at annual doses above 1.5 rad, (c) the ratio Ω of this collective dose fraction to that of the reference distribution, and (d) the total collective dose or the number of workers. The last two parameters are of more interest if the beneficial results of the practice causing the doses can also be quantified. The Committee also recommends that when workers are classified into particular occupational categories, care

should be taken in defining the categories so that they are clear and mutually exclusive. The definition of the category should be described in detail when doses to workers in a particular category are reported.

168. In the data supplied to the Committee, the benefit derived per unit practice was clearly quantified only in the case of certain sections of the nuclear power industry and one aspect of nuclear medicine. More effort should be expended on this aspect of the justification of radiation exposure.

169. On the basis of a comparison of the parameters describing the occupational dose distribution with those of the reference distribution, a number of specific occupations have been identified which merit continuing surveillance. The group most liable to overexposure are industrial radiographers working with radionuclide sources. Radiological protection for these workers should, if possible, be improved, although it is recognized that it would be extremely difficult to do so in view of their unsupervised working conditions. Medical workers handling radium sources are also liable to receive high doses, but the use of these sources is decreasing. Other medical workers receive very low doses in some countries and comparatively large doses in others. Some groups of workers at nuclear power reactors receive relatively high doses, particularly those engaged in maintenance and health physics work. The highest average doses to groups of workers of moderate numbers were reported for fuel reprocessing workers. Since these were all at one establishment, it is not clear whether doses at these levels are a necessary concomitant to the work. Lung doses to miners are still high but appear to be decreasing. Doses to aircrews form a special case, as they will be uniform and high doses are virtually impossible. These workers constitute a group where individual monitoring is unjustified, but where estimates of doses should continue to be made.

170. A number of groups of workers and occupations have been identified for which $\overline{D} \leqslant 0.1$ rad or $\Omega \leqslant 0.1$. The need for routine individual monitoring of these workers should be kept under review. Examples of these groups are certain categories of medical workers including dentists, chiropractors and veterinarians together with certain industrial workers.

171. A great deal of data has been presented on occupational doses to workers in the nuclear fuel cycle, especially reactor workers. Bearing in mind the uncertainties discussed in paragraph 81, the collective dose per unit electricity generated appears now to be approximately distributed among the activities as shown in table 45.

172. It should be noted that most of the information on which these estimates are based comes from a relatively small number of countries, and the estimates for some parts of the cycle are based only on data from the United Kingdom and the United States. The estimates of collective dose per unit energy generated received in the fuel reprocessing and reactor parts of the cycle are comparable with those made in the 1972 report, 1.6 and 0.7 man rad per MW(e) y, respectively. The increase in collective dose attributable to reactors could be a consequence of the increased maintenance problems with light-water reactors. Associated research and development also makes a large contribution. The dose shown is probably an overestimate, as no deduction was made, in the case of large, diversified organizations, for doses received in work unrelated to the nuclear fuel cycle.

TABLE 45. COLLECTIVE DOSE PER UNIT ENERGY GENERATED RECEIVED IN THE DIFFERENT PARTS OF THE NUCLEAR FUEL CYCLE

Part of cycle	*Occupational collective whole-body dose (man rad per MW(e) y)*
Uranium mining, milling and fuel fabrication	0.2
Reactors	1.0
Fuel reprocessing	1.2[a]
Associated research and development	1.4[b]
Total (rounded)	4

[a] Based only on past experience with the reprocessing of natural uranium, Magnox fuel. Unlikely to be appropriate for the reprocessing of mixed oxide fuel.

[b] Assuming that all the doses incurred are in support of the nuclear fuel cycle.

173. Predictions of expected lifetime doses for workers who spend 40 y at the same job have been made, usually on the basis of linear extrapolation from cumulative doses to workers with 5-15 y of employment. Most of the information from which predictions could be made related to the nuclear power industry, and the situation varied greatly from one country to another. The highest lifetime dose estimates were for fuel reprocessing workers in the United Kingdom and the United States, with a reasonable probability that some workers will receive cumulative lifetime doses exceeding 100 rad, although practically none will be expected to receive more than 200 rad. Workers at power reactors and other jobs associated with the nuclear industry appear more likely to receive maximum lifetime doses of 50-100 rad, but only a few specialized workers will be in this category.

174. On the basis of the data supplied, which is fragmentary and may be biassed towards countries where doses are generally relatively low, lifetime doses to medical workers are unlikely to exceed 50 rad based on current practices. Lifetime doses to workers now reaching the end of their working lives may be considerably greater, but much of the dose will have been received using techniques that are no longer acceptable.

175. Estimates of lifetime doses to industrial workers are also based on scanty data but again appear unlikely to exceed 50 rad. This is the case for industrial radiographers, if the data from termination reports in the United States may be applied elsewhere.

CONSTRUCTION OF THE REFERENCE DISTRIBUTION

1. The distribution of the annual doses x is defined such that:

(a) It is a log-normal distribution as specified in chapter III, paragraph 36;

(b) The average of the annual doses is equal to 0.5 rad;

(c) The probability that an annual dose will lie between 0 and 5 rad is 99.9 per cent.

2. The probability that a value of x will lie between 0 and X is given by

$$P_X = \frac{1}{\sigma\sqrt{2\pi}} \int_0^X \frac{1}{x} e^{-\frac{(\ln x - \mu)^2}{2\sigma^2}} dx$$

Substituting $y = \ln x$ and $Y = \ln X$

$$P_X = \frac{1}{\sigma\sqrt{2\pi}} \int_{-\infty}^{Y} e^{-\frac{(y-\mu)^2}{2\sigma^2}} dy$$

and further substituting $t = \frac{y-\mu}{\sigma}$, the probability becomes

$$P_X = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\frac{Y-\mu}{\sigma}} e^{-\frac{t^2}{2}} dt$$

and can therefore be assessed from tables of the normal distribution. As the reference distribution is defined to have arithmetic mean $\alpha = 0.5$ rad and $P_{5.0} = 0.999$, which corresponds to $\frac{Y-\mu}{\sigma} = 3.09083$, given by the normal distribution tables, it follows that $\frac{\ln 5 - \mu}{\sigma} = 3.09083$. By substitution, $\exp[\ln 5 - 3.090830\sigma + 0.5\sigma^2] = 0.5$, and therefore $\sigma^2 - 6.18166\sigma + 4.60517 = 0$, whence $\sigma = 5.3152$ or 0.86641. The second of these values can be shown to be the relevant one by substitution into the formula relating the average dose to the median dose. The desired solution is therefore $\sigma = 0.86641$, determining also $\mu = -1.06849$.

3. The following characteristics of the reference distribution may be calculated.

(a) *Probability of the annual dose lying in a certain range*

(i) The probability of an annual dose lying in the range 0-0.5 rad is given by

$$P_{0.5} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\frac{Y-\mu}{\sigma}} e^{-\frac{t^2}{2}} dt$$

where $\frac{Y-\mu}{\sigma} = (\ln 0.5 + 1.06849)/0.86641 = 0.43322$; therefore

$$P_{0.5} = 0.66756$$

(ii) The probability of an annual dose lying in the range 0-1.5 rad is

$$P_{1.5} = 0.95554$$

(iii) The probability of an annual dose lying in the range 0-5 rad is

$$P_{5.0} = 0.999 \quad \text{(by definition)}$$

(b) *Fraction of the collective dose contributed by a certain dose range*

The mean of all values of the log-normal distribution up to a certain value X is given by

$$\alpha_X = \int_0^X x P(x)\, dx$$

or

$$\alpha_X = \int_0^X \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{(\ln x - \mu)^2}{2\sigma^2}} dx$$

Substituting

$$z = (\ln x - \mu - \sigma^2)/(\sigma\sqrt{2}),\ dz = \frac{1}{\sigma\sqrt{2}} \frac{1}{x} dx$$

$$x = e^{z\sigma\sqrt{2} + \mu + \sigma^2}$$

therefore

$$\alpha_X = \frac{1}{\sqrt{\pi}} e^{\mu + \frac{\sigma^2}{2}} \int_{-\infty}^{(\ln X - \mu - \sigma^2)/(\sigma\sqrt{2})} e^{-z^2} dz$$

Substituting $\frac{t}{\sqrt{2}} = z$

$$\alpha_X = \frac{1}{\sqrt{2\pi}} e^{\mu + \frac{\sigma^2}{2}} \int_{-\infty}^{(\ln X - \mu - \sigma^2)/(\sigma\sqrt{2})} e^{-\frac{t^2}{2}} dt$$

where by definition

$$e^{\mu + \frac{\sigma^2}{2}} = 0.5$$

The fraction of the total collective dose contributed by doses in the range 0 to X is given by

$$S_X = \frac{\alpha_X P_X}{0.5}$$

(i) For annual doses in the range 0-0.5 rad:

$$\frac{\ln X - \mu - \sigma^2}{\sigma\sqrt{2}} = \frac{\ln 0.5 + 1.06849 - 0.86641^2}{0.86641\sqrt{2}} = -0.30631$$

$$\alpha_{0.5} = 0.5 \times 0.37969, \text{ and}$$

$$\text{therefore } S_{0.5} = 0.25347$$

(ii) For annual doses in the range 0-1.5 rad:

$$\frac{\ln X - \mu - \sigma^2}{\sigma\sqrt{2}} = \frac{\ln 1.5 + 1.06849 - 0.86641^2}{0.86641\sqrt{2}} = 0.59030$$

$$\alpha_{1.5} = 0.5 \times 0.72249, \text{ and}$$

$$\text{therefore } S_{1.5} = 0.69037$$

(iii) For annual doses in the range 0-5 rad:

$$\frac{\ln X - \mu - \sigma^2}{\sigma\sqrt{2}} = \frac{\ln 5.0 + 1.06849 - 0.86641^2}{0.86641\sqrt{2}} = 1.57290$$

$$\alpha_{5.0} = 0.5 \times 0.94212, \text{ and}$$

$$\text{therefore } S_{5.0} = 0.94117$$

(c) *Fraction of the collective dose contributed by annual doses within certain dose ranges*

Annual dose range (rad)	*Fraction of workers in dose range*	*Fraction of the collective dose contributed by annual doses in the dose range*
0-0.5	0.668	0.253
0-1.5	0.956	0.690
0-5.0	0.999	0.941

Appendix II

TABLES 46-96

Some of the tables of data supplied to the Committee are collected in this appendix; the table titles are listed below for ease of reference. Except for editing to obtain some uniformity of presentation, the information is reproduced as received.

Table

46 Frequency distribution of radon exposure among French uranium miners (underground workers), 1971-1975

47 Frequency distribution of external doses to French uranium miners

48 Data on nuclear power plants in the United States, 1969-1975

49 Distribution of occupational dose to workers at French nuclear power plants, 1970, 1971 and 1974

50 Data on nuclear power plants in the Federal Republic of Germany, 1973-1975

51 Data relating to occupational doses at nuclear power plants in Sweden, 1971-1975

52 Distribution of occupational doses to contract workers at two Swiss nuclear power plants in 1975

53 Distribution of occupational external doses at the Comisión Nacional de Energía Atómica (CNEA) and Atucha nuclear power plant, Argentina, 1968-1975

54 Distribution of occupational dose from exposure to tritium at Atucha, Argentina, 1974-1975

55 Data on nuclear power plants in the United Kingdom

56 Distribution of eye dose at five United Kingdom reactor sites, 1971-1973

57 Distribution of occupational dose to fuel-reprocessing workers at Windscale, United Kingdom, 1971-1975

58 Distribution of occupational dose in Belgium, 1973

59 Distribution of occupational dose to United States Atomic Energy Commission (AEC) employees and contractors

60 Distribution of occupational dose received by workers at United Kingdom Atomic Energy Authority establishments, 1972-1974

61 Distribution of occupational dose received by workers at Berkeley Nuclear Laboratories, United Kingdom, 1972-1974

62 Occupational doses in India, 1970-1973

63 Occupational doses in Thailand, 1974

64 Occupational external doses recorded by the National Film Badge Monitoring Service in Israel, 1969-1972

65 Summary of doses to medical workers in Illinois, United States, 1970

66 Distribution of occupational dose in medical departments in Denmark, 1974

67 Frequency distribution of annual recorded occupational dose by type of medical establishment, France, 1975

68 Frequency distribution of the annual dose to a sample of 2579 industrial and research workers in France, 1975

69 Frequency distribution of doses from tritium to French medical research workers, 1968-1976

70 Number and categories of persons monitored for exposure in New Zealand, 1975

71 Distribution of occupational dose by type of establishment, Switzerland, 1974

72a Distribution of occupational dose in the German Democratic Republic by type of establishment, 1970

Table

72b Distribution of occupational dose in the German Democratic Republic by type of establishment, 1971

72c Distribution of occupational dose in the German Democratic Republic by type of establishment, 1972

73 Distribution of annual dose received by a sample of industrial workers in the United Kingdom, 1974

74 Annual average dose in medicine, research and industry in several states of the Federal Republic of Germany, and in West Berlin, 1969-1974

75 Distribution of occupational dose for United States Nuclear Regulatory Commission licensees not connected with the nuclear power industry, 1974

76 Frequency distribution of occupational dose-rate to industrial radiographers in Hungary, 1974

77 Distribution of annual dose to industrial workers (other than luminizers and workers in the nuclear industry) in Switzerland, 1969-1975

78 Frequency distribution of quarterly doses to site radiographers in the United Kingdom

79 Frequency distribution of quarterly doses to factory radiographers in the United Kingdom

80 Distribution of quarterly whole-body doses in excess of 3 rem received by industrial radiographers in the United Kingdom, 1969-1974

81 Annual dose to luminizers in the United Kingdom, 1974

82 Distribution of doses to tritium luminizers in Switzerland, 1969-1975

83 Distribution of annual dose to tritium luminizers in France, 1968-1976

84 Distribution of mean annual dose to workers handling tritium in the luminous paint industry in the Federal Republic of Germany, 1966-1975

85 Annual dose to workers in the Hungarian National Oncological Institute, 1936-1975

86 Annual average dose to groups of workers at Trawsfynydd nuclear power station, United Kingdom, 1972-1974

87 Annual average dose to groups of workers at Hunterston nuclear power station "A", United Kingdom, 1972-1974

88 Average annual dose to groups of workers at Ontario Hydro, Canada

89 Average dose rate to some selected groups of fuel reprocessing workers at Windscale, United Kingdom, 1973-1975

90 Distribution of doses received by workers at the Radiochemical Centre, United Kingdom, 1972-1974

91 Distribution of annual average dose for different groups of workers at Ontario Hydro, Canada

92 Distribution of the cumulative dose for different lengths of employment (power reactors)

93 Distribution of the cumulative dose for different lengths of employment (fuel reprocessing)

94 Distribution of the cumulative dose for different lengths of employment (fuel fabricating and scrap recovery)

95 Age distribution of persons in specific occupational groups in Australia

96 Distribution of the cumulative dose for different lengths of employment (industrial radiography)

TABLE 46. FREQUENCY DISTRIBUTION OF RADON EXPOSURE AMONG FRENCH URANIUM MINERS (UNDERGROUND WORKERS), 1971-1975

Year	Exposure range (fraction of MAC)[a]									Mean annual exposure (WL)
	⩽ 0.10	0.11-0.20	0.21-0.30	0.31-0.40	0.41-0.50	0.51-0.60	0.61-0.80	0.81-1.00	> 1.00	
	Percentage of workers									
1971	36.08	22.39	19.90	13.12	6.22	2.14	0.15			0.18
1972	37.30	22.55	21.13	12.27	4.36	2.24	0.15			0.17
1973	37.70	19.32	19.43	14.40	7.72	1.43				0.18
1974	43.38	26.89	21.46	6.21	1.35	0.71				0.13
1975	53.91	24.71	16.03	4.58	0.66	0.11				0.11

Source: Reference 54.

[a] For each worker the annual exposure is represented by the mean annual air concentration and is expressed as a fraction of the maximum annual concentration (MAC). Given the administrative arrangements and the effective state of equilibrium between radon and its daughters, the MAC is practically equivalent to 1 WL.

TABLE 47. FREQUENCY DISTRIBUTION OF EXTERNAL DOSES TO FRENCH URANIUM MINERS

Year	Location of work site	Annual dose range (rem)								Mean annual dose (rem)
		0-0.5	0.5-1.0	1.0-1.5	1.5-2.0	2.0-2.5	2.5-3.0	3.0-4.0	4.0-5.0	
		Percentage of workers								
1971	Underground	35.91	24.71	22.41	11.78	3.01	1.58	0.60		0.88
	Surface	92.19	6.05	0.94	0.67	–	–	0.15		0.25
1972	Underground	34.54	20.91	21.23	12.83	5.86	3.80	0.83		0.97
	Surface	92.57	5.94	0.74	0.37	0.37	–	–		0.21
1973	Underground	42.81	23.43	15.93	11.40	4.84	1.59			0.78
	Surface	92.12	4.87	2.25	0.62	0.14	–			0.18
1974	Underground	48.88	25.55	15.00	7.13	1.78	1.33	0.33		0.67
	Surface	91.91	6.91	0.93	–	0.12	–	0.12		0.18
1975	Underground	63.85	21.04	9.16	3.95	1.35	0.65			0.49
	Surface	94.38	4.81	0.40	0.26	–	0.15			0.13

Source: Reference 54.

TABLE 48. DATA ON NUCLEAR POWER PLANTS IN THE UNITED STATES, 1969-1975

Energy generated, personnel and dose

Plant	Year	Electrical energy generated (MW y)	Number of employees			Annual collective dose (man rem)					Annual average dose (rem)	Collective dose per unit energy generated (man rem per MW(e) y)
			Total	Contractor	Utility	Total	Operations	Maintenance	Contractor	Utility		
ARKANSAS 1	75	588.0	147			46					0.31	0.1
Docket 50-313, DPR-51												
First commercial operation-8/74												
Type – PWR												
Capacity – 850 MW												
BIG ROCK POINT	69	43.2	165			136					0.82	3.1
Docket 50-155, DPR-6	70	43.5	290			194					0.67	4.5
First commercial operation-3/63	71	44.4	260			184					0.7	4.1
Type – BWR	72	43.5	195			181					0.92	4.1
Capacity – 72 MW	73	50.9	119			336			140	196	2.8	6.6
	74	40.7	281			276	54	222	42	234	0.98	6.6
	75	35.1	216			180	58	122	20	160	0.83	5.1
BROWN'S FERRY 1	75	328.9	2 380			325					0.14	1.0
Docket 50-259, DPR-33												
First commercial operation-8/74												
Type – BWR												
Capacity – 1 065 MW												
HADDAM NECK	69	397.6	138	75	63	106			27	79	0.77	.5
Docket 50-213, DPR-61	70	424.7	734	657	77	689			463	226	0.94	1.7
First commercial operation-1/68	71	502.2	289	216	73	342			166	176	1.18	.8
Type – PWR	72	515.6	355	285	70	325			181	144	.91	.7
Capacity – 575 MW	73	293.1	841	770	71	673			525	148	0.80	2.1
	74	519.1	550			201					0.37	.4
	75	494.3	795			669	19	650			0.84	1.4
COOPER STATION	75	456.4	175	71	104	96	25	71	16	80	0.55	0.2
Docket 50-298, DPR-46												
First commercial operation-7/74												
Type – BWR												
Capacity – 778 MW												
DRESDEN 1, 2, 3	69	89.4				286						3.2
Docket 50-10, 50-237, 50-249	70	304.0				143						.5
DPR-10, 19, 25	71	394.5				715						1.8
First commercial operation-7/60,	72	1 243.7				728						.6
6/72, 11/71	73	1 112.2	1 341			909	138	771	333	576	0.68	.8
Type – BWR	74	842.5	1 594	318	1 276	1 662			57	1 605	1.04	2.0
Capacity MW 200, 809, 809	75	708.1	3 671	3 076	595	3 209	254	2 955	2 111	1 098	0.87	4.5
FORT CALHOUN	75	252.3	469	369	100	298			93	205	0.63	1.2
Docket 50-285, DPR-40												
First commercial operation-6/74												
Type – PWR												
Capacity – 457 MW												

GINNA	70	268.5	170	56	114	207	94	113	15	192	1.21	.8
Docket 50-244, DPR-18	71	327.8	340	134	206	430	69	361	108	322	1.26	1.3
First commercial operation-3/70	72	295.6	677	266	411	1 032	71	961	278	754	1.52	3.4
Type – PWR	73	409.5	421			244	60	184	91	153	0.58	.6
Capacity – 490 MW	74	253.7	884			1 224					1.38	4.8
	75	365.2	558			496					0.89	1.4
HUMBOLDT BAY	69	40.6	125	41	84	164	69	95	12	152	1.31	4.0
Docket 50-133, DPR-7	70	49.3	115	35	80	209	130	79	37	172	1.81	4.3
First commercial operation-2/63	71	39.6	140	53	87	292	114	178	65	227	2.1	7.7
Type – BWR	72	43.1	127	54	73	253	81	172	57	196	1.99	5.9
Capacity – 65 MW	73	50.1	235			261	59	202			1.11	5.3
	74	43.4	296	221	75	318	103	215			1.07	7.1
	75	45.3	303	230	73	332	128	204	110	222	1.10	7.3
INDIAN POINT 1, 2	69	183.3				298						1.6
Docket 50-3, 50-247. DPR-5, 26	70	43.3				1 639						33.0
First commercial operation-10/62,	71	154.0				768						5.0
8/73	72	142.3				967						6.6
Type – PWR	73	0	2 998			5 134	692	4 442	2 778	2 356	1.71	
Capacity – 265 MW, 873 MW	74	556.1	1 019	114	905	910					0.89	1.6
	75	584.4	480	73	407	626	147	479	42	584	1.3	1.1
KEWAUNEE	75	401.9	54	23	41	25	1	24	11	14	.5	.06
Docket 50-305, DPR-43												
First commercial operation-6/74												
Type – PWR												
Capacity – 560 MW												
LACROSSE	71	33.1	218			158					0.72	5.0
Docket 50-409, DPR-45	72	29.2	151			172					1.13	5.9
First commercial operation-9/69	73	24.4	157			221					1.41	9.1
Type – BWR	74	37.9	115	21	94	139	89	50	6	133	1.21	3.7
Capacity – 50 MW	75	32.0	165			234					1.42	7.3
MAINE YANKEE	73	408.7	422	309	113	121			61	60	0.29	.3
Docket 50-209, DPR-36	74	432.6	620	485	135	420	64	356	188	232	0.68	1.0
First commercial operation-12/72	75	542.9	577	418	159	347	16	331	197	150	0.60	0.6
Type – PWR												
Capacity – 790 MW												
MILLSTONE POINT 1	72	377.6	612	487	125	596	50	546	340	256	0.97	1.6
Docket 50-245, DPR-21	73	225.1	1 152	982	170	620	117	503	395	225	0.54	2.7
First commercial operation-3/71	74	430.3	2 477			1 430					0.58	3.3
Type – BWR	75	465.4	2 587			2 022					0.78	4.3
Capacity – 690 MW												
MONTICELLO	72	424.4	99	9	90	61	40	21	1	60	0.61	.1
Docket 50-363, DPR-22	73	389.5	276	145	131	154	42	112	59	95	0.56	.4
First commercial operation-7/71	74	349.3	842	477	365	349			91	258	0.41	1.0
Type – BWR	75	344.8	1 353			1 353					1.0	3.9
Capacity – 545 MW												
NINE MILE POINT	70	227.0	821	660	161	44	12	32	17	27	0.05	.2
Docket 50-220, DPR-63	71	346.5	1 006	738	268	195	43	152	63	89	0.19	.6
First commercial operation-12/69	72	381.8	735	450	285	285	59	226	28	198	0.38	.8
Type – BWR	73	411.0	550	318	232	517	127	390	108	409	0.94	1.3
Capacity – 610 MW	74	385.9	740	463	277	824	42	782	279	545	1.11	2.1
	75	359.0	649	329	320	681	68	613	203	478	1.04	1.9

TABLE 48 *(continued)*

Plant	*Year*	*Electrical energy generated (MW y)*	*Number of employees*			*Annual collective dose (man rem)*					*Annual average dose (rem)*	*Collective dose per unit energy generated (man rem per MW(e) y)*
			Total	*Contractor*	*Utility*	*Total*	*Operations*	*Maintenance*	*Contractor*	*Utility*		
OCONEE 1, 2, 3	74	724.3	844	253	591	517	18	499	144	373	0.61	.7
Docket 50-269, 270, 287 DPR-38, 47, 55	75	1 838.3	541	112	429	457	66	391	83	374	0.84	.3
First commercial operation-7/73, 9/74, 12/74												
Type – PWR												
Capacity – 886, 886, 886 MW												
OYSTER CREEK	69	40.1										
Docket 50-219, DPR-16	70	413.6	95	32	63	63	21	42	11	52	0.66	.2
First commercial operation-12/69	71	448.9	249	164	85	240	50	190	92	148	0.96	.5
Type – BWR	72	515.0	339	242	97	582	150	432	167	415	1.71	1.1
Capacity – 650 MW	73	424.6	782	635	147	1 236	195	1 041	683	553	1.58	2.9
	74	434.5	935	346	589	984	166	818	162	822	1.05	2.3
	75	373.6	1 210			1 132	168	964	269	863	0.94	3.0
PALISADES	72	216.8				78						
Docket 50-255, DPR-20	73	286.8	901	608	293	1 109	16	1 093	647	462	1.23	3.8
First commercial operation-12/71	74	10.5	774			627					0.81	60
Type – PWR	75	300.2	474			292					0.62	0.97
Capacity – 821 MW												
PEACH BOTTOM 2, 3	75	1 234.3	971			228					0.84	0.18
Docket 50-277, 278, DPR 44, 56												
First commercial operation-12/74												
Type – BWR												
Capacity – 1 065, 1 065 MW												
PILGRIM	73	484.0	53			74	29	45			1.4	.2
Docket 50-293, DPR-35	74	234.1	454			415					0.91	1.8
First commercial operation-12/72	75	308.1	473			744	132	612	384	360	1.6	2.4
Type – BWR												
Capacity – 655 MW												
SURRY 1 & 2	73	829.4	936			152					0.16	.2
Docket 50-280, 281, DPR-32, 37	74	717.4	1 715			884	72	812			0.52	1.2
First commercial operation-12/72, 5/73	75	1 029.7	808			1 549	25	1 524	1 000	549	1.91	1.5
Type – PWR												
Capacity – 823 MW, 823 MW												
THREE MILE ISLAND 1	75	675.9	168			83			21	62	0.49	0.1
Docket 50-289, DPR-50												
First commercial operation-9/74												
Type – PWR												
Capacity – 819 MW												
TURKEY POINT 3 & 4	73	565.9	444			78					0.18	.1
Docket 50-250, 251, DPR-31, 41	74	966.4	794			454	88	366	202	252	0.57	.5
First commercial operation-12/72, 9/73	75	1 003.7	1 175			875	270	605	558	317	0.74	0.87

Type – PWR Capacity – 745 MW												
VERMONT YANKEE	73	222.1	244			85					0.35	.4
Docket 50-271, DPR-28	74	303.5	357			216	24	192	103	113	0.61	.7
First commercial operation-11/72	75	429.0	247	164	83	139	64	75	57	82	0.66	.3
Type – BWR Capacity – 514 MW												
YANKEE ROWE	69	123.1	193	117	76	215	46	169	78	91	1.1	1.8
Docket 50-29, DPR-3	70	146.1	355	280	75	255	60	195	98	97	0.71	1.8
First commercial operation-7/61	71	173.5	155	60	95	90	44	46	19	71	0.58	.5
Type – PWR	72	78.7	282	210	72	255	60	195	147	108	0.90	3.2
Capacity – 175 MW	73	127.1	263	158	105	146			70	76	0.56	1.1
	74	111.3	243	149	94	205			99	106	0.84	1.8
	75	145.1	210	134	76	138	62	76	78	60	0.66	1.0
ZION 1, 2	74	425.3	306	87	219	56			13	43	0.18	.2
Docket 50-295, 304, DPR-39, 48	75	1 181.5	1 433	938	495	117	16	101	45	72	.08	0.1
First commercial operation-12/73, 9/74 Type – PWR Capacity – 1 050 MW												
POINT BEACH 1 & 2	72	378.3				580						1.5
Docket 50-266, 301, DPR-24, 27	73	693.7	729			570	70	500			0.78	.8
First commercial operation-12/70,	74	760.2	400			295	70	225	81	214	0.74	.4
4/73	75	801.2	339			456					1.3	0.6
Type – PWR Capacity – 497 MW, 497 MW												
PRAIRIE ISLAND 1,2	74	181.9	150	56	94	18			5	13	0.12	.1
Docket 50-282, 306, DPR-42, 60	75	836.0	477			123					0.26	0.15
First commercial operation-12/73, 12/74 Type – PWR, PWR Capacity – 530 MW, 530												
QUAD CITIES 1 & 2	73	1 209.6	533			201	28	173	59	142	0.37	.2
Docket 50-254, 265, DPR-29, 30	74	958.1	678	488	190	482			36	446	0.71	.5
First commercial operation-2/73,	75	833.6	1 972	1 418	554	1 385	98	1 287	592	793	0.70	1.7
3/73 Type – BWR Capacity – 809 MW, 809 MW												
ROBINSON	71	295.3	283	242	41	364	7	357	351	13	1.28	1.2
Docket 50-261, DPR-23	72	580.0	245	147	98	215	42	173	137	78	0.87	.4
First commercial operation-3/71	73	455.1	831			695					0.83	1.5
Type – PWR	74	578.1	853			672	185	487			0.78	1.2
Capacity – 707 MW	75	501.8	849			1 142					1.35	2.3
SAN ONOFRE 1	69	289.8	123	32	91	42	10	32	5	37	0.34	.2
Docket 50-206, DPR-13	70	365.9	251	92	159	155	13	142	59	96	0.61	.4
First commercial operation-1/68	71	362.1	121	12	109	50	12	38	3	47	0.41	.1
Type – PWR	72	372.2	326	141	185	256	29	227	117	139	0.78	.7
Capacity – 450 MW	73	273.7	878	547	331	329	37	292	157	172	0.37	1.2
	74	377.8	219			71					0.32	.2
	75	389.0	424			292					0.75	0.7

Source: Reference 78.

TABLE 49. DISTRIBUTION OF OCCUPATIONAL DOSE TO WORKERS AT FRENCH NUCLEAR POWER PLANTS, 1970, 1971 AND 1974

Dose range (rad)	*1970*	*1971*	*1974*
		Number of workers	
< 0.1	880	970	
0.1-0.2	139	116	
0.2-0.3	83	65	1 120
0.3-0.4	60	44	
0.4-0.5	44	35	
0.5-0.6	38	44	
0.6-0.7	30	43	
0.7-0.8	21	37	145
0.8-0.9	20	28	
0.9-1.0	12	24	
1.0-1.5	57	102	130
1.5-2.0	27	65	105
2.0-2.5	21	35	29
2.5-3.0	26	12	24
3.0-3.5	11	15	11
3.5-4.0	4	5	12
4.0-4.5	1	1	3
4.5-5.0	1	1	2
5.0-6.0			12
6.0-7.0	3	2	2
> 7.0			0
Total	1 478	1 644	1 598
Average annual dose (rad)	0.34	0.39	0.55
Collective dose (man rad)	504	648	879
Ω^a	1.5	1.2	1.7

Sources: References 28, 29, 12 (for 1970, 1971 and 1974, respectively).
[a]Obtained by fitting a log-normal distribution.

TABLE 50. DATA ON NUCLEAR POWER PLANTS IN THE FEDERAL REPUBLIC OF GERMANY, 1973-1975

Energy generated, personnel and dose

Plant		Year	Availability (%)	Gross energy (GW(e) h)	Plant personnel			External personnel			Total personnel		
					Number of persons	Collective dose (man rem)	Average dose (rem)	Number of persons	Collective dose (man rem)	Average dose (rem)	Number of persons	Collective dose (man rem)	Average dose (rem)
VAK Kahl													
Capacity	16 MW(e)	1973	37.2	50	83	178	2.14	27	10	0.37	110	188	1.77
Type	BWR	1974	67.8	91	87	206	2.37	75	69	0.92	162	275	1.69
First criticality	1961	1975	52.6	76	96	205	2.14	97	69	0.71	193	274	1.42
First commercial operation	11/61												
MZFR Karlsruhe													
Capacity	58 MW(e)	1973	20.2	100	107	83	0.77	87	77	0.88	194	160	0.82
Type	D_2O-PWR	1974	73.1	367	110	66	0.66	70	63	0.90	170	129	0.76
First criticality	5/65	1975	73.6	370	104	58	0.56	75	68	0.91	179	126	0.70
First commercial operation	12/66												
KRB Gundremming													
Capacity	250 MW(e)	1973	79.4	1 727	109	375	3.44	373	286	0.77	482	661	1.37
Type	BWR	1974	88.1	1 920	118	342	2.90	307	323	1.05	425	665	1.56
First criticality	8/66	1975	88.4	1 896	125	304	2.43	324	355	1.10	449	659	1.47
First commercial operation	3/67												
KWL Lingen													
Capacity	252 MW(e)	1973	60.2	1 332	139	158	1.14	141	125	0.88	280	283	1.01
Type	BWR	1974	20.9	481	168	175	1.04	245	253	1.05	413	433	1.05
First criticality	2/68	1975	71.8	1 614	156	228	1.46	577	798	1.38	733	1 026	1.40
First commercial operation	10/68												
AVR Jülich													
Capacity	15 MW(e)	1973	89.8	115	122	45	0.37	4	0	0.1	126	45	0.36
Type	HTR	1974	70.8	91	127	58	0.46	32	2	0.05	159	60	0.37
First commercial		1975	37.6	112	128	55	0.43	6	0	0.02	134	55	0.41
operation	1968												
KWO Obrigheim													
Capacity	345 MW(e)	1973	89.8	2 629	144	261	1.81	408	415	1.02	552	676	1.22
Type	PWR	1974	92.1	2 570	144	251	1.74	394	335	0.85	538	586	1.09
First commercial		1975	91.5	2 732	146	277	1.90	391	405	1.04	537	682	1.27
operation	4/69												
KKS Stade													
Capacity	662 MW(e)	1973	73.1	4 131	149	137	0.92	756	266	0.35	905	403	0.44
Type	PWR	1974	92.0	5 328	144	127	0.88	402	172	0.43	546	299	0.55
First criticality	1/72	1975	84.8	4 776	146	162	1.14	473	226	0.48	619	388	0.63
First commercial operation	5/72												

TABLE 50 *(continued)*

Plant		*Year*	*Availability (%)*	*Gross energy (GW(e) h)*	*Plant personnel*			*External personnel*			*Total personnel*		
					Number of persons	*Collective dose (man rem)*	*Average dose (rem)*	*Number of persons*	*Collective dose (man rem)*	*Average dose (rem)*	*Number of persons*	*Collective dose (man rem)*	*Average dose (rem)*
KWW Würgassen													
Capacity	670 MW(e)	1973	49.6	2 065	162	32	0.20	717	63	0.09	879	95	0.11
Type	BWR	1974	11.1	488	173	73	0.42	1 543	425	0.27	1 716	498	0.29
First criticality	10/71	1975	46.3	1 830	178	55	0.31	1 101	166	0.15	1 279	221	0.17
First commercial operation	1972												
KNK Karlsruhe													
Capacity	21 MW(e)	1973	22.2	21	93	5	0.05	73	2	0.02	166	6	0.04
Type	Na-ZrH	1974	34.9	43	97	3	0.03	173	6	0.04	270	10	0.03
First criticality	8/71	1975	0	0	93	15	0.16	136	31	0.23	229	46	0.20
First commercial operation	1973												
Biblis A Biblis													
Capacity	1204 MW(e)	1974	46.7	883	303	1	0.004	10	–	–	313	1	0.004
Type	PWR	1975	82.5	8 419	377	17	0.05	45	2	0.04	422	19	0.05
First criticality	7/74												
First commercial operation	2/75												

Source: Reference 72a.

TABLE 51. DATA RELATING TO OCCUPATIONAL DOSES AT NUCLEAR POWER PLANTS IN SWEDEN, 1971-1975

Plant	Installed capacity (MW(e))	Year	Employees (E) or Contractors (C)	Collective dose (man rad)	Number of persons with registered doses[a]	Average annual dose to persons with registered doses (rad)	Collective dose per unit energy generated (man rad per MW(e) y)
Oskarshamm 1 (BWR)	440	1971	E	0	1	0.10	0.38
			C	2	3	0.83	
		1972	E	2	–	–	0.06
			C	8	–	–	
		1973	E	5	–	–	0.09
			C	17	–	–	
Oskarshamm 1 (BWR)	440	1974	E	19	91	0.21	0.71
Oskarshamm 2 (BWR)	580		C	118	578	0.20	
		1975	E	17	81	0.21	0.13
			C	67	448	0.15	
Ringhals 1 (BWR)	750	1974	E	1	1	0.80	0.06
Ringhals 2 (PWR)	820		C	1	5	0.26	
		1975	E	47	277	0.16	0.32
			C	119	723	0.16	
Barsebäcks 1 (BWR)	580	1975	E	5	40	0.13	0.05
			C	5	52	0.09	

Source: Reference 69a.

[a] Persons receiving annual doses in excess of 0.1 rad for 1971-1973 or in excess of 0.03 rad for 1974-1975.

TABLE 52. DISTRIBUTION OF OCCUPATIONAL DOSES TO CONTRACT WORKERS AT TWO SWISS NUCLEAR POWER PLANTS IN 1975

Annual dose range (rad)	Beznau I and II	Mühleberg
	Number of workers	
< 0.1	64	57
0.1-0.5	63	69
0.5-1.0	28	21
1.0-1.5	18	14
1.5-2.0	6	4
2.0-2.5	11	6
2.5-3.0	4	4
Total	194	175
Collective dose (man rad)	110	82

Source: Reference 61.

TABLE 53. DISTRIBUTION OF OCCUPATIONAL EXTERNAL DOSES AT THE COMISION NACIONAL DE ENERGIA ATOMICA (CNEA) AND ATUCHA NUCLEAR POWER PLANT, ARGENTINA, 1968-1975

	Annual dose range (rad)				
	< 0.1	0.1-0.5	0.5-1.0	1.0-5.0	> 5.0
	Number of workers				
CNEA					
1968	584	98	28	14	0
1969	771	96	10	4	0
1970	885	49	7	7	0
1971	842	66	20	13	0
1972	884	44	11	9	0
1973	741	98	18	40	0
1974	713	104	24	15	1
Atucha N.P.P.					
1974	36	201	25	9	0
1975	34	188	71	24	0

Sources: References 21, 25.

TABLE 54. DISTRIBUTION OF OCCUPATIONAL DOSE FROM EXPOSURE TO TRITIUM AT ATUCHA, ARGENTINA, 1974-1975

	Annual dose range (rem)				
Year	*0-0.1*	*0.1-0.5*	*0.5-1.0*	*1.0-5.0*	*> 5.0*
	Number of workers				
1974	242	24	4	1	0
1975	265	43	8	1	0

Note: These values may be overestimated by perhaps a factor of two because of uncertainties in the date of the contamination.

TABLE 55. DATA ON NUCLEAR POWER PLANTS IN THE UNITED KINGDOM

Dose distribution, collective dose and energy

(Number of workers)

	Dose distribution								
	Dose range (rem)								
Plant	*≤ 0.5*	*> 0.5 ≤ 1.5*	*> 1.5 ≤ 4.0*	*> 4.0 ≤ 5.0*	*> 5.0*	*Total*	*Collective dose (man rem)*	*Electricity generated (10^6 MW h)*	*Electricity supplied to grid (10^6 MW h)*
				(a) 1972					
Berkeley	169	198	25	0	0	392	271	2.318	1.954
Bradwell	291	123	1	0	0	415	164	2.123	1.811
Hinkley Point	588	107	22	0	0	717	253	3.530	2.975
Trawsfynydd	242	133	125	12	1	513	575	2.802	2.372
Dungeness	533	11	0	0	0	544	135	3.351	3.230
Sizewell	467	7	0	0	0	474	53	3.236	2.689
Oldbury	425	16	0	0	0	441	75	2.754	2.650
Wylfa	315	0	0	0	0	315	37	2.820	2.418
Hunterston	367	302	4	0	0	673	364	2.576	1.985
				(b) 1973					
Berkeley	202	173	43	0	0	418	302	2.478	2.086
Bradwell	409	98	1	0	0	507	146	1.889	1.606
Hinkley Point	1 083	174	43	1	0	1 301	410	2.796	2.344
Trawsfynydd	357	141	100	0	0	598	430	2.418	2.038
Dungeness	630	3	0	0	0	633	129	3.327	3.207
Sizewell	621	22	3	0	0	646	84	3.469	2.906
Oldbury	399	21	0	0	0	420	73	2.652	2.554
Wylfa	601	0	0	0	0	601	63	3.186	2.604
Hunterston	513	173	4	0	0	690	277	2.293	1.938
				(c) 1974					
Berkeley	182	189	33	0	0	404	284	2.338	1.966
Bradwell	306	92	1	0	0	399	129	2.098	1.787
Hinkley Point	1 331	271	40	0	0	1 642	515	3.657	3.070
Trawsfynydd	466	111	29	0	0	606	260	3.820	3.242
Dungeness	683	3	0	0	0	686	135	3.524	3.401
Sizewell	496	13	5	0	0	514	82	3.762	3.158
Oldbury	404	22	0	0	0	426	71	2.911	2.807
Wylfa	597	0	0	0	0	597	72	4.417	3.723
Hunterston	503	199	16	0	0	718	344	2.467	2.127

Sources: References 39, 85.

TABLE 56. DISTRIBUTION OF EYE DOSE AT FIVE UNITED KINGDOM REACTOR SITES, 1971-1973

(Number of workers)

Site No.	Year	Annual dose range (rem)															Total
		< 0.99	1.00-1.99	2.00-2.99	3.00-3.99	4.00-4.99	5.00-5.99	6.00-6.99	7.00-7.99	8.00-8.99	9.00-9.99	10.00-10.99	11.00-11.99	12.00-12.99	13.00-13.99	14.00-14.99	> 15	
	1971	440	21	6	4	1	3	1	1									477
1	1972	470	21	11	0	2	3	1	0									508
	1973	479	18	3	1	0	0	0	0									501
	1971	268	79	20	1	0	1	0	1									370
2	1972	254	89	12	3	0	0	0	0									358
	1973	234	93	20	5	0	0	0	0									352
	1971	368	87	55	31	21	7	5	0	2	3	0	0	3	0	0	0	582
3	1972	215	83	42	33	24	16	12	13	16	19	15	9	3	8	3	1	512
	1973	295	88	47	34	20	12	5	2	2	2	0	0	0	0	0	0	507
	1971	480	45	26	17	21	6	5	11	2	2	1	2	2	0	3		623
4	1972	532	74	24	21	17	7	6	5	3	3	1	0	0	0	0		693
	1973	618	85	51	33	38	16	11	7	4	2	1	1	0	0	0		867
	1971	407	0															407
5	1972	386	6															392
	1973	361	8															369
	Total	5 807	797	317	183	144	71	46	40	29	31	18	12	8	8	6	1	7 518

Source: Reference 85.

TABLE 57. DISTRIBUTION OF OCCUPATIONAL DOSE TO FUEL-REPROCESSING WORKERS AT WINDSCALE, UNITED KINGDOM, 1971-1975

Dose range (rem)	*1971*	*1972*	*1973*	*1974*	*1975*
			Number of workers		
< 0.5	1 286	1 272	1 195	1 295	1 603
0.5-1.0	377	415	429	459	507
1.0-1.5	193	218	257	313	283
1.5-5.0	583	603	603	649	952
> 5.0	99	144	111	112	36
Total	2 538	2 652	2 595	2 828	3 381
Collective dose (man rem)	3 051	3 379	3 255	3 486	4 028
Average dose (rem)	1.20	1.27	1.25	1.23	1.19

Source: Reference 48.

TABLE 58. DISTRIBUTION OF OCCUPATIONAL DOSE IN BELGIUM, 1973

(Number of workers)

Occupational category	*Annual dose range (rad)*					*Total*
	0	*0-0.15*	*0.15-1.5*	*1.5-5.0*	*> 5.0*	
Medical	856	2 320	1 295	174	2	4 647
All workers	6 547	5 343	3 049	406	16	15 361
Producers (nuclear fuel cycle)[a]	1 055	549	393	127	13	2 137

Source: Reference 73.
[a]Including Mol and Eurochemie.

TABLE 59. DISTRIBUTION OF OCCUPATIONAL DOSE TO UNITED STATES ATOMIC ENERGY COMMISSION (AEC) EMPLOYEES AND CONTRACTORS

(Number of recorded doses)

Year and employee type	*Total number monitored*[a]	*Dose range (rad)*								
		< 1.25	*1.25-2*	*2-3*	*3-4*	*4-5*	*5-6*	*6-7*	*11-12*	*> 12*
1971										
AEC	1 428	1 424	4	–	–	–	–	–	–	–
Contractors	170 259 (75 939)	167 692	1 327	855	262	110	7	3	1	2
1972										
AEC	1 615	1 611	2	1	1	–	–	–	–	–
Contractors	156 905 (69 060)	154 688	1 097	847	185	78	8	2		
		0-1	*1-2*	*2-3*	*3-4*	*4-5*	*5-6*	*6-7*		
1973										
AEC	1 686	1 680	3	3	–	–	–	–		
Contractors	152 431 (62 000)	149 523	1 947	726	172	60	2	1		

Sources: References 111, 112, 113.
[a]The number in parentheses is the number of visitors.

TABLE 60. DISTRIBUTION OF OCCUPATIONAL DOSE RECEIVED BY WORKERS AT UNITED KINGDOM ATOMIC ENERGY AUTHORITY ESTABLISHMENTS, 1971-1974

Dose range (rem)	*1972*	*1973*	*1974*
	Number of workers		
< 1.5	5 949	5 798	6 136
1.5-3	694	648	587
3-4	258	189	142
4-5	152	115	97
5-6	25	4	3
6-7	2	1	1
7-8		1	
8-9	1		
9-10			
> 10		1	2[a]
Total	7 088	6 757	6 968
Collective dose recorded[b] (man rem)	5 021	4 455	3 960
Estimated collective dose for lost films (man rem)	424	437	428
Average dose (rem)	0.71	0.66	0.57

Source: Reference 33.
[a]Unlikely to be doses received by workers.
[b]Including estimated collective dose for lost films.

TABLE 61. DISTRIBUTION OF OCCUPATIONAL DOSE RECEIVED BY WORKERS AT BERKELEY NUCLEAR LABORATORIES, UNITED KINGDOM, 1972-1974

Dose range (rem)	*1972*[a]	*1973*	*1974*
	Number of workers		
≤ 0.5	488	569	630
> 0.5 ≤ 1.5	34	22	18
> 1.5 ≤ 4.0	7	4	1
> 4.0 ≤ 5.0	0	0	0
> 5	0	0	0
Total	529	595	649
Collective dose (man rem)	126	110	98

Source: Reference 85.
[a]Not including contractors.

TABLE 62. OCCUPATIONAL DOSES IN INDIA, 1970-1973

(Number of radiation workers N *and average dose* $\bar{D}$ *(rad))*

	Occupational category							
	Medical		*Industrial*		*Research*		*Atomic energy*[a]	
Year	N[b]	$\bar{D}$[c]	N[b]	$\bar{D}$[c]	N[b]	$\bar{D}$[c]	N[b]	$\bar{D}$[c]
1970	6 059	0.24	1 118	0.40	1 008	0.05	4 094	0.58
1971	6 893	0.25	1 247	0.21	1 294	0.04	4 676	0.38
1972	7 304	0.18	1 538	0.31	1 328	0.03	5 142	0.77
1973	7 739	0.12	1 760	0.32	1 562	0.02	5 578	0.75

Source: Reference 50.
[a]Operations conducted by the Department of Atomic Energy.
[b]Number of radiation workers.
[c]Average dose (rad).

TABLE 63. OCCUPATIONAL DOSES IN THAILAND, 1974

Type of work	*Number of institutions monitored*	*Number of radiation workers*	*Annual average dose (rad)*
Industrial	7	40	0.060
Research	9	53	0.620
Research reactor	1	68	0.547
Medical			
Radium	8	150	0.460
Nuclear medicine	9	303	0.255
X rays	300	1 660	0.120

Source: Reference 94.

TABLE 64. OCCUPATIONAL EXTERNAL DOSES RECORDED BY THE NATIONAL FILM BADGE MONITORING SERVICE IN ISRAEL, 1969-1972

	Annual collective dose (man rad)				*Annual average dose (rad)*			
Type of work	*1969*	*1970*	*1971*	*1972*	*1969*	*1970*	*1971*	*1972*
Medical (diagnostic, therapeutic, dental)	101	89	91	118	0.071	0.063	0.060	0.080
Industrial and agricultural	18	16	12	19	0.076	0.064	0.028	0.046
Research and education	26	16	11	34	0.040	0.023	0.013	0.037
Atomic energy	52	84	79	91	0.057	0.114	0.099	0.114
Overall Ω value[a]	0.9	1.5	2.0	2.1				

Source: Reference 7.

[a] Calculated by fitting a log-normal distribution.

TABLE 65. SUMMARY OF DOSES TO MEDICAL WORKERS IN ILLINOIS, UNITED STATES, 1970

Category	*Number of reports*	*Mean dose (rem per quarter)*	*Collective dose (man rem per quarter)*
Dentists	24	0.024	0.58
Physicians	75	0.043	3.22
Osteopaths	0	0	0
Chiropractors	10	0.003	0.03
Veterinarians	6	0.098	0.59
Podiatrists	0	0	0
Nursing institutions	3	0.023	0.069
Hospitals	1 125	0.085	95.6
Clinics	45	0.080	3.6
Private laboratories	3	0.057	0.17

Source: Reference 64.

TABLE 66. DISTRIBUTION OF OCCUPATIONAL DOSE IN MEDICAL DEPARTMENTS IN DENMARK, 1974

Derived from film badges[a]

	X-ray department (hospitals)	*Lung clinics*	*Surgical department (hospitals)*	*Other departments (hospitals)*	*Dermatologists*	*Hospitals in Greenland*	*Medical practitioners*	*Public dental clinics*	*Chiropractors*	*Veterinary x-ray personnel*	*Isotope laboratories*	*X-ray analysis*	*Industrial x and gamma rays*	*X-ray firms*	*Radium centres*	*Total*
Number of departments	127	40	14	11	30	19	21	10	63	72	122	30	44	15	21	639
								Number of badges								
Dose range (mrem)																
0-10	21 386	2 453	2 126	1 152	985	1 692	1 093	1 028	1 094	1 026	12 588	2 250	2 227	2 068	3 062	56 230
10-50	4 586	286	175	224	177	53	107	33	25	62	454	10	198	128	443	6 961
50-100	430	13	33	28	30	3	8	1	1	11	86	6	100	23	312	1 085
100-400	216	10	8	2	34	1	2	2		2	72	1	90	8	389	837
400-1 000	15		2		5						5		2		21	50
1 000-3 000	3				1									2	3	9
5 000-10 000																
Total	26 641	2 762	2 345	1 407	1 233	1 749	1 210	1 064	1 120	1 101	13 205	2 267	2 618	2 234	4 230	65 186
Number of contaminated films	22										601		2		52	677
Total dose (mrem)	165 154	7 515	8 460	6 575	15 200	1 305	2 820	960	415	2 260	29 940	745	25 850	13 715	114 070	394 984
Mean exposure per film (mrem)	6.2	2.7	3.1	4.5	12.4	0.7	2.3	0.9	0.4	2.0	2.3	0.3	9.8	6.1	26.9	6.1
Number of persons	2 422	251	213	128	112	159	110	97	102	100	1 200	206	238	203	385	5 926
Summary of individual doses	> 5 000 mrem y^{-1}, 0; >500 mrem y^{-1}, 137; > 3 000 mrem in 13 weeks, 0; > 1 500 mrem y^{-1}, 21															

[a]The personal dosimetry service covers about 6000 persons. The films are changed each month, except during June and July, which together make one measuring period.

Source: Reference 118.

TABLE 67. FREQUENCY DISTRIBUTION OF ANNUAL RECORDED OCCUPATIONAL DOSE BY TYPE OF MEDICAL ESTABLISHMENT, FRANCE, 1975

Type of establishment	Annual dose range (rad)					Annual average dose (rad)	Number of workers
	< 0.5	0.5-1.0	1.0-1.5	1.5-5.0	> 5.0		
	Percentage of recorded doses						
Radiodiagnostic							
Hospitals	93.0	4.1	1.7	1.0	0.2	0.17	6 787
Private specialized medicine, clinics	88.7	6.1	3.7	1.4	0.1	0.22	1 378
Private radiology	85.0	7.9	4.4	2.5	0.2	0.22	1 101
Private general medicine	92.3	4.2	2.2	1.1	0.2	0.15	625
Industrial medicine, dispensaries	97.7	1.6	0.4	0.3	0.0	0.05	4 194
Dental surgeries, stomatology	99.0	0.7	0.2	0.1	0.0	0.04	2 661
Total	94.3	3.3	1.5	0.8	0.1	0.13	16 746
Radiotherapeutic							
Conventional	87.0	7.8	3.0	2.1	0.1	0.36	713
Curie	87.0	7.7	3.1	2.0	0.2	0.20	484
Cobalt	90.2	5.9	2.1	1.6	0.2	0.17	797
High-energy	88.4	9.2	1.7	0.7	0.0	0.14	456
Nuclear medicine	93.0	5.6	1.1	0.3	0.0	0.16	1 321

Source: Reference 88.

TABLE 68. FREQUENCY DISTRIBUTION OF THE ANNUAL DOSE TO A SAMPLE OF 2579 INDUSTRIAL AND RESEARCH WORKERS IN FRANCE, 1975

Type of work	Annual dose range (rad)					Number of workers
	< 0.5	0.5-1.0	1.0-1.5	1.5-5.0	> 5.0	
	Percentage of workers					
Industrial radiography (x and gamma)	98.6	0.7	0.6	0.1	0.0	839
Research and industrial application of sealed sources	98.2	1.3	0.4	0.1	0.0	752
Other non-medical	91.3	4.1	3.4	1.1	0.1	988

Source: Reference 88.

TABLE 69. FREQUENCY DISTRIBUTION OF DOSES FROM TRITIUM TO FRENCH MEDICAL RESEARCH WORKERS, 1968-1976

Derived from urine monitoring

Year	Number of workers monitored	Dose range (rem)					Mean annual dose (rem)
		< 0.1	0.1-0.5	0.5-1.5	1.5-5	> 5	
		Percentage of workers					
1968	37	100	0	0	0	0	< 0.001
1969	112	97.3	1.8	0.9	0	0	< 0.01
1970	124	97.6	2.4	0	0	0	< 0.008
1971	137	99.0	1.0	0	0	0	< 0.003
1972	218	100	0	0	0	0	< 0.002
1973	310	99.7	0.3	0	0	0	< 0.004
1974	379	100	0	0	0	0	< 0.001
1975	465	99.8	0.2	0	0	0	< 0.002
1976	548	98.4	1.1	0.5	0	0	0.012

Source: Reference 88.

TABLE 70. NUMBER AND CATEGORIES OF PERSONS MONITORED FOR EXPOSURE IN NEW ZEALAND, 1975

Category of exposure	*Number of establishments*	*Number of persons*
Medical diagnostic	110	1 200
Medical therapeutic	22	400
Dental	457	1 100
Chiropractic	63	130
Veterinary	72	230
Research and education	19	170
Industrial	36	170
	Total	3 400

Source: Reference 127.

TABLE 71. DISTRIBUTION OF OCCUPATIONAL DOSE BY TYPE OF ESTABLISHMENT, SWITZERLAND, 1974

Annual dose range (rad)	*Industrial*	*Hospital*	*Clinic*	*Medical (private)*	*Dental (private)*	*Chiro-practic*	*Other*
			Number of workers				
< 0.2	240	1 586	715	3 991	3 107	30	946
0.2-0.5	10	140	20	103	61	1	29
0.5-1.5	7	44	5	31	18	0	12
1.5-5.0	1	12	3	11	5	0	1
> 5.0	1	6	1	1	4	0	0
Total	259	1 788	744	4 137	3 195	31	988
Average dose (rad)	0.231	0.139	0.047	0.032	0.089	0.019	0.036
Annual collective dose (man rad)	60	249	35	132	284	1	36

Source: Reference 30.

TABLE 72a. DISTRIBUTION OF OCCUPATIONAL DOSE IN THE GERMAN

(Number and, in parentheses,

Dose range (rad)	Medicine						Universities, schools and nuclear facilities				
	X	B	R	A	D	T	X	B	R	A	T
< 0.49	15 226 (99.2)	530 (78.4)	307 (87.5)	9 (100)	184 (96.4)	16 250 (98.1)	1 627 (99.1)	73 (86.9)	1 574 (85.8)	128 (94.1)	3 402 (92.0)
0.5-1.49	105 (0.7)	95 (14.2)	30 (8.5)		5 (2.6)	235 (1.4)	12 (0.7)	4 (4.8)	155 (8.5)	5 (3.7)	176 (4.8)
1.5-4.99	21 (0.1)	49 (7.2)	11 (3.1)		2 (1.0)	83 (0.5)	4 (0.2)	6 (7.1)	101 (5.5)	3 (2.2)	114 (3.1)
5.0-11.99		1 (0.1)	3 (0.9)			4		1 (1.2)	2 (0.1)		3 (0.1)
12.0-24.99	1					1			1 (0.1)		1
> 25	(0.1)	1				1					
Total	15 357 (92.6)	676 (4.1)	351 (2.0)	9 (0.1)	191 (1.2)	16 580 (100)	1 643 (44.5)	84 (2.3)	1 833 (49.6)	136 (3.7)	3 696 (100)

Source: Reference 65.
Note: X = x rays; B = brachytherapy; R = radionuclide (excluding brachytherapy); A = accelerator; D = deep therapy; T = total.

TABLE 72b. DISTRIBUTION OF OCCUPATIONAL DOSE IN THE GERMAN

(Number and, in parentheses,

Dose range (rad)	Medicine						Universities, schools and nuclear facilities					
	X	B	R	A	D	T	X	B	R	A	D	T
< 0.49	17 516 (99.3)	516 (82.0)	398 (93.9)	12 (100)	136 (94.4)	18 578 (98.4)	1 677 (98.7)	136 (90)	1 709 (89.3)	116 (95.9)	36 (92.3)	3 674 (93.6)
0.5-1.49	111 (0.6)	79 (12.6)	22 (5.2)		5 (3.5)	217 (1.3)	20 (1.2)	8 (5.3)	131 (6.8)	5 (4.1)	2 (5.1)	166 (4.2)
1.5-4.99	22 (0.1)	34 (5.4)	4 (0.9)		3 (2.1)	63 (0.3)	2 (0.1)	6 (4.0)	69 (3.6)		1 (2.6)	78 (2.0)
5.0-11.99	3					3		1 (0.7)	6 (0.3)			7 (0.2)
⩾ 12.0												
Total	17 652 (93.6)	629 (3.3)	424 (2.2)	12 (0.1)	144 (0.8)	18 861 (100)	1 699 (43.3)	151 (3.8)	1 915 (48.8)	121 (3.1)	39 (1.0)	3 925 (100)

Source: Reference 66.
Note: X = x rays; B = brachytherapy; R = radionuclide (excluding brachytherapy); A = accelerator; D = deep therapy; T = total.

TABLE 72c. DISTRIBUTION OF OCCUPATIONAL DOSE IN THE GERMAN

(Number and, in parentheses,

Dose range (rad)	Medicine						Universities, schools and nuclear facilities					
	X	B	R	A	D	T	X	B	R	A	D	T
< 0.49	16 939 (99.5)	395 (71.8)	407 (92.5)	13 (100)	127 (96.1)	17 881 (98.5)	1 323 (99.2)	68 (89.4)	1 810 (86.8)	145 (94.7)	6 (100)	3 352 (91.7)
0.5-1.49	70 (0.4)	105 (19.0)	31 (7.0)		3 (2.3)	209 (1.1)	11 (0.8)	3 (4.0)	188 (9.0)	7 (4.6)		209 (5.7)
1.5-4.99	19 (0.1)	48 (8.7)	2 (0.5)		1 (0.8)	70 (0.4)		3 (4.0)	77 (3.7)	1 (0.7)		81 (2.2)
5.0-11.99		3 (0.5)			1 (0.8)	4 (0.0)		2 (2.6)	7 (0.3)			9 (0.3)
12.0-24.99									1 (0.1)			1 (0.0)
⩾ 25.0									2 (0.1)			2 (0.1)
Total	17 028 (93.7)	551 (3.1)	440 (2.4)	13 (0.1)	132 (0.7)	18 164 (100)	1 334 (36.5)	76 (2.1)	2 085 (57.1)	153 (4.2)	6 (0.1)	3 654 (100)

Source: Reference 67.
Note: X = x rays; B = brachytherapy; R = radionuclide (excluding brachytherapy); A = accelerator; D = deep therapy; T = total.

DEMOCRATIC REPUBLIC BY TYPE OF ESTABLISHMENT, 1970

percentage of workers)

Industry				*Other*					*Total*						*Un-specified*
X	*R*	*A*	*T*	*X*	*B*	*R*	*A*	*T*	*X*	*B*	*R*	*A*	*D*	*T*	
1 708	1 654	15	3 377	1 373	3	784	16	2 176	19 938	606	4 319	168	184	25 215	4 602
(99.0)	(97.5)	(100)	(98.3)	(99.5)	(100)	(96.1)	(100)	(98.2)	(99.3)	(79.6)	(92.0)	(95.5)	(96.4)	(97.3)	(98.6)
13	33		46	4		26		30	134	99	244	5	5	487	51
(0.8)	(1.9)		(1.3)	(0.3)		(3.2)		(1.4)	(0.6)	(13.0)	(5.2)	(2.8)	(2.6)	(1.8)	(1.2)
4	9		13	2		5		7	31	55	126	3	2	217	11
(0.2)	(0.5)		(0.4)	(0.1)		(0.6)		(0.3)	(0.1)	(7.1)	(2.7)	(1.7)	(1.0)	(0.8)	(0.2)
	1		1	1		1		2	1	2	7			10	2
	(0.1)			(0.1)		(0.1)		(0.1)		(0.2)	(0.1)			(0.1)	
									1		1			2	
										1				1	1
										(0.1)					
1 725	1 697	15	3 437	1 380	3	816	16	2 215	20 105	763	4 697	176	191	25 932	4 667
(50.2)	(49.4)	(0.4)	(100)	(62.3)	(0.1)	(36.8)	(0.7)	(100)	(77.6)	(2.9)	(18.2)	(0.6)	(0.7)	(100)	

DEMOCRATIC REPUBLIC BY TYPE OF ESTABLISHMENT, 1971

percentage of workers)

Industry				*Other*					*Total*						*Un-specified*
X	*R*	*A*	*T*	*X*	*B*	*R*	*A*	*T*	*X*	*B*	*R*	*A*	*D*	*T*	
1 775	1 828	11	3 614	1 325	1	885	14	2 225	22 293	653	4 820	153	172	28 091	4 045
(99.2)	(98.0)	(100)	(98.6)	(99.6)	(100)	(95.4)	(93.3)	(97.9)	(99.2)	(83.6)	(93.9)	(96.2)	(94.0)	(97.9)	(98.2)
15	29		44	2		32	1	35	148	87	214	6	7	462	64
(0.8)	(1.6)		(1.2)	(0.2)		(3.5)	(6.7)	(1.5)	(0.7)	(11.2)	(4.2)	(3.8)	(3.8)	(1.6)	(1.6)
	5		5	3		10		13	27	40	88		4	159	9
	(0.3)		(0.1)	(0.2)		(1.1)		(0.6)	(0.1)	(5.1)	(1.7)		(2.2)	(0.5)	(0.2)
	2		2						3	1	8			12	1
	(0.1)		(0.1)							(0.1)	(0.2)				
1 790	1 864	11	3 665	1 330	1	927	15	2 273	22 471	781	5 130	159	183	28 724	4 119
(48.8)	(50.8)	(0.4)	(100)	(58.5)		(40.8)	(0.7)	(100)	(78.3)	(2.7)	(17.9)	(0.5)	(0.6)	(100)	(100)

DEMOCRATIC REPUBLIC BY TYPE OF ESTABLISHMENT, 1972

percentage of workers)

Industry				*Other*					*Total*						*Un-specified*
X	*R*	*A*	*T*	*X*	*B*	*R*	*A*	*T*	*X*	*B*	*R*	*A*	*D*	*T*	
1 607	1 704	11	3 322	1 180	5	326	4	1 515	21 049	468	4 247	173	133	26 070	7 117
(99.3)	(98.0)	(100)	(98.6)	(100)	(100)	(93.7)	(100)	(98.5)	(99.5)	(74.0)	(92.0)	(95.5)	(96.4)	(97.5)	(98.8)
10	32		42			15		15	91	108	266	7	3	475	62
(0.6)	(1.8)		(1.2)			(4.3)		(1.0)	(0.4)	(17.1)	(5.8)	(3.9)	(2.2)	(1.8)	(0.9)
2	4		6			7		7	21	51	90	1	1	164	18
(0.1)	(0.2)		(0.2)			(2.0)		(0.5)	(0.1)	(8.1)	(2.0)	(0.6)	(0.7)	(0.6)	(0.3)
										5	7		1	13	3
										(0.8)	(0.2)		(0.7)	(0.1)	(0.0)
											1			1	2
											(0.0)			(0.0)	(0.0)
											2			2	1
											(0.0)			(0.0)	(0.0)
1 619	1 740	11	3 370	1 180	5	348	4	1 537	21 161	632	4 613	181	138	26 725	7 203
(48.2)	(51.5)	(0.3)	(100)	(76.8)	(0.3)	(22.6)	(0.3)	(100)	(79.2)	(2.3)	(17.3)	(0.7)	(0.5)	(100)	(100)

TABLE 73. DISTRIBUTION OF ANNUAL DOSE RECEIVED BY A SAMPLE OF INDUSTRIAL WORKERS IN THE UNITED KINGDOM, 1974

Dose range (rem)	*Number of workers*
< 0.5	809
0.5-1.0	258
1.0-1.5	38
1.5-5.0	37
> 5.0	3
Total	1 145

Sources: References 81, 109.

TABLE 74. ANNUAL AVERAGE DOSE IN MEDICINE, RESEARCH AND INDUSTRY IN SEVERAL STATES OF THE FEDERAL REPUBLIC OF GERMANY, AND IN WEST BERLIN, 1969-1974

(rad)

	1969		*1970*		*1971*		*1972*		*1973*		*1974*	
	A	*B*	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*
Niedersachsen												
Medicine	0.530	0.250	0.460	0.330	0.480	0.320	0.370	0.210	0.320	0.240	0.350	0.120
Research	0.079	1.000	0.120	0.220	0.140	0.089	0.088	0.073	0.094	0.079	0.079	0.130
Industry	1.400	0.245	1.820	0.290	1.230	0.195	0.525	0.110	0.290	0.120	0.170	0.095
Total	0.710	0.210	0.760	0.300	0.560	0.260	0.340	0.170	0.220	0.200	0.190	0.120
Hamburg												
Medicine	0.950	0.260	0.930	0.280	0.970	0.290	0.700	0.220	0.420	0.190	0.310	0.120
Research	0.066	0.160	0.053	0.120	0.070	0.130	0.055	0.200	0.050	0.100	0.031	0.092
Industry	0.290	0.140	0.430	0.100	0.270	0.110	0.260	0.090	0.180	0.080	0.160	0.100
Total	0.330	0.190	0.360	0.180	0.340	0.180	0.270	0.160	0.180	0.130	0.140	0.110
West Berlin												
Medicine	0.190	0.073	0.180	0.092	0.210	0.089	0.200	0.620	0.180	0.062	0.120	0.036
Research	0.075	0.160	0.036	0.160	0.034	0.110	0.017	0.130	0.023	0.120	0.080	0.082
Industry	0.150	0.042	0.320	0.025	0.380	0.040	0.410	0.028	0.350	0.044	0.160	0.020
Total	0.170	0.085	0.160	0.083	0.190	0.083	0.180	0.062	0.160	0.062	0.150	0.035
Schleswig-Holstein												
Medicine	0.800	0.420	1.660	0.610	1.650	0.270	0.048	0.095	0.059	0.170	0.120	0.071
Industry	0	1.640	0	0.160	0	0	0	0	0.100	0.210	0.090	0.021
Total	0.130	0.520	0.650	0.540	0.820	0.230	0.048	0.088	0.029	0.180	0.075	0.072

Source: Reference 10a.
Note: A = radiation sources; B = x rays only.

TABLE 75. DISTRIBUTION OF OCCUPATIONAL DOSE FOR UNITED STATES NUCLEAR REGULATORY COMMISSION LICENSEES NOT CONNECTED WITH THE NUCLEAR POWER INDUSTRY, 1974

Dose range (rad)	*Occupational category*	
	Industrial radiography	*Manufacturing and distribution*
	Number of persons	
Unmeasurable	3 849	1 513
< 0.10	1 740	748
0.10-0.25	939	504
0.25-0.50	635	144
0.50-0.75	424	84
0.75-1.00	323	69
1-2	547	125
2-3	209	59
3-4	74	46
4-5	22	17
5-6	17	21
6-7	5	7
7-8	2	1
8-9	3	2
9-10	0	0
10-11	1	0
11-12	2	0
> 12	0	0
Total	8 792	3 340
Annual collective dose (man rad)	2 938	1 050
Annual average dose (rad), excluding unmeasurable exposures	0.59	0.57
Annual average dose (rad), all exposures	0.33	0.31

Source: Reference 18.

TABLE 76. FREQUENCY DISTRIBUTION OF OCCUPATIONAL DOSE-RATE TO INDUSTRIAL RADIOGRAPHERS IN HUNGARY, 1974

Type of radiography	*Total number of workers*	*Dose-rate range (rad/month)*			
		< 0.04	*0.04-0.4*	*0.4-1.5*	*1.5-5.0*
		Percentage of workers			
X-ray	582	97.9	2.0	0.1	
Gamma-ray	1 283	88.6	9.9	1.4	0.1

Source: Reference 15.

TABLE 77. DISTRIBUTION OF ANNUAL DOSE TO INDUSTRIAL WORKERS (OTHER THAN LUMINIZERS AND WORKERS IN THE NUCLEAR INDUSTRY) IN SWITZERLAND, 1969-1975

Dose range (rad)	*1969*	*1970*	*1971*	*1972*	*1973*	*1974*	*1975*
	Number of workers						
< 0.1	580	370	450	560	640	745	1 187
0.1-0.5	90	60	70	80	80	80	158
0.5-1	25	10	15	15	25	40	31
1-1.5	20	2	5	4	5	10	9
1.5-2	8	2	6	1	1	1	5
2-2.5	4	2	0	0	0	1	2
2.5-3	2	2	1	0	0	0	1
3-3.5	5	0	0	0	0	0	0
3.5-5	0	0	0	0	0	0	0
> 5	0	0	0	0	0	1	0
Annual collective dose (man rad)	123	61	66	70	81	114	170

Sources: References 60, 61.

TABLE 78. FREQUENCY DISTRIBUTION OF QUARTERLY DOSES TO SITE RADIOGRAPHERS IN THE UNITED KINGDOM

Firm size (employees)	*Firm No.*	*Dose range (rad)*			
		< 0.375	*0.376-1.25*	*1.26-3.00*	*> 3.00*
		Percentage of doses			
6-10	B 1	25.0	59.1	15.9	0.0
	B 2	26.4	58.5	15.1	0.0
	B 3	60.7	21.4	16.1	1.8
	B 4	28.2	35.6	21.5	14.7
	B 5	76.6	19.4	2.9	1.1
	B 6	71.6	27.8	0.6	0.0
	B 7	43.7	35.7	18.5	2.1
11-20	B 8	56.5	28.0	11.3	4.2
	B 9	41.4	40.4	17.7	0.5
	B 10	43.7	55.0	1.3	0.0
	B 11	23.5	47.3	25.7	3.5
21-50	B 12	48.8	28.2	16.9	6.1
	B 13	65.6	24.0	9.2	1.2
	B 14	45.1	32.6	15.5	6.8
	B 15	43.2	44.2	10.8	1.8
	B 16	51.7	41.0	6.0	1.3
51-200	B 17	48.9	37.0	12.0	2.1
	B 18	62.5	28.6	6.8	2.1
	B 19	53.2	36.0	7.8	3.0
	B 20	59.4	30.9	8.2	1.5
	Overall	52.4	35.2	9.9	2.5

Source: Reference 6.

TABLE 79. FREQUENCY DISTRIBUTION OF QUARTERLY DOSES TO FACTORY RADIOGRAPHERS IN THE UNITED KINGDOM

Firm size (employees)	*Firm No.*	*Dose range (rad)*			
		< 0.375	*0.376-1.26*	*1.26-3.00*	*> 3.00*
		Percentage of doses			
1-5	A 1	100.0	0.0	0.0	0.0
	A 2	60.9	34.8	10.0	4.3
	A 3	62.5	33.3	0.0	4.2
	A 4	67.5	30.0	2.5	0.0
6-10	A 5	92.2	7.8	0.0	0.0
	A 6	100.0	0.0	0.0	0.0
	A 7	98.5	1.5	0.0	0.0
	A 8	41.4	23.0	35.6	0.0
	A 9	86.3	13.7	0.0	0.0
	A 10	92.4	6.3	0.0	1.3
	A 11	100.0	0.0	0.0	0.0
11-12	A 12	39.5	25.3	33.0	2.2
	A 13	96.0	2.0	1.3	0.7
	A 14	64.4	33.1	1.9	0.6
21-50	A 15	62.4	33.1	4.5	0.0
	Overall	72.6	20.0	6.9	0.5

Source: Reference 6.

TABLE 80. DISTRIBUTION OF QUARTERLY WHOLE-BODY DOSES IN EXCESS OF 3 REM RECEIVED BY INDUSTRIAL RADIOGRAPHERS IN THE UNITED KINGDOM, 1969-1974

Quarterly dose range (rem)	*1969*	*1970*	*1971*	*1972*	*1973*	*1974*
	Number of workers					
3.0-3.5	11	8	15	10	5	2
3.5-5.0	26	23	31	13	7	8
5.0-10.0	12	8	11	4	10	6
10.0-25.0	8	9	6	4	7	9
25.0-50.0	1	2	1	2	6	1
50.0-100	4	0	1	0	1	0
> 100	1	0	1	1	1	1
Accurate evaluation not possible	0	1	2	1	1	0

Source: Reference 121.

TABLE 81. ANNUAL DOSE TO LUMINIZERS IN THE UNITED KINGDOM, 1974

Dose range (rem)	*Annual average dose (rem)*	*Number of workers*	*Annual collective dose (man rem)*
< DIL[a]	0.3	89	27
< 1.5[b]	0.5	30	15
1.5-3	2.25	8	18
3-4.5	3.75	6	22
4.5-6	5.25	2	10
6-7.5	6.75	1	7
	Total	136	99

Source: Reference 46.

[a] DIL = derived investigation level (0.05 rad in two weeks). Doses to workers providing samples below the DIL were not recorded. The values in the table are estimates.

[b] Recorded.

TABLE 82. DISTRIBUTION OF DOSES TO TRITIUM LUMINIZERS IN SWITZERLAND, 1969-1975

Dose range (rad)	*1969*	*1970*	*1971*	*1972*	*1973*	*1974*	*1975*
	Number of workers						
< 0.1	3	2	0	0	0	0	3
0.1-0.5	53	43	45	39	58	90	68
0.5-1.0	65	79	67	63	73	78	65
1.0-1.5	68	70	45	57	40	47	52
1.5-2.0	34	41	34	33	28	40	17
2.0-2.5	23	32	16	23	12	15	16
2.5-3.0	27	11	11	7	6	7	7
3.0-3.5	12	11	2	2	2	7	6
3.5-4.0	18	11	4	3	0	4	1
4.0-4.5	9	5	1	1	1	0	
4.5-5.0	4	4	1		0	1	
5.0-5.5	2	2			1	0	
5.5-6.0	5	1				1	
6.0-6.5	0	1					
6.5-7.0	3						
7.0-7.5	3						
7.5-8.0	2						
8.0-8.5	1						
8.5-9.0	0						
9.0-9.5	1						
Annual collective dose (man rad)	618	478	276	268	231	316	239

Sources: References 60, 61.

TABLE 83. DISTRIBUTION OF ANNUAL DOSE TO TRITIUM LUMINIZERS IN FRANCE, 1968-1976

Data derived by urine monitoring

Year	Dose range (rcd)					Annual average dose (rad)
	< 0.1	0.1-0.5	0.5-1.5	1.5-5.0	> 5.0	
	Number of workers					
1968	25	–	–	5	–	0.52
1969	17	1	2	4	–	0.47
1970	9	1	1	4	–	0.86
1971	26	5	4	–	–	0.17
1972	25	3	2	3	–	0.29
1973	31	13	15	6	2	0.66
1974	45	11	17	10	1	0.55
1975	49	15	16	10	–	0.49
1976	50	8	15	7	–	0.35

Source: Reference 88.

TABLE 84. DISTRIBUTION OF MEAN ANNUAL DOSE TO WORKERS HANDLING TRITIUM IN THE LUMINOUS PAINT INDUSTRY IN THE FEDERAL REPUBLIC OF GERMANY, 1966-1975

Year	Number of monitored persons	Number of plants	Dose range (rad)				Annual average dose (rad)
			< 0.1	0.1-1.5	1.5-5	> 5	
			Percentage of monitored persons				
1966	108	25	34.3	36.1	16.6	13.0	0.87
1967	89	16	33.7	58.4	7.9	0	0.41
1968	108	16	28.7	52.7	16.7	1.9	0.49
1969	99	21	26.3	61.6	11.1	1.0	0.39
1970	124	16	40.0	50.4	8.7	0	0.54
1971	166	22	61.4	28.3	10.2	0	0.78
1972	122	14	58.2	37.7	4.1	0	0.32
1973	78	10	31	40	28	1	1.11
1974	79	12	24	44	31	1	1.08
1975	56	6	39	28	28	5	1.35

Source: Reference 19.

TABLE 85. ANNUAL DOSE TO WORKERS IN THE HUNGARIAN NATIONAL ONCOLOGICAL INSTITUTE, 1936-1975

Period	Worker category	Annual dose (rad)	Annual integral dose (g rad)
1936-1947	Physician	20	860
	Assistant	24	800
	Surgeon's assistant	35	3 700
	Hospital porter	12	200
1947-1957	Physician	1	340
	Assistant	2	640
	Surgeon's assistant	10	2 900
	Hospital porter	12	200
1957-1975	Physician	0.5	170
	Assistant	0.4	270
	Surgeon's assistant	7	2 200
	Hospital porter	10	170

Source: Reference 15.

TABLE 86. ANNUAL AVERAGE DOSE TO GROUPS OF WORKERS AT TRAWSFYNYDD NUCLEAR POWER STATION, UNITED KINGDOM, 1972-1974

Group	1972		1973		1974	
	Number of workers	*Annual average dose (rem)*	*Number of workers*	*Annual average dose (rem)*	*Number of workers*	*Annual average dose (rem)*
Mechanical maintenance	82	0.77	84	1.08	80	0.58
Electrical maintenance	33	0.58	32	0.35	27	0.27
Instrument maintenance	26	0.32	28	0.31	30	0.22
Operations	113	2.23	108	1.38	112	0.80
Health physics	25	3.09	33	1.77	42	1.02
Stores, Station Warden, work study	34	0.19	46	0.20	26	0.17

Source: Reference 85.

TABLE 87. ANNUAL AVERAGE DOSE TO GROUPS OF WORKERS AT HUNTERSTON NUCLEAR POWER STATION "A", UNITED KINGDOM, 1972-1974

Group	1972		1973		1974	
	Average number of workers	*Annual average dose (rem)*	*Average number of workers*	*Annual average dose (rem)*	*Average number of workers*	*Annual average dose (rem)*
Administration	40	0.34	41	0.25	67	0.18
Technical	23	0.33	22	0.20	23	0.16
Health physics						
Monitors	28	0.88	27	0.73	36	0.95
Others	22	0.40	24	0.31	28	0.37
Chemistry	13	0.31	13	0.29	13	0.31
Operations	203	0.52	198	0.47	179	0.51
Maintenance	222	0.56	219	0.42	237	0.55
Fuel handling						
Maintenance	39	0.98	37	0.57	–	–
Others	60	0.62	61	0.42	65	0.44
Contractors	31	1.000	15	0.24	37	0.30
Others	51	0.43	50	0.26	81	0.29

Source: Reference 39.

TABLE 88. AVERAGE ANNUAL DOSE TO GROUPS OF WORKERS AT ONTARIO HYDRO, CANADA

Group	*Length of time employed as an "Atomic Radiation Worker" (y)*	*Average annual dose[a] (rad)*	*Number of workers*
Operators	1-4	1.5	206
	5-9	1.96	188
	10-14	1.23	42
	15-19	0.68	1
	All	1.67	437
Mechanical maintainers	1-4	1.87	182
	5-9	2.55	67
	10-14	2.25	21
	All	2.07	270
Control technicians	1-4	1.00	134
	5-9	1.27	83
	10-14	0.88	17
	All	1.09	234
All nuclear station workers	1-4	0.82	1 355
	5-9	1.39	557
	10-14	0.97	160
	15-19	0.19	5
	20-24	0.73	2
	All	0.98	2 079

Source: Reference 125.

[a] Defined as the total dose received while employed by Ontario Hydro divided by the length of time employed as an Atomic Radiation Worker.

TABLE 89. AVERAGE DOSE RATE TO SOME SELECTED GROUPS OF FUEL REPROCESSING WORKERS AT WINDSCALE, UNITED KINGDOM, 1973-1975

(rem y^{-1})

Group	*1973*	*1974*	*1975*
Operations	3.90 (206)	4.16 (217)	3.15 (293)
Mechanical maintenance	3.30 (131)	2.96 (136)	2.59 (188)
Electrical and instrument maintenance	1.07 (161)	1.03 (169)	1.21 (182)
Health physics	2.02 (85)	1.65 (95)	1.48 (127)
Laboratory services	0.75 (44)	0.48 (50)	0.45 (46)

Source: Reference 48.

Note: The number in parentheses is the number of workers in the group.

TABLE 90. DISTRIBUTION OF DOSES RECEIVED BY WORKERS AT THE RADIOCHEMICAL CENTRE, UNITED KINGDOM, 1972-1974

Dose range (rem)	*1972*	*1973*	*1974*
	Number of workers		
< 1.5	446	527	653
1.5-3	99	87	71
3-4	51	43	49
4-5	18	13	14
> 5	6	1	0
Total	620	671	787
Collective dose (man rem)	690	603	599
Average dose (rem)	1.11	0.90	0.76

Source: Reference 82.

TABLE 91. DISTRIBUTION OF ANNUAL AVERAGE DOSE FOR DIFFERENT GROUPS OF WORKERS AT ONTARIO HYDRO, CANADA

(Number of workers)

Average annual dose (rem)	*Time since hiring as an Ontario Hydro Radiation Worker (y)*				
	1-4	*5-9*	*10-14*	*15-19*	*20-24*
	All nuclear station workers				
⩽ 0.49	720	178	58	4	1
0.5-0.99	180	67	32	1	0
1.0-1.49	137	64	37	0	1
1.5-1.99	118	75	13	0	0
2.0-2.49	94	65	10	0	0
2.5-2.99	50	47	5	0	0
3.0-3.49	34	37	4	0	0
3.5-3.99	16	22	1	0	0
4.0-4.49	0	2	0	0	0
4.5-4.99	1	0	0	0	0
⩾ 5	5	0	0	0	0
	Reactor operators				
⩽ 0.49	51	20	3	0	0
0.5-0.99	20	16	11	1	0
1.0-1.49	29	21	17	0	1
1.5-1.99	33	43	7	0	0
2.0-2.49	40	28	3	0	0
2.5-2.99	18	26	1	0	0
3.0-3.49	9	20	0	0	0
3.5-3.99	4	14	0	0	0
4.0-4.49	0	0	0	0	0
4.5-4.99	0	0	0	0	0
⩾ 5	2	0	0	0	0

Average annual dose (rem)	Time since hiring as an Ontario Hydro Radiation Worker (y)		
	1-4	5-9	10-14
		Control technicians	
0.0-0.49	54	18	5
0.5-0.99	23	17	4
1.0-1.49	24	20	6
1.5-1.99	14	8	2
2.0-2.49	6	11	0
2.5-2.99	5	7	0
3.0-3.49	5	2	0
3.5-3.99	2	0	0
4.0-4.49	0	0	0
4.5-4.99	0	0	0
5 or more	1	0	0
		Mechanical maintainers	
0.0-0.49	29	2	1
0.5-0.99	15	1	1
1.0-1.49	17	7	2
1.5-1.99	33	9	4
2.0-2.49	36	14	5
2.5-2.99	21	11	3
3.0-3.49	20	13	4
3.5-3.99	10	8	1
4.0-4.49	0	2	0
4.5-4.99	0	0	0
5 or more	1	0	0

Source: Reference 124.

TABLE 92. DISTRIBUTION OF THE CUMULATIVE DOSE FOR DIFFERENT LENGTHS OF EMPLOYMENT

Derived from termination reports of United States power reactor licensees

Cumulative dose (rad)	Length of employment (y)					
	1-5	5-10	10-15	15-20	20-25	> 25
			Number of workers			
0 or minimal	340	18	10	0	0	4
> 0-0.49	742	39	11	3	0	3
0.5-0.99	163	9	7	1	1	1
1.0-1.9	141	13	5	1	1	1
2.0-2.9	144	14	5	0	0	2
3.0-3.9	81	5	3	1	1	0
4.0-4.9	56	6	3	1	1	0
5.0-9.9	137	17	8	1	0	3
10.0-14.9	25	16	5	1	0	1
15.0-19.9	8	8	1	1	0	0
20.0-25.0	4	7	1	0	0	0
> 25.0	0	3[a]	3[b]	0	1[c]	0

Source: Reference 74.
[a] Average cumulative dose 53 rad.
[b] Average cumulative dose 31 rad.
[c] Cumulative dose 33 rad.

TABLE 93. DISTRIBUTION OF THE CUMULATIVE DOSE FOR DIFFERENT LENGTHS OF EMPLOYMENT

Derived from termination reports of United States fuel reprocessor licensees

Cumulative dose (rad)	*Length of employment (y)*			
	1-5	*5-10*	*10-15*	*> 15*
	Number of workers			
⩽ 0.99	26	0	0	0
1.0-1.9	23	1	0	0
2.0-2.9	12	2	0	0
3.0-3.9	17	3	1	0
4.0-4.9	17	1	0	0
5.0-9.9	92	7	0	0
10.0-14.9	37	9	1	0
15.0-19.9	15	6	0	0
20.0-25.0	17	9	0	0
> 25.0[a]	12	45	5	0

Source: Reference 74.

[a]The average cumulative doses to the workers in this range are respectively 28, 39, and 52 rad.

TABLE 94. DISTRIBUTION OF THE CUMULATIVE DOSE FOR DIFFERENT LENGTHS OF EMPLOYMENT

Derived from termination reports of United States fuel fabricators and scrap-recovery licensees

Cumulative dose (rad)	*Length of employment (y)*					
	1-5	*5-10*	*10-15*	*15-20*	*20-25*	*> 25*
	Number of workers					
0 or minimal	96	30	16	6	3	0
> 0-0.49	949	196	71	20	12	2
0.50-0.99	222	60	33	14	10	0
1.0-1.9	179	61	55	29	6	1
2.0-2.9	93	33	23	9	4	2
3.0-3.9	41	15	18	5	1	1
4.0-4.9	22	7	8	5	2	1
5.0-9.9	65	34	19	7	6	2
10.0-14.9	17	9	5	5	0	0
15.0-19.9	3	9	8	0	1	0
20.0-25.0	1	6	1	2	0	1
> 25.0[a]	0	8	5	2	0	2

Source: Reference 74.

[a]The average cumulative doses to the workers in this range are respectively, 30, 33, 25 and 51 rad.

TABLE 95. AGE DISTRIBUTION OF PERSONS IN SPECIFIC OCCUPATIONAL GROUPS IN AUSTRALIA

(Percentage)

Occupational group[a]	*Sex*	*Age range (y)*									
		18-20	*21-25*	*26-30*	*31-35*	*36-40*	*41-45*	*46-50*	*51-55*	*56-60*	*> 60*
Radiologists	M	–	4	26	20	12	13	10	5	5	5
Radiographers	M	17	22	13	12	9	9	6	8	2	2
	F	25	30	12	10	6	6	7	3	1	–
Assistants	F	11	34	19	4	9	10	5	6	1	1
Nurses	F	19	21	18	5	11	8	4	10	3	1
Nuclear medicine	M	4	26	24	22	7	8	6	3	–	–
	F	18	35	21	16	5	2	2	1	–	–
Dentists	M	–	13	19	15	12	11	13	10	4	3
Dental nurses	F	58	31	6	1	2	1	1	–	–	–
X-ray analysts	M	2	16	19	17	16	16	10	4	–	–
Enclosed installations	M	3	5	19	15	20	10	9	13	5	1
Open installations	M	4	16	23	22	11	7	6	10	1	–
Tracers	M	7	24	16	17	11	13	7	3	2	–
Engineers	M	2	14	23	19	8	13	9	5	5	2

Source: Reference 106.

[a]See tables 20 and 25 for fuller description of these occupational groups.

TABLE 96. DISTRIBUTION OF THE CUMULATIVE DOSE FOR DIFFERENT LENGTHS OF EMPLOYMENT

Derived from termination reports of United States industrial radiography licensees

Cumulative dose (rad)	*Length of employment (y)*					
	1-5	*5-10*	*10-15*	*15-20*	*20-25*	*> 25*
	Number of workers					
0 or minimal	1 014	284	153	40	75	386
> 0-0.49	1 758	807	586	161	171	880
0.50-0.99	452	173	159	40	25	100
1.0-1.9	553	231	166	31	24	134
2.0-2.9	370	146	98	18	19	76
3.0-3.9	235	86	64	25	13	65
4.0-4.9	168	79	53	14	13	40
5.0-9.9	284	201	177	42	43	109
10.0-14.9	66	143	94	18	14	37
15.0-19.9	9	65	38	16	11	26
20.0-25.0	2	20	46	6	4	9
> 25.0[a]	8	24	38	18	13	13

Source: Reference 74.

[a] The average cumulative doses to the workers in this range are respectively 60, 34, 36, 63, 51 and 64 rad.

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ANNEX F

Medical irradiation

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Introduction

1. The Committee has previously presented data on the medical irradiation of patients in its reports of 1958 (242), 1962 (243) and 1972 (244). Medical exposures are of particular interest since they contribute the highest man-made *per caput* doses in the population, are given with high instantaneous dose rates and cause the highest individual organ doses short of accidental exposures. From the radiation protection point of view,

they also offer the largest scope for implementing methods of dose reduction without loss of the information required. They differ from many other types of exposure in that they usually involve irradiation of limited regions of the body. They also differ in that the individuals who are irradiated are those who may expect to benefit directly from the particular treatment or examination.

2. A particularly difficult problem, however, arises when risk of medical irradiation is compared with the risk from other sources of man-made exposure or from natural background radiation. The organ doses received in diagnostic radiology may range over four orders of magnitude (from a few millirads to a few tens of rads) and will usually be given at high dose rates, compared with other man-made and natural sources. The various effects of radiation depend in a complex manner on the dose, the part of the body exposed, the dose rate and the length of time during which the total dose was received (described in Annexes H, I and J). Therefore, the detailed estimation of the risk from medical exposure is very complex; however, it is possible, by making simple assumptions about the relationship between dose and effect (as has been described in Annex A), to use the product of the number of persons in a subgroup and the dose received by a particular organ as a measure of the relative radiation detriment. The Committee has used this concept of collective dose for the estimation of the relative risk in diagnostic radiology.

3. However, since in radiotherapeutic practice, as compared with diagnostic practice, considerably higher doses are given to smaller groups of patients, and since the dose-effect relationship is likely to be different, the Committee has followed the practice of quoting, for radiotherapy the average organ dose together with the number of patients in the treated group. In this way it is hoped that there will be a clear indication that there may well be differences between the relative risk estimates from a given collective dose from diagnostic radiology and those from an equivalent numerical product for a radiotherapeutic practice. For this reason, it is important that the risks from the two practices should not be compounded or summed.

4. A vast amount of information on medical exposures was summarized in the 1958, 1962 and 1972 reports. Nevertheless, since the variation in practice and performance is large, not only from one country to another, but also between different hospitals and different radiologists, it is difficult to give a comprehensive presentation of the situation. Some of these variations arise from the differing needs of the individual patients, e.g., in the extent or duration of a particular examination; other variations occur because of the type of equipment available and the standard of the performance. The Committee has found no reason to compile data merely for recording purposes, but has tried to present information which might be useful for risk assessment, trend consideration and radiation-protection evaluation.

5. In the previous reports special emphasis was put on assessments of the annual genetically significant dose (GSD). The presentation of such data has encouraged further studies, so that it is now relatively clear to what extent medical exposures contribute to the total genetic dose in both developing and developed countries. In the developing countries the level of the GSD will usually reflect the availability of x-ray facilities. In order to meet the medical need, such services may need to be expanded. This is likely to increase the genetic dose in these countries in spite of any recommendations for good practice that are aimed at decreasing GSD.

6. The emphasis on the GSD may have detracted attention from exposure of organs other than the gonads and may therefore have led to an under-estimation of the overall risk from certain types of examination that usually cause very low gonad doses. One example is the chest examination, which involves irradiation of such radiosensitive tissues as lung, breast, marrow and sometimes also thyroid. The 1972 report, accordingly, gave more information on the dose in the active marrow. A number of groups of patients were also reported who had been identified as receiving high doses, and some had been shown to have a higher incidence of certain diseases than comparable but non-irradiated groups. In this report, further attention is given to identifying examinations in which particular organs may receive high doses. An attempt is also made to give a fuller picture of the patient's dose distribution, including data on doses in radiosensitive tissues such as bone marrow, thyroid, lung and breast.

7. In presenting data on dose levels in medical procedures, the Committee has three different purposes in mind. Firstly, it is of interest to know, for individuals, the doses to particular organs from the various types of medical irradiation and, particularly, the extent of the variation of such doses for any one type of investigation, as a basis for any attempt to weigh the radiation risks against the expectation of benefit to the individual patient and for differential cost-benefit analyses of protective measures (100). Secondly, it may be of interest to know both the individual and the collective organ doses from various medical practices as part of the presentation of man's total radiation exposure. Thirdly, the identification of some highly exposed groups may be of interest in epidemiological studies; for this purpose, the collective dose would be of interest.

8. As has been stated in paragraph 1, medical exposure is unique in the sense that the benefit is usually limited to the individuals who are irradiated. Assessments of individual doses in relation to the expected benefit are therefore usually sufficient for justification and optimization purposes. Only in special cases, e.g., public health examinations (267), or medico-legal examinations, is there an expected benefit to society in addition to that measured by the benefit to the individual. In such cases there may also be a need to assess the collective dose from a given practice as a whole.

9. The information sought for any individual is the dose to those particular organs which are considered to be at risk (see Annex G). Only then would it be possible to make a complete assessment of the radiation risk from that irradiation. Such complete information has only rarely been presented, principally for a few

therapeutic procedures, e.g. a survey of the radiation treatment of ankylosing spondylitis (see Annex G). However, the general awareness of the problem has resulted in further studies.

I. BASIC INFORMATION

A. METHOD OF DATA PRESENTATION

10. Medical irradiation comprises irradiation for both diagnostic and therapeutic purposes, and these will be treated separately in chapters II and III of this Annex. In each chapter, individual dose per unit procedure and the collective dose to various organs from different diagnostic procedures will be reported and discussed in separate sections. The individual dose will be influenced by the differences in techniques. In addition, the contributions to the collective dose will be proportional to the number of individual irradiations at a given dose level.

B. INDIVIDUAL DOSE PER UNIT PROCEDURE

11. The determination of the dose to a particular organ for a given examination, investigation or treatment may be direct: a dosimeter can be placed at representative sites in the organ of interest. More frequently, however, the method of dose determination has to be indirect: the organ may be inaccessible and measurements must be made elsewhere; calculations or further measurements are needed to determine the organ dose.

12. Measurements are normally made on the skin surface, although for the estimation of ovary dose measurements have been made in the vagina and rectum. The skin measurements combined with measurements on man-like phantoms have been used to estimate the dose to the bone marrow. The determination of the radiation doses to other organs has principally been undertaken by Monte Carlo methods (171) or by using skin measurements in conjunction with phantom measurements, percentage-depth dose data or isodose curves (239). For organs outside the main beam, scatter function curves are used (47, 86, 111, 137, 222). Alternatively, in the case of the administration of radiopharmaceuticals, calculations based on the distribution of the radiopharmaceuticals and on the physical properties of the nuclides need to be undertaken (140). Monte Carlo type calculations have also been made to facilitate such estimates (212). Considerable errors may arise in the determination of dose, but in general the direct method of measurement is expected to be subject to the least error.

13. Studies involving measurements on man-like phantoms require that such phantoms be sufficiently like Reference Man or normal patients in relevant characteristics to keep errors within reasonable limits (147). Reports such as that of the ICRP on Reference Man (101) enable anthropometric considerations as well as physiological variations to be taken into account in the choice of models or design of phantoms.

14. The difficulties in assessing the true organ doses will introduce systematic errors but will also to some extent increase the apparent spread of doses in each type of irradiation. For example, the gonad dose will vary dependent on the position of the stomach during radiological investigations of the gastro-intestinal tract (127). The doses actually received by individual patients, however, will also differ, depending upon the clinical requirements, the standards of the equipment and the skill of the operators. It has been claimed that spread of individual organ doses in each type of examination with x rays may fit a log-normal distribution (120). However, it has also been shown that, with some limitations, measured doses in x-ray examinations will fit a normal distribution (17). This will be discussed in more detail in chapter II. It seems reasonable to assume, however, that there is no *a priori* reason to expect a log-normal distribution of patient doses. Since each type of medical irradiation has a special objective (e.g., to destroy a tumour or produce an x-ray image) and is subject to optimization, it could rather be expected that the resulting doses would follow a normal distribution around the optimum value. Even this assumption, however, is usually an over-simplification.

C. COLLECTIVE DOSE PER TYPE OF PROCEDURE

1. Purpose of assessment

15. Ideally, the detriment from a unit procedure (e.g., a treatment course or a particular type of diagnostic examination) should be assessed by the weighted sum of all significant organ and tissue doses, but in practice the necessary weighting factors are not known. Lacking this information, it is still of interest to know the various organ doses, e.g., for relative risk assessments and optimization evaluations on the basis of various assumed risk factors.

16. As indicated in paragraphs 7 and 8, there is usually no need to assess collective doses from various medical practices for the purpose of justification and optimization considerations; instead, the individual doses may be used for the same purpose, because the risks and benefits relate to the same individuals. However, certain protection measures are of an administrative nature and may involve considerations of a practice as a whole. For example, in planning education and information, it may be of value to know where efforts might yield the best results. The doses to patients in dental examinations requiring two or three pictures are in general low and would not justify much attention in the individual case, but because of the very large number of examinations improved education might result in a larger reduction in the collective dose with higher individual doses but fewer individuals exposed. For this reason, national authorities may wish to have information not only on high individual doses but also on practices causing high collective doses. Also, the total collective dose from all medical practices would be of interest in the assessment of man's overall radiation exposure.

17. There is also an obvious interest in knowing the collective dose to various organs in those irradiated population groups which could be subject to epidemiological studies. The requirements are discussed in paragraph 31.

2. Limitations in the use of the collective dose as a measure of detriment from medical exposures

18. It has been shown in Annex A that for a given radiation the collective dose may be used as a relative measure of detriment if doses are so low that effects are proportional to dose and independent of dose rate. Doses are considered in this report to be sufficiently small in most diagnostic examinations so that the collective dose concept is applicable, and the relatively high dose rates utilized in these examinations are of little significance as far as the validity of the collective dose concept is concerned. However, this concept should not be extended to the case of therapeutic exposures where there is a risk of acute effects and where cell killing may reduce the risk of late deleterious effects. A further limitation arises from the fact that for some late effects of radiation it is not yet known which particular cell or tissue is at risk and therefore what tissue dose should be calculated.

3. Weighting for relevance

19. Neither collective doses nor *per caput* doses will reflect the detriment in a population if a substantial fraction of the *per caput* dose is contributed by the exposure of individuals who, for biological reasons, are not at risk. This would be the case with regard to genetic risks and carcinogenic effects when doses are received by individuals who would not be expected to be able to make the possible biological effect manifest because they are not expected to have children or to live long enough.

20. In such cases weighting procedures are called for. Weighting for the individual's child expectancy is part of the calculation of the GSD. A weighting for life expectancy could properly be an element in the derivation of a weighted *per caput* dose for the production of a particular somatic effect if sufficient data were available (see paragraph 86).

4. Assessment of collective dose

21. As was shown in Annex A, the radiation detriment from a given source k can be assessed, at least on a relative basis, by means of collective dose S_k (measured in man rad), which can be derived from the weighted product of the individual dose and the number of individuals:

$$S_k = \int_0^\infty D N_D(D)\, dD \qquad (1)$$

where $N_D(D)dD$ is the number of individuals receiving a dose in a specified organ or tissue in the range D to $D + dD$. The collective dose can apply to the world population, to a subpopulation or to one person. The defined group may comprise individuals who live at different times or individuals living in a given year, depending upon the purpose of the assessment.

22. In the context of medical irradiation, the collective dose to a certain organ, p, in the patients receiving a given type of examination or treatment, x, can be formulated as

$$S_{p,x} = K \Sigma_i D_{p,x,i} \qquad (2)$$

where K = 1 man since each group i is composed of one person.

23. In practice it is not often possible to ascertain the dose $D_{p,x,i}$ for each individual in the total number of patients involved N_x. As data can usually be obtained only for a sample n_x of individuals within the relevant patient population, some simplifying approximations to the summation over all individuals have to be made. If sampling is unbiased and can be considered representative, then the collective dose to the organ p from procedure x can be estimated by

$$S_{p,x} = (N_x/n_x)\, S_{p,x,n_x} \qquad (3)$$

where S_{p,x,n_x} is the collective dose in the sample.

24. A further approximation is required when information about doses delivered by a given procedure is only available for a different group of patients who have undergone a similar procedure but do not form part of the patient population under study. The collective dose can be estimated by

$$S_{p,x} = N_x \bar{D}^*_{p,x} \qquad (4)$$

where $\bar{D}^*_{p,x}$ is the average individual dose in the outside group for which information is available.

25. The approximation given by equation 4 is obviously not as reliable as that of equation 3, because there may be unspecified factors in the outside group that may be different in the patient population under study. This approximation would be used, for example, when the relevant average dose is available in one country and an estimate of the collective dose is required for a patient population in another country where no direct information on the individual doses is available.

26. An alternative way of presenting information on population exposures is the *per caput* dose $\bar{D}_{p,x}$, which is simply the collective dose divided by the total population size N:

$$S_{p,x} = N \bar{D}_{p,x} \qquad (5)$$

5. Accuracy of assessments

27. The accuracy of any estimate of collective dose obviously depends on the accuracy of the determination of the two main factors, i.e., the individual dose and the number of irradiated individuals. The accuracy would depend on which of the above equations is used for the calculations.

28. In the case of studies which use equation 3, i.e., when measurement data are obtained from only a sample of the patient population, it is important that such a sample group should be large enough (37). In practice it has been found that, to obtain a reliable distribution of the doses received in a particular medical practice, it is necessary to have at least 200-300 measurements (23). Obviously, it is also essential that the individuals in the sample should be selected so as to be representative of the patient population being studied.

29. In some collective dose surveys, the number of exposed individuals will be obvious, e.g., when investigating a group of individuals who have all had a particular investigation or treatment during a defined time at a limited number of centres, such as the

radium-224 patients surveyed in reference 215. However, more generally, for an estimate of the collective dose to individuals who undergo x-ray examinations in current practice, e.g., in the examination of the stomach in Japan, it is necessary to obtain data on the frequency of these examinations in the country concerned. This requires a sample to be taken over a period of time from a selected sample of the hospitals in the country. Such frequency surveys have formed part of most of the studies undertaken for the estimation of the GSD, and samples of frequency data have usually covered about 1-4 per cent of the year's radiological examinations. Some surveys have shown that fluctuations in the frequency of particular examinations throughout the year also need to be taken into account (36).

30. In the determination of the collective dose, the least error is involved if the organ doses for all the irradiated individuals are known. In this case the overall error is in the determination of the doses to the particular organ concerned. When direct measurements of the skin dose or the male gonad dose are being made during x-ray examinations, modern techniques should enable the measurement errors to be of the order of 5 per cent. In other cases the errors in the measurement or estimation of the organ dose may be considerably greater. The bigger the contribution from a particular practice to the total collective dose, the more effort should be applied to improve the precision of the dose determination. In those surveys in which only a sample of the individuals are measured, there will be, in addition to the measurement error, sampling errors for both the measurement sample selection and the frequency sample used.

D. GROUPS OF POTENTIAL EPIDEMIOLOGICAL INTEREST

31. When a group is being studied to determine the incidence of a deleterious effect caused by radiation, it is essential that an estimate be made of the incidence in a control group. The appropriate size of an exposed population for this purpose has been studied recently by Goss (65). Table 1 gives the size of collective dose needed to have a 95% chance of detecting an increased risk at the 5% level of significance. It is obvious that at low doses very large groups of patients are required, but at therapeutic dose levels it is possible to observe the required number of patients with relative ease.

TABLE 1. SIZE OF COLLECTIVE DOSE NEEDED TO GIVE A 95% PROBABILITY OF DETECTING AN INCREASED RISK

Age group and investigated risk	*Collective dose (10^3 man rad)*	*Observation period (y)*
Children		
Leukaemia	310	10
Thyroid cancer (incidence)	700	10
Other cancers	310	10
Adults		
Leukaemia	100	20
Breast cancer (females)	420[a]	20
Lung cancer	4 000	20
Other cancers	12 000	20

Source: Reference 65.

[a] Corrected by the Committee.

II. DIAGNOSTIC USES OF RADIATION

A. X-RAY DIAGNOSTIC RADIOLOGY

1. Trends in frequency and technique

32. In most countries the distribution of x-ray apparatus is non-uniform and the number of installed machines increases with population density. A study of this in Japan (115) showed a good correlation between population and number of units. The study also showed that in some areas non-trained or unlicensed staff were used to take up to 60 per cent of the radiographs made in practitioners' offices.

33. In the 1972 report of the Committee, the overall rate of increase in the number of radiological examinations reported for the 1960s by a number of countries with technically advanced medical services was reported to be between 2 and 6 per cent per year. When corrected for the increased population the growth was estimated to be about 3 per cent per year. However a more recent report from the Netherlands (175) for the same period has shown an annual growth rate of 8.5 per cent. Reports quoted by Puijlaert (176) indicate that for a number of countries the annual growth rate *per caput* for the late 1960s and early 1970s was between 5 and 15 per cent.

34. Further analysis of surveys made in the United States of America in 1964 and 1970 (27, 250, 251) indicates a number of interesting trends in frequency, technique and dose (table 2). As can be seen from the table, the trend pattern is rather complex.

TABLE 2. CHANGES IN DATA PERTAINING TO DIAGNOSTIC X-RAY PROCEDURES IN A SIX-YEAR PERIOD

United States of America, 1964 and 1970

	1964	*1970*	*Increase[a] (per cent)*
Number of persons having x-ray examinations	108 10^6	130 10^6	+ 20
Number of x-ray procedures	173 10^6	212 10^6	+ 22
Number of films exposed	506 10^6	661 10^6	+ 30
Average number of films per examination	2.2	2.4	+ 9
Fraction of thoracic examinations with two or more films	31 %	47 %	+ 52
Mean ratio of beam area to film area (in hospitals)	1.9	1.2	− 37
Estimated mean skin exposures for posterior-anterior and anterior-posterior views of the abdomen	480 mR	620 mR	+ 29[b]
Mean skin exposure per dental film	1 140 mR	910 mR	−20[c]

Sources: References 27, 250, 251.

[a] The population of the United States increased by 7 per cent over the six-year period.

[b] This increase may be due to the increased frequency of high-exposure examinations, the increase in the use of grids, and the use of higher tube potentials and currents without a corresponding increase in filtration.

[c] This decrease is due to the increased use of faster film.

TABLE 3. ESTIMATED ANNUAL NUMBER AND DISTRIBUTION OF MEDICAL X-RAY PROCEDURES BY TYPE OF FACILITY AND SUPERVISION

United States, 1964 and 1970

Type of facility	Number of medical x-ray procedures (thousands)		Per cent of medical x-ray procedures		Number of procedures supervised by radiologists (thousands)		Per cent of procedures supervised by radiologists	
	1964	1970	1964	1970	1964	1970	1964	1970
All types	118 919	144 355	100.0	100.0	72 346	100 530	60.8	69.6
Hospital	68 490	92 489	57.6	64.1	63 080	91 356	92.1	98.8
Private office	24 195	27 136	20.3	18.8	...	...	...	...
Radiologist	5 335	4 223	4.5	2.9	5 335	4 223	100.0	100.0
Other	18 860	22 913	15.8	15.9	...	...	...	...
Private group	7 861	9 903	6.6	6.9	3 931	4 951	50.0	50.0
Health agencies and others	18 374	14 826	15.5	10.3	...	...	...	...

Note: Table reproduced from reference 251.

35. The estimated number and distribution of diagnostic x-ray procedures in the United States in 1964 and in 1970 (251), by type of facility and supervision, are shown in table 3. There was a 6.5 per cent increase in the use of hospital radiological facilities, and an increase from 92.1 per cent to 98.8 per cent in the proportion of films taken in hospitals under the supervision of radiologists.

36. An analysis of the trend in the number of medical x-ray visits by age group for the years 1960, 1964 and 1970 is shown in table 4 (250). The major increases occurred in the age groups <15, ⩾45 and, particularly, >65 years. According to this information, the fractional number of patients under 30 decreased from 22.3 per cent in 1960 to 20.5 per cent in 1970.

37. The United States surveys (255) showed no significant change in the annual GSD between 1964 and 1970, in spite of the increased number of examinations and the indication of higher abdominal doses. (See paragraph 107.) An analysis of the increase in frequency of abdomen and thoracic examinations shows, however, that these examinations increased principally in the age groups above 30, which might be one explanation for the lack of significant change in GSD. Additional patient protection was used in 10 per cent and 8.5 per cent of

TABLE 4. ANALYSIS OF THE INCREASING FREQUENCY OF MEDICAL X-RAY VISITS BY AGE AND SEX

United States, 1960-1970

(Visits per 100 persons per year)

Category	July 1960-June 1961	April-June 1964	April-September 1970
Age (y)			
< 15	16.4	20.9	24.4
15-29	57.1	55.2	55.4
30-44	63.0	61.1	65.9
⩾ 45	66.5	69.8	81.5
45-64	71.2	73.6	82.3
⩾ 65	55.4	61.5	79.9
Sex			
Male	49.7	50.6	56.6
Female	46.2	49.0	55.3
Overall	47.9	49.8	55.9

Source: Reference 250.

TABLE 6. NUMBER OF X-RAY EXAMINATIONS IN MASS

Breakdown (10^3)

Sex								Age (y)
							(a)	*Mass chest*
		⩽ 10	*11-15*	*16-18*	*19-24*	*25-29*	*30-34*	*35-39*
Male		655	634	2 278	3 340	2 426	2 053	1 830
Female		622	606	2 296	2 201	1 849	1 565	1 432
	Total	1 277	1 240	4 574	5 541	4 275	3 618	3 262
							(b)	*Mass stomach*
				⩽ 19	*20-24*	*25-29*	*30-34*	*35-39*
Male				4.7	22.2	70.9	136.1	310.1
Female				2.3	11.1	30.1	94.9	216.5
	Total			7.0	33.3	101.0	231.0	526.6
							(c)	*Dental*
		0-5	*6-10*	*11-14*	*15-19*	*20-24*	*25-29*	*30-34*	*35-39*
Male and female		1 261	2 495	2 595	5 061	9 731	11 360	11 510	12 762

Sources: Chest screening, reference 84; stomach screening, 83; dental radiography, 138.

TABLE 5. ANALYSIS OF THE INCREASING FREQUENCY OF DIAGNOSTIC X-RAY EXAMINATIONS BY TYPE

Japan, 1958-1975

Type of examination	*Number of examinations per 1000 persons*			*Ratio*	
	a. *Radiography*				
	1959 (A)	*1969 (B)*	*1974 (C)*	*B/A*	*C/B*
Head, cervical spine	8.8	58	60	6.6	1.03
Shoulder	22	33	48	1.5	1.45
Chest	144	277	289	1.92	1.02
Barium meal	19.4	86	108	4.4	1.25
Abdomen	1.5	14	23	9.3	1.64
Barium enema	5.9	6.2	6.5	1.05	1.04
Dorsal spine	3.3	7.0	5.0	2.1	0.71
Lumbar or sacral spine	7.1	37	41	5.2	1.11
Urography, cystography	5.1	7.7	9.6	1.51	1.24
Hip and joint	8.5	14	19	1.65	1.35
Lower leg	15.8	44	56	2.8	1.27
Tomography	–	5.0	7.3		1.46
Pelvimetry, obstetrical (abdomen)	1.6	2.8	1.9	1.75	0.68
Other	13.9	54	63	3.9	1.16
Total	259	641	729	2.5	1.14
	b. *Dental radiography*				
	1958 (A)		*1974 (C)*		*C/A*
Dental x-ray examinations	13		833		64
	c. *Photofluorography*				
	1963 (A)	*1968 (B)*	*1973 (C)*	*1975 (D)*	*B/A*	*C/B*	*D/B*
Chest	434	641	486	313	1.47	0.76	0.49
Barium meal	–	18	31	40		1.72	2.22

Sources: References 74, 79, 146, 181.

the diagnostic x-ray examinations in 1964 and 1970, respectively, whereas in dental radiography the use of additional patient protection increased from 18.8 per cent to 27.2 per cent (251).

38. A survey by Bederke *et al.* (202) in 1974 in the Kopenick ward of Berlin (GDR) of out-patient radiological examinations showed that, of the 29 000 patients examined, 30 per cent were under 30 years of age. On the average, the patients had 2.5 exposures per examination; in the case of barium meals and enemas, the average was 5.0. Fluoroscopy was used in 17 per cent of the examinations, and 49 per cent of the patients had radiographs of the abdomen or pelvis with relatively high gonad doses. The total number of examinations per year was 40 000 for out-patients and about the same number for in-patients. With a total population of 131 000, that would indicate an examination rate of 67 per 100 persons per year.

39. In Japan, nation-wide radiological surveys were made in 1959, 1969 and 1974 (74, 78, 80, 81, 181). The frequency data from these surveys are summarized in table 5. There was a considerable increase in the number of x-ray examinations between 1959 and 1969; the increases according to type were by factors that ranged from 1.05 to 9.3, with an overall factor of 2.5. However, during the five years 1969-1974, the rate of increase was much reduced for many of the examination types, and the overall rate of increase in the number of examinations was assessed at about 3 per cent per year. The most important increases from the collective dose aspect are those for barium-meal examinations and for abdomen, lumbar spine and sacral spine examinations. There was also a very significant rise in the number of dental x-ray examinations (see paragraph 44).

40. Table 6 gives the frequency of mass chest and stomach screening and dental radiography by age group in Japan. The mass chest screening during school age is carried out only at the time of admission into the primary school (age 5-6) and at the second class of the junior high school (age 13-14). The largest numbers are radiographed in the 19-24 y group for chest examinations and in the 40-44 and 45-49 y groups for the stomach examinations.

SCREENING AND DENTAL RADIOGRAPHY IN JAPAN, 1974 AND 1975

by age and sex

						Total
screening, 1975						
40-44	*45-49*	*50-54*	*55-59*	*⩾ 60*		
1 762	1 559	1 109	469	537		18 652
1 407	1 273	1 094	345	438		15 128
3 169	2 832	2 203	814	975		33 780
screening, 1975						
40-44	*45-49*	*50-54*	*55-59*	*60-69*	*⩾ 70*	
492.6	496.8	369.2	224.0	205.6	51.8	2 384
331.3	331.3	279.1	193.2	207.5	39.7	1 737
823.9	828.1	648.3	417.2	413.1	91.5	4 121
radiography, 1974						
40-49		*50-59*		*⩾ 60*		
16 668		10 055		6 423		89 921

41. A comparison between the 1974 Swedish survey by Bengtsson *et al.* (17) and the 1955 survey by Larsson (128) shows that x-ray examinations (excluding dental) increased by 51 per cent between 1955 and 1974. During this period the Swedish population increased by 11 per cent, which means that the net increase was 36 per cent, or less than 2 per cent per year. The disappearance of tuberculosis as a significant problem is reflected in decreased frequencies of mass photofluoroscopy, but this trend may not be representative of other countries. There is a remarkable increase in the number of dental exposures, almost by a factor of five. The frequency data are summarized in table 7.

TABLE 7. ANALYSIS OF THE INCREASING FREQUENCY OF DIAGNOSTIC X-RAY EXAMINATIONS BY TYPE

Sweden, 1955 and 1974

Type of examination	*Number of examinations per 1000 persons*		*Ratio*
	1955 (Population 7.3 10^6)	*1974 (Population 8.1 10^6)*	*1974/1955 (Population ratio 1.11)*
Hip and femur	9.6	18.9	2.0
Pelvis	8.2	15.4	1.9
Pelvimetry	0.5	1.3	2.6
Lumbosacral region	16.1	25.0	1.6
Urography, retrograde pyelography	9.1	23.9	2.6
Urethrocystography	1.2	2.7	2.3
Stomach, small intestine	30.0	33.0	1.1
Colon	9.0	16.0	1.8
Abdomen	5.0	12.9	2.6
Obstetrical abdomen	0.6	1.4	2.3
Hysterosalpingography	1.2	0.8	0.7
Cholecystography, cholangiography	12.0	18.4	1.5
Dorsal spine	5.8	13.3	2.3
Lung, ribs, heart	79.4	161.6	2.0
Lung (photofluorography)	139	110	0.8
Dental (single exposures)	307	1 500	4.9
Other	103	195	1.9
Total (excluding dental)	430	650	1.51

Sources: References 17, 128.

42. An interesting study reported by Berry and Oliver (20) shows that in the United Kingdom of Great Britain and Northern Ireland, 18 per cent of the x-rayed patients had spoilt films, principally because of exposure or positioning faults.

43. The annual number of dental exposures per 1000 of population in Sweden increased from about 300 in 1955 to 570 in 1969 (151), i.e., by about 6 per cent per year. The subsequent increase to 1500 in 1974 (table 7) corresponds to about 20 per cent per year over that last five-year period. Of the 13 million dental films exposed in Sweden in 1974, about 3 million were exposed in bite-wing examinations of school children. Of the remaining 10 million films, about 50 per cent have been estimated to have been used in bite-wing examinations. The increasing number of bite-wing examinations is partly explained by deliberate efforts to make full-mouth examinations irrespective of whether the dentist knows beforehand that the film will be needed. This practice is defended on the basis of claimed earlier detection of small cavities. Such dental examinations are therefore health investigations rather than diagnostic examinations. The yield has been estimated to be about 10 per cent in those examinations for which there were no clinical indications, but this number is uncertain. No estimate has been made on how many of the bite-wing exposures were made without clinical indication.

44. Similar observations have been made in other countries. For example, in the 1970 United States survey (251) it was reported that there were an estimated 68 million dental x-ray visits, corresponding to an average of 340 x-ray examinations per 1000 of population. As each examination consisted of, on the average, 4.1 films, the total number was approximately 1400 films per 1000 of population, in line with the practice in Sweden. The annual number of dental exposures per 1000 of the population in Japan increased from 13 in 1958 to 855 in 1974 (146). The age distribution of the population in Japan having dental examinations during 1974 is given in table 6. The study (138) also includes information on the numbers in each age group for the different types of intra-oral examination.

45. In contrast, it has been estimated that 4 million x-ray films were used in the United Kingdom in 1973 (52), an average of only 73 per 1000 of population. This compares with an estimated 2 million films used in 1957.

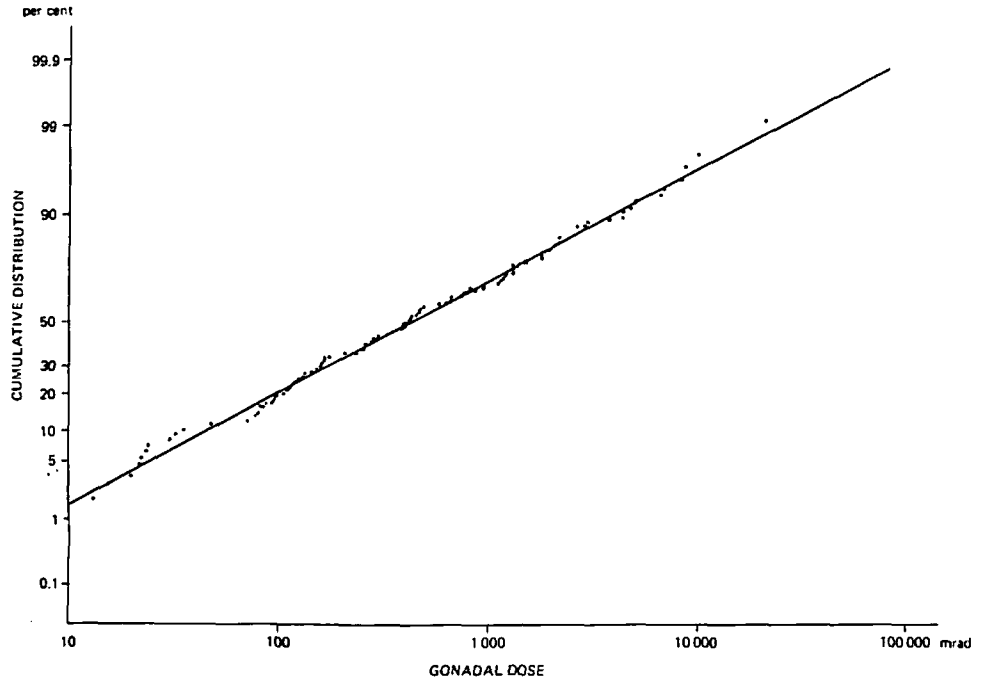
46. Interesting sociological variations in the United States in the frequency of x-ray visits for dental examinations are shown by the fact that the rate of x-ray visits per 100 of population were 11.2, 29.2 and 50.3 for those people having under 9, 9-12 and 13 or more years of education, respectively (250). This finding agrees with the findings of the 1964 survey for dental examinations, but not with those shown by the analysis of x-ray visits for medical examinations.

2. Individual dose per unit procedure

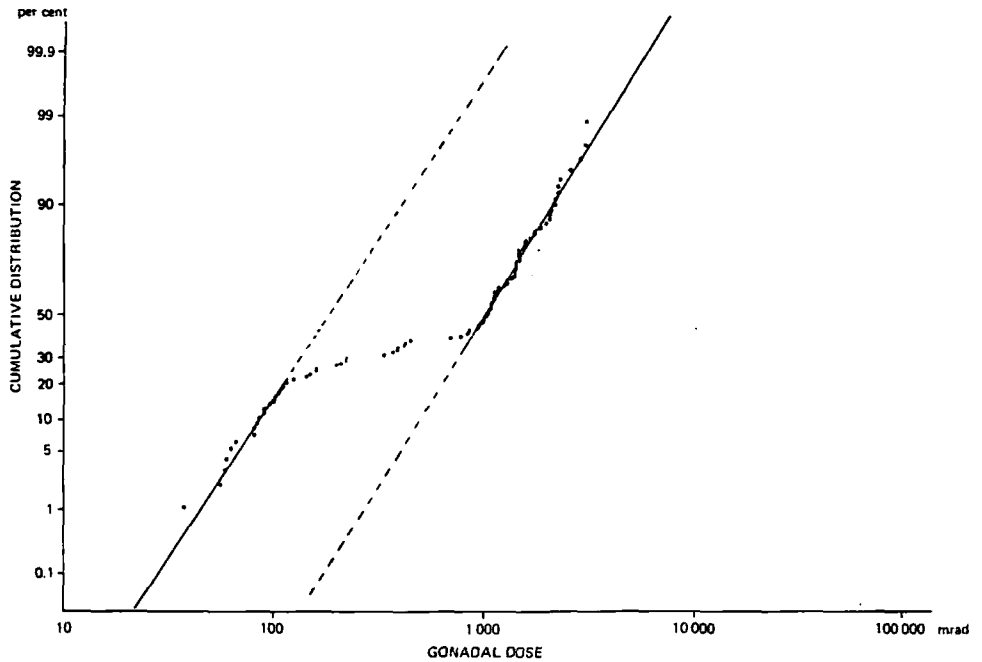
(a) *Accuracy of dose estimates and reasons for variation*

47. Previous reports of the Committee have shown that individual organ doses in each type of examination vary considerably from one clinic or individual radiologist to another. Some of this variation arises from differences in the actual extent and needs of the examination itself and some from differences in the selection of field sizes and localization of the beam. However, there is also a large variation in the skin exposures, both because of differences in the technical operation of the equipment (89), including the use of grids, and in the dimensions of the patients. Additionally, the sensitivity of the recording medium influences the results.

48. The use of equipment that measures the product of the exposure and area at the beam collimator is sometimes used as an indication of the total energy emerging from the x-ray tube towards the patient. These



(a) Intravenous pyelography; $\bar{D}$ = 1300 mrad; s = 2600 mrad; median = 370 mrad; 102 patients



(b) Lumbosacral region examination; $\bar{D}$ = 1048 mrad; s = 855 mrad; median = 1079 mrad; 93 patients. This examination type forms the unique exception to the log-normal distributions found in all other types (120)

Figure I. Cumulative distribution of male gonadal doses from intravenous pyelography and lumbosacral region examinations; $\bar{D}$ = mean dose; s = standard deviation

instruments are useful as comparative instruments between one operator and another, but do not give a true value of skin exposure. When the beam size is large and misses the patient, the recorded value obviously shows a larger variation than the skin exposure. A United States study (the NEXT program) has shown such a variation for lumbar spine and chest examinations (30, 31). A correction also has to be applied for the energy transmitted completely through the patient. A comparison undertaken for the British Committee on Radiological Units showed that there was poor agreement between exposure-area product and bone-marrow dose (48). Stieve (226) reports that the error in estimating dose using the exposure-area product may be 200 per cent.

49. The spread of individual doses in any given type of x-ray examination may be quite large even within one and the same hospital. The distribution is usually skewed, with a preponderance of doses lower than the mean. It has been suggested by Koen and Weber (120) that the distribution is sometimes log-normal, and they have illustrated this with distribution diagrams for the male gonadal dose (fig. I). For some examinations, e.g.,

of the lumbosacral region in male patients, the gonadal dose will increase by an order of magnitude when the direct beam falls on the gonads. This will be equivalent to two distinct groups of patients and hence will, when the data are plotted on probability paper, provide two distinctive but overlapping populations. Subsequently, more detailed information from the same survey (121) showed that various distributions were obtained when all the doses for a particular examination from all the hospitals surveyed were included.

50. Bengtsson *et al.* (17) have analyzed the skewed distribution in further detail. Figure *II* gives an example of the distribution of mean whole body absorbed dose in

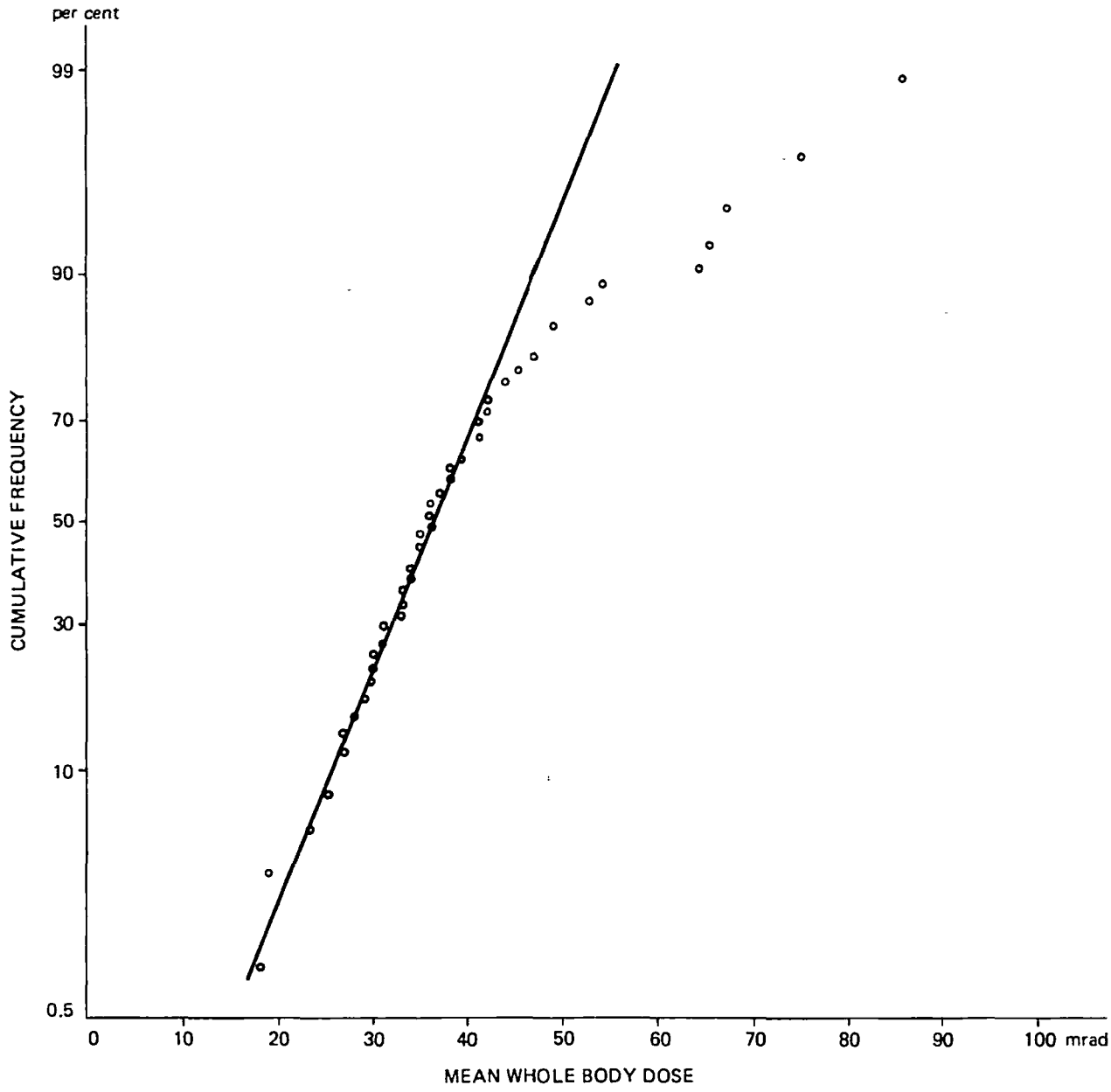


Figure II. Distribution of mean whole body dose from chest examinations at one Swedish hospital. The deviation from normal distribution results mainly from the taking of an additional film (17)

chest examinations at one Swedish hospital. The figure shows a significant deviation from the normal distribution at high patient doses. A closer review revealed that with some patients three exposures were required whereas with most patients two were sufficient. If the three-exposure cases were excluded, a good fit to a normal distribution was obtained. This illustrates (as in paragraph 49) that basically there may be a normal distribution when the number of parameters is limited, but as further parameters are introduced, the distribution may become quite complex.

51. In this Swedish study, neither chest nor stomach examinations fitted a log-normal distribution. The mean whole body dose in stomach examinations was found to follow closely a normal distribution whereas the distribution of the energy imparted to the whole body showed some deviation from a normal distribution.

(b) *Doses to various organs*

52. There is an increasing number of publications on measurements carried out during radiological procedures. Even though they may reflect particular conditions in the clinics and hospitals concerned, they are nevertheless useful in illustrating the levels of radiation dose to patients. Typical publications on patient dose are referred to in each of the following sections and in references 7, 58, 71, 116, 207 and 234. A number of reports referring to technical advances are referred to, such as those on the improved sensitivity of image recording (10, 11, 12, 55, 196). It is particularly useful if patient studies are directed at measuring the total absorbed dose to each of the organs of interest that is accumulated from all radiological studies during a particular patient's period of ill health. Examples of this are given by Trott *et al.* (238).

(i) *Incident skin dose*

53. As has been described in paragraph 12, the dose to organs in the primary x-ray beam may be derived *inter alia* from knowledge of the incident skin dose. A summary of typical skin doses for three broad groups of examinations giving rise to high, medium and low skin doses was given in the 1972 report (244) and is reproduced here as table 8 except for the entry for mammography examinations, for which new techniques requiring lower doses are now available (see paragraph 71). New data on skin exposure in diagnostic procedures were obtained during the 1970 United States survey for radiographic examinations (251) and also by studies in the Federal Republic of Germany (25). The doses are in general similar to those shown in table 8.

TABLE 8. TYPICAL SKIN DOSE IN THE PRIMARY BEAM IN DIAGNOSTIC X-RAY EXAMINATIONS

(rad)

	Per exposure		*Per examination*	
Dose group	*Median value*	*Range of average values*	*Median value*	*Range of average values*
High skin dose				
Barium swallow R			1.4	
Barium swallow F	6.4[a]		8.5	
Barium meal R	0.9	0.9-2.2	1.7	
Barium meal F	4.4[a]		2.1	6-25
Barium enema R	0.7	0.4-1.0	1.5	
Barium enema F	4.9[a]		20	5-26
Whole chest R	0.02	0.006-0.09	0.14	0.07-0.15
Whole chest F	2.0[a]		12	3-22
Mammography			6[b]	0.2-7.8[b]
Pelvimetry	2	0.8-3.8	8	6-10
Lumbosacral spine	2.7	0.5-2.9	5	5-6
Lumbar spine	1.5	0.7-2.9	4.5	
Cardiac catheterization			47	
Medium skin dose				
Head	0.4	0.3-1.5	1.5	1.4-1.9
Cervical spine	0.3	0.03-0.8	1.5	0.6-1.9
Clavicle and shoulder	0.9		0.3	0.3-0.4
Dorsal spine	1.8		2.8	2.0-4.7
Thorax	0.4		0.8	0.6-0.9
Cholecystography	0.8	0.2-1.2	2.2	1.5-2.8
Abdomen	0.2	0.15-1.3	1.2	1.0-1.4
Abdomen (obstetric)	2.0	0.4-3.9	3.2	2.7-3.8
Urography (descending)	1.2		3.2	1.7-5.0
Urography (retrograde)			2.9	1.4-2.4
Salpingography R			1.2	
Salpingography F			3.4	
Placentography			3.0	
Cystography	0.2		3.1	
Pelvis	1.4	0.4-1.7	3.3	2.1-4.5
Hip and upper femur	1.1	0.4-1.7	1.4	1.1-3.0
Dental	0.4		2.5	1.6-3.4
Angiography (head)			1.0	
Angiography (abdomen)			3.3	
Tomography (chest)			1.1	0.8-1.4
Mass survey chest	0.9		1.0	0.6-1.4
Low skin dose				
Arm and hand	0.1		0.3	0.1-1.7
Chest	0.02	0.006-0.09	0.14	0.07-0.15
Femur (lower two thirds)	0.03		0.4	
Leg and foot	0.1		0.4	0.3-0.4

Source: Reference 244.

Note: R = radiography; F = fluoroscopy.

[a] R min^{-1}.

[b] New data (see paragraph 71).

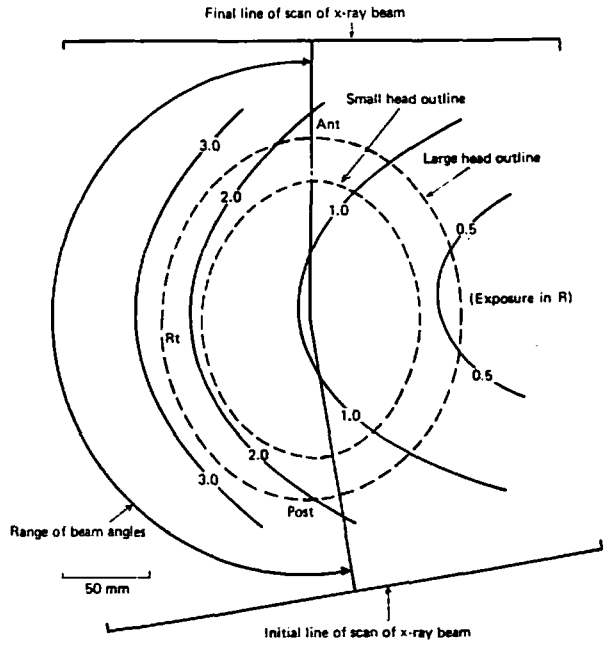


Figure III. Isodose curves in a water phantom for single complete scan (165)

54. The new technique of computerized tomography (CT) scanning utilizes a narrow beam of x rays either in a pencil or a fan shape. The skin dose to the patient per complete scan is increased as the matrix element size of the display is decreased. Typical skin doses have been measured by Perry and Bridges (165) and are shown in figure III for a single complete scan of the head. The increase in dose for subsequent consecutive scans will depend on the amount of overlap. The width of the beam is about 1 cm and the overlap may be between one third and one half of the width of the beam. The radiation dose will therefore be of the same order as in comparable x-ray examinations of the head or the trunk.

55. High skin doses have been reported for such types of examinations as cardiac catheterization, pace-maker insertions and cine investigations in voiding urethrocystography. Gough, Davis and Stacey (66) indicate mean skin doses of 47 rad in a group of 85 patients undergoing cardiac catheterization, with a maximum value of 140 rad. The frequency of undertaking this examination is not accurately known. Other surveys also indicate high doses (8, 10, 46, 153, 192). A comparison of the skin doses received in different techniques of investigations of the heart and large vessels are given in table 9 (235).

56. Recent detailed measurements (52) during 24 cardiac catheterization studies have shown a reasonable correlation between dose and exposure expressed as the current-time product. Typically, for a study involving an x-ray tube operating for 10^4 mAs a posterior skin dose of 8-20 rad was received, the anterior skin dose being 1-2 rad. The mean marrow dose, deduced from the skin dose, was 0.5-1.2 rad and the gonad dose 5-100 mrad.

57. Pace-maker insertions are controlled by x-ray fluoroscopy. Gough *et al.* (66) have reported an average skin dose of 132 rad per insertion for a group of six patients. This dose is likely to be repeated a number of times for each patient. The high skin-dose rates in cine investigations have been mentioned by several authors and may be of the order of 50 rad min^{-1} (192, 258).

(ii) *Dose to the head and thyroid, particularly from dental x-ray examinations*

58. The considerable increase in the frequency of dental x-ray examinations reported in paragraphs 41-44 merits the inclusion of recent measurements of the dose

TABLE 9. MEAN ENERGY IMPARTED TO PATIENTS DURING RADIOLOGICAL INVESTIGATIONS OF THE HEART AND LARGER VESSELS

	Typical conditions					*Dose*		
						Per procedure		*Per examination*
Method of investigation	*Skin-focus distance (cm)*	*Voltage (kV)*	*Area (cm^2)*	*Time (min)*	*Filter (mm Al)*	*(R)*	*(kg rad)*	*(kg rad)*
Fluoroscopy	60	60	200	1.5	0.5	7.5-10		8.5-11.35
Radiography								
Direct	80	70	1 200		0.5	0.25-0.5	1.64-3.3	
Lateral	60	80	800		0.5	0.5-1	2.3-4.7	
Tele	150	90	1 200		0.5	0.3	2.0	
Photofluorography	80	70	800		0.5	0.5-1	2.3-4.6	4.6-9.2
Tomography	70	70	1 200		0.5	1-2	6.8-12.6	20.4-37.8
Kymography								
Direct	80	90	720		1	8	32.9	
Lateral	70	90	720		1	12	51	
Electrokymography	60	60	50	10	1	25		7
Angiocardiography	70	110	1 200		1	0.5	3.6	55
Heart catheterization	40	70	100	22	1	30-232		145
Heart catheterization with image intensifier	40	60	400	22	3	21		58.4
Cine with image intensifier	60	70	400	22	3	12.5		32

Source: Reference 235.

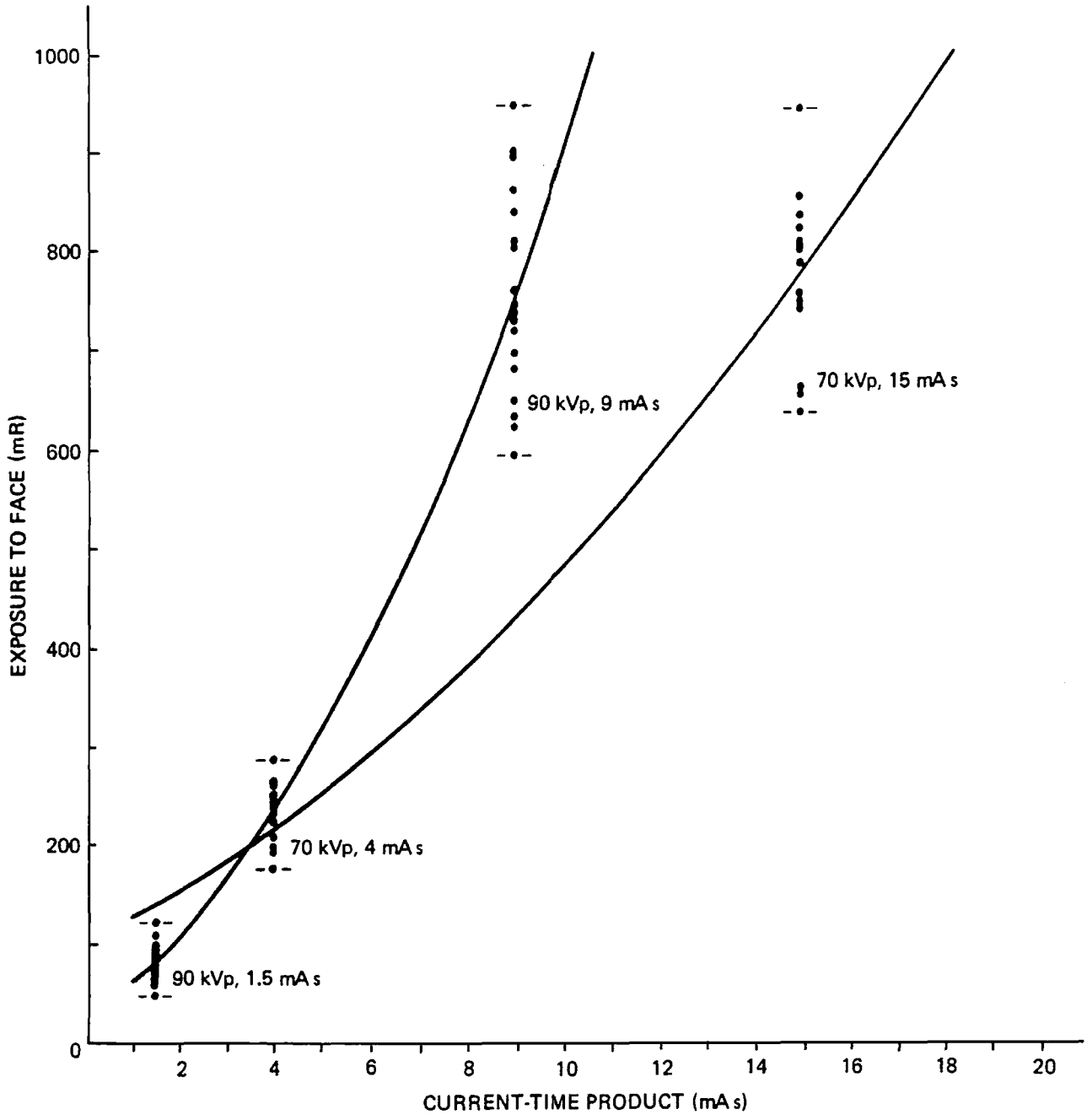


Figure IV. Dependence of exposure at the face on current-time product in dental x-ray examinations (187)

distribution from various dental x-ray techniques. The relationship between the radiation exposure and the current-time product of the x-ray tube has been investigated by Roessler and his co-workers (187), and is given in figure IV. In order to give information on the distribution of radiation over the head and neck from dental exposure, Alcox (5) measured the exposure at the skin surface over sites of interest and the reported values are given in tables 10 and 11. The exposure to the lens of the eye may be estimated from those to the infraorbital, supraorbital and nasion regions, which represent the maximum, minimum and most probable exposure to the lens. The maximum values reported are 84 mR for the two-film technique and up to 1.66 R for the whole-mouth examination. The exposure to the thyroid was between 2.4 and 9.0 mR for the two-film, and between 35 and 70 mR for the full-mouth, examination. Similar studies have been carried out for children (260). These measurements are similar to those reported in Finland by Altonen *et al.* (6), in Sweden by Bengtsson *et al.* (17), in the Union of Soviet Socialist Republics (235), and in the United States survey (251).

59. In the 1974 Japanese survey of dental practice, Maruyama *et al.* (138) made measurements on a man-like phantom of the doses received by the eyes, thyroid and gonads for a variety of dental examinations and tube voltages. The measurements, given in table 12, show the large variations in doses received caused by the different beam directions, for a current-time product of 10 mAs.

60. Measurements of the dose in the head during orthopantomography have been made in Norway by

TABLE 10. INTRA- AND EXTRA-ORAL EXPOSURES IN A TWO-FILM POSTERIOR BITE-WING EXAMINATION

	Mean measured exposure (mR)					
	Short-cone technique			*Long-cone technique*		
Anatomic location	*50 kVp 4-inch TFD*	*70 kVp 8-inch TFD*	*90 kVp 8-inch TFD*	*50 kVp 8-inch TFD*	*70 kVp 16-inch TFD*	*90 kVp 16-inch TFD*
Intra-oral						
Upper molar	152.0	204.6	258.0	252.0	156.6	141.6
Lower molar	140.0	198.3	250.0	240.0	153.1	137.3
Palate	31.0	54.9	93.0	46.0	46.5	52.0
Front of film	18.0	28.8	47.8	26.2	24.3	31.0
Back of film	7.0	7.6	23.2	6.4	9.5	11.3
Extra-oral						
Supra-orbital	4.0	4.5	5.1	2.7	2.5	2.4
Nasion	6.0	3.8	24.7	2.6	2.4	1.7
Infraorbital	50.0	35.9	84.3	19.3	11.6	9.4
TMJ area	5.0	8.0	9.4	3.4	13.5	71.7
Molar area	311.0	415.4	390.0	425.0	310.8	189.2
Philtrum	61.0	11.7	28.5	23.0	4.6	5.9
Lower lip	116.0	10.4	52.9	51.4	5.0	65.1
Thyroid	9.0	2.4	5.0	2.6	2.4	4.0
Total beam	839.0	868.0	919.0	1 139.0	659.0	525.0
Exposure per film	416.0	434.0	460.0	570.0	330.0	263.0
Number of patients	18	12	12	15	16	12

Source: Reference 5.
Note: TFD = tooth-focus distance.

TABLE 11. INTRA- AND EXTRA-ORAL EXPOSURES IN AN 18-FILM FULL-MOUTH EXAMINATION

	Mean measured exposure (mR)					
	Bisecting-angle technique			*Right-angle technique*		
Anatomic location	*50 kVp 8-inch TFD*	*70 kVp 8-inch TFD*	*90 kVp 8-inch TFD*	*50 kVp 8-inch TVD*	*70 kVp 16-inch TFD*	*90 kVp 16-inch TFD*
Intra-oral						
Upper molar	1 329.0	1 462.0	944.0	1 085.0	1.103.4	704.6
Lower molar	1 503.0	1 414.0	932.0	1 198.0	1 070.6	657.4
Palate	443.0	538.0	368.0	339.0	435.3	311.3
Extra-oral						
Supra-orbital	76.0	65.0	46.9	49.0	42.2	29.5
Nasion	163.0	156.0	190.0	90.0	57.7	35.6
Infraorbital	1 660.0	1 547.0	835.0	1 187.0	1 003.3	507.3
TMJ area	24.6	39.4	29.3	21.0	44.3	48.3
Molar area	1 726.0	1 386.0	983.0	1 149.0	995.6	417.6
Philtrum	2 095.0	2 084.0	1 329.0	2 041.0	1 387.1	831.8
Lower lip	1 820.0	1 465.0	1 042.0	1 427.0	1 053.0	539.0
Thyroid	67.0	43.0	70.0	59.0	39.2	35.4
Total beam	9 905.0	6 727.0	4 885.0	7 949.0	4 657.0	3 130.0
Exposure per film	550.0	374.0	271.0	442.0	259.0	174.0
Number of patients	15	13	12	14	13	12

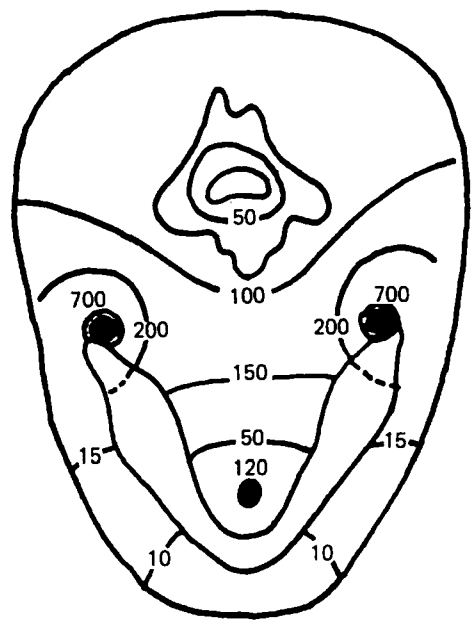
Source: Reference 5.
Note: TFD = tooth-focus distance.

TABLE 12. ABSORBED DOSES IN CRITICAL ORGANS DURING INTRA-ORAL DENTAL EXAMINATIONS
(mrad)

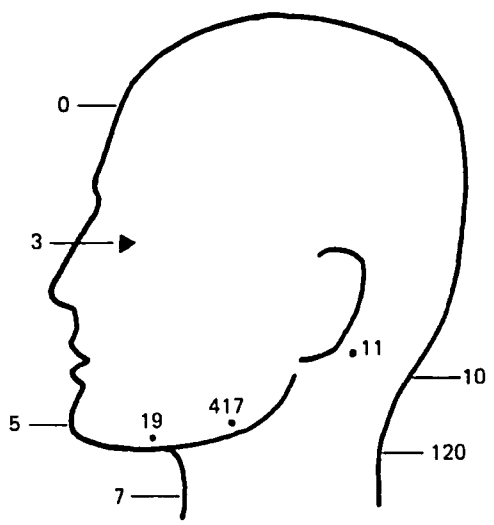
		Location of examination					
		Upper jaw			*Lower jaw*		
Organ	*Tube voltage (kV)*	*Molar and premolar*	*Canine*	*Incisor*	*Molar and premolar*	*Canine*	*Incisor*
Eye	50	85	6.25	2.00	2.00	25.0	2.75
	60	118	8.25	2.75	3.00	47.7	4.25
	70	156	10.5	3.75	4.50	86.5	6.00

Organ	Tube voltage (kV)	Location of examination: Upper jaw: Molar and premolar	Upper jaw: Canine	Upper jaw: Incisor	Lower jaw: Molar and premolar	Lower jaw: Canine	Lower jaw: Incisor
Thyroid	50	2.75	20.2	6.25	23.0	3.0	5.25
	60	3.50	26.7	8.00	33.2	5.5	9.50
	70	4.25	33.7	9.75	45.5	9.5	15.2
Testis	50	0.12	0.08	0.18	0.10	0.12	0.10
	60	0.21	0.17	0.28	0.18	0.20	0.22
	70	0.34	0.29	0.35	0.30	0.31	0.45
Ovary	50	0.0000	0.0000	0.0026	0.0000	0.0000	0.0000
	60	0.0007	0.0000	0.0055	0.0000	0.0000	0.0000
	70	0.0015	0.0000	0.0105	0.0000	0.0000	0.0000

Source: Reference 138.



(a) Dose distribution in cross-section of the head through the lower jaw. The figures are absorbed doses (mrad) in soft tissue. The rotational axes are shown as black spots



(b) Skin exposure (mR)

Figure V. Distribution of head dose and skin exposure from orthopantomography (221)

the State Institute of Radiation Hygiene (221) and by Casebow (32) in the United Kingdom. Figure V shows the cross-section dose distribution and the skin exposure from the Norwegian study. There are high-dose regions (700 mrad) around the rotational axes.

61. The Norwegian report gives the dose to the bone marrow as 1.0, 7 and 2 mrad for molar bite-wing, 10-exposure whole-mouth and orthopantomography examinations, respectively. The dose to the gonads from one exposure has been estimated as 5 μrad for adults and 25 μrad for children.

(iii) *Gonad doses*

62. Data on gonad doses in different types of examinations are presented in the review of the annual GSD in paragraphs 93 to 108.

(iv) *Thyroid doses*

63. In addition to thyroid doses from the direct radiation incident during cervical spine and barium swallow examinations, thyroid doses of the order of 1 mrad may also be received in examinations of the head, sinus and dorsal spine (17), and somewhat higher doses during dental examinations (see paragraph 58).

(v) *Bone-marrow doses*

64. In the 1972 report (244), the bone-marrow doses per examination for three major national surveys were published, and these data are reproduced here as table 13, together with data obtained in new studies in Japan, Sweden and the United States. From the data given in the previous report, the maximum values of bone-marrow dose observed for any one examination type were about two orders of magnitude greater than the mean value when the examination included fluoroscopy. When it did not involve fluoroscopy, the maximum values were about one order of magnitude greater than the mean. These effects also reflect the extent of the examination both in beam area and skin dose, i.e., the number of films and the exposure per film, which is dependent on the film-screen combination.

TABLE 13. BONE-MARROW DOSE PER EXAMINATION

Country surveys
(mrad)

Type of examination	*Germany, Federal Republic of (25)*	*Japan (73)*		*Nether-lands (259)*	*Sweden (17)*	*United Kingdom (37)*		*United States (208)*	
		1969	*1974*			*Male*	*Female*	*1964*	*1970*
Head	12-90	29	44	90	120	32	39	65	78
Cervical spine	8-51	43	37	8	38	54	49	31	52
Barium swallow	359-1 180	140	747	50	420	1 300	590		
Arm and hand									
Clavicle and shoulder		18			60	38	81		
Dorsal spine	67-208	140	370	105	470	200	220	232	247
Whole chest	7-40	9	25	10,[a] 40[b]	29	12	13	10	10
Thorax (ribs and sternum)	6-106	34	40	6	54	180	37	124	143
Barium meal	359-1 180	210	705	80	350	510	800	624	535
Cholecystography	36-590	73	237	36	150	150	150	183	168
Abdomen	39-125	59	202	93	300	120	130	183	147
Abdomen (obstetric)	56-206	72	70	56	220		210[c]		
Descending urography	200-1 160	110	262	433	240	580	450	453	420
Retrograde urography	257-386			257	300	440	330		
Salpingography	21-300	50	212	282	170		210		
Placentography									
Pelvimetry		170	98				280[d]	288	595
Cystography	168-1 160	37	116	168	680	170	940	183	147
Barium enema	50-940	210	1 114	359	940	530	1 060	624	875
Pelvis	39-138	70		138	190	130	140	116	93
Lumbar spine	56-270	150	248	140	410	270	270	336	347
Lumbosacral joint	61-651	92	140	651	100	290	220	418	450
Hip and upper femur (upper third)	21-58	43	169	47	250	57	60	97	72
Rest of femur	4-50	8							21
Leg and foot			0.3						
Dental					1	1.8	1.8	13.2	9.4
Angiography (head)						130[e]	130		
Angiography (abdomen)						380[e]	380		
Tomography (chest)						360	390		
Cardiac catheterization						190[e]	190		
Bronchogram						31	31		
Mass survey chest		35		47	90	61	101	65	44
Mass survey stomach		60							

[a] Radiography.
[b] Fluoroscopy.
[c] Foetal contribution, 500 mrad.
[d] Foetal contribution, 1100 mrad.
[e] Assuming equal frequencies of male and female examinations.

65. The basic data used in the 1957 United Kingdom survey have recently been published by Ellis, Healy, Shleien and Tucker (50). These include the conversion factors for the bone marrow site-to-skin exposure for square fields, the appropriate conversion factors for rectangular and circular fields and the computer programme for the calculation of mean bone-marrow dose. The measurement data are for 16 marrow sites irradiated at seven qualities, half-value layers (HVL) from 1.0 mm Al to 20.0 mm Al, for source-to-skin distances of 20, 40, 60 and 80 cm and for five square-field sizes from 16 to 900 cm^2.

66. An analysis of the variation of the bone-marrow dose with HVL, source-to-skin distance and beam area were also undertaken and the results are shown for a number of examinations in figures VI, VII and VIII. Reasonable agreement exists between the studies of Ellis *et al.* (50) and Epp *et al.* (54) for examinations not involving the passage of the beam through the lungs, from the anterior projection. For examinations involving this passage, the differences probably result from the fact that the mean lung densities used in the two phantoms were 0.2 and 0.3 g cm^{-3}, respectively.

67. An extensive Monte Carlo type computational study has been undertaken by Rosenstein and his co-workers (190) for the estimation of organ doses from diagnostic radiological procedures. The method involves the simulation and recording of the energy deposited by x-ray photons as they undergo physical interactions in a mathematically described heterogeneous anthropomorphic phantom. The general techniques have been developed by Snyder *et al.* (211, 212) for use in determining doses from internal radiation. Tissue-air ratios have been generated for the testes, ovaries, active bone marrow, thyroid and embryo (uterus) of a reference adult patient for several photon energies from 20 to 100 keV. From these ratios a compilation of the five organ doses per unit entrance exposure free in air (mrad R^{-1}) has been developed as a function of six beam qualities from 1.5 to 4.0 mm Al HVL for 34 projections common in diagnostic radiology. An example of the data for one of these projections is given in table 14. Similar studies using the Monte Carlo system and the Snyder phantom have been published by Kramer *et al.* (123).

68. A comparison of the Monte Carlo system (190) with that using direct ionization measurements of the

dose to the bone marrow (50) shows that there is general agreement between the two methods. The tissue-air ratios for six AP projections, when compared for the two methods, lie between 0.4 and 0.7 of each other; for three PA projections the ratios between 1 and 2.4; and for two lateral projections they are both about 0.7 of the direct measurement values (50). These differences occur because of the differences between the measure-

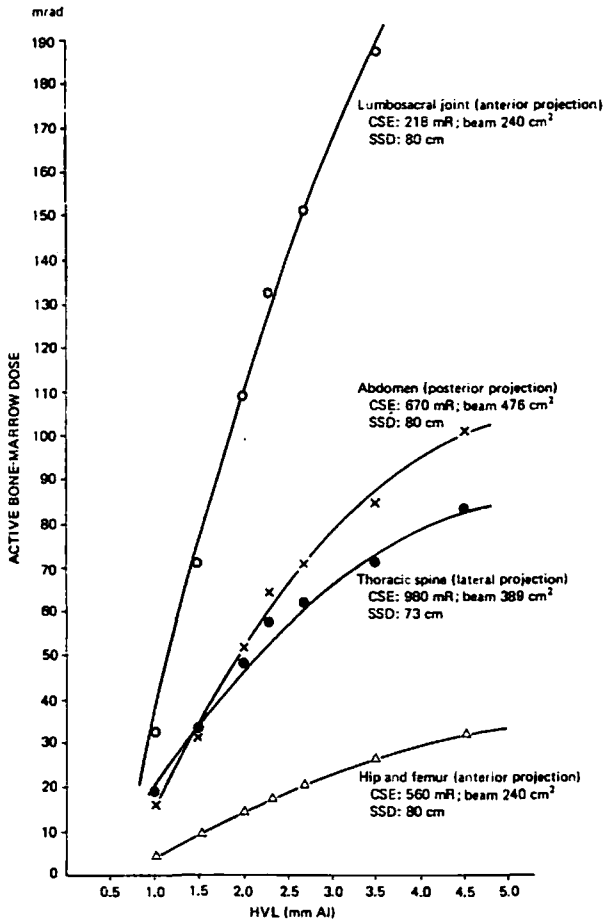


Figure VI. Dependence of active bone-marrow dose on the half-value layer (HVL) in various x-ray examinations (208)

CSE = central skin exposure
SSD = source-to-skin distance

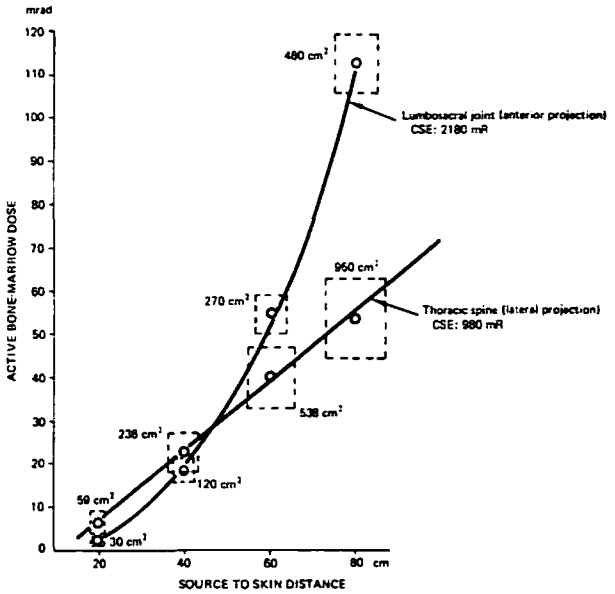


Figure VII. Dependence of active bone-marrow dose on beam area and source-to-skin distance (SSD) in thoracic spine and lumbosacral joint x-ray examinations (208). HVL constant at 2 mm Al

CSE = central skin exposure

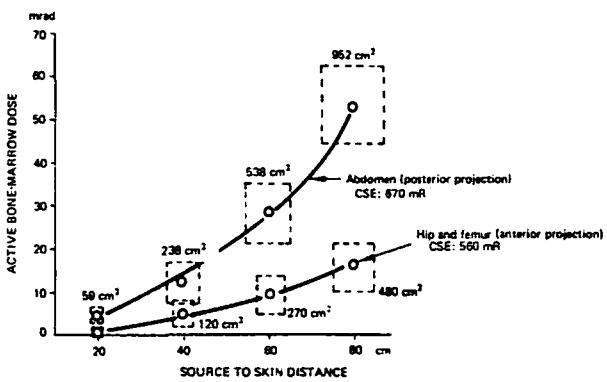


Figure VIII. Dependence of active bone-marrow dose on beam area and source-to-skin distance (SSD) in abdominal and hip and femur x-ray examinations (208). HVL constant at 2 mm Al

CSE = central skin exposure

TABLE 14. DOSES TO ORGANS DURING LUMBAR SPINE EXAMINATIONS

(Dose in millirads per 1000 mR entrance skin exposure free in air)

		Beam quality (HVL in mm Al)					
Organ	*Projection*	*1.5*	*2.0*	*2.5*	*3.0*	*3.5*	*4.0*
Testis	AP	1.1	2.2	3.7	5.6	7.8	10
	Lateral	0.2	0.4	0.7	1.1	1.6	2.3
Ovary	AP	91	139	188	238	288	336
	Lateral	15	27	41	58	76	96
Thyroid	AP	0.05	0.2	0.3	0.5	0.8	1.1
	Lateral	–	–	–	–	–	–
Active bone marrow	AP	13	21	32	46	62	81
	Lateral	8.2	13	19	27	37	48
Embryo (uterus)	AP	128	189	250	309	366	419
	Lateral	9.4	17	27	39	53	68

Notes: (a) Conditions: Source to image-detector distance, 102 cm; film size (= field size), 35.6 cm × 43.2 cm.

(b) A dash (–) signifies a value of less than 0.01 mrad.

ment phantom and the mathematical phantom, the effect of the amount of compact bone overlying any specific dosimeter and the thickness of the homogeneous mixture of bone and marrow assumed in the skeleton of the mathematical phantom. The comparisons reported made corrections for the differences in the x-ray spectra and the assumed volume and density of the lung that were used in the two studies.

(vi) *Breast doses*

69. The breasts are exposed to radiation in a number of common x-ray examinations. The highest doses to the breast are caused during urography examinations, photofluorography of the lung, examinations of the dorsal spine and stomach examinations, in the order mentioned, with doses between 100 and 540 mrad (17). Photofluorography of the lung is of special interest because of the high frequency of examinations.

70. In addition to these common examinations, special examinations may cause higher doses. Direct radiography of the female breast, i.e., mammography, is of particular interest because the technique is also being used in health investigations. The organization of a number of large population mass-screening surveys caused concern when high-dose techniques were in use and when regular re-examinations were carried out on young women. The justification for such examinations was questioned because of the increase of breast cancer that might be induced by radiation (13, 49, 182).

71. In the 1972 report the radiation dose in the breast per mammography examination was reported to be in the range 10-35 rad. However, since then considerable progress has occurred in techniques for reduction of the radiation dose. The use of the low-dose technique (very sensitive films with high-efficiency intensifying screens in vacuum packing) has enabled radiographs to be taken with a maximum skin dose to the breast of 0.1 rad (13, 173, 229, 268). With two-film techniques being accepted for screening examinations, surveys can be undertaken with a breast dose of less than 200-300 mrad. The use of xeroradiography leads to doses which are an order of magnitude higher, i.e., 1-5 rad per examination (22, 56, 191), while the use of industrial film leads to doses between 1.8 and 18 rad (13, 60, 229).

(vii) *Lung doses*

72. The density of the lungs at full inspiration is about 0.1-0.15 g cm^{-3}, while an average value of 0.25 g cm^{-3} is more appropriate when the main vessels are included. These changes make accurate assessment of the lung dose difficult. In typical x-ray examinations the transmission through the chest is about 10 per cent. Lung doses may therefore be estimated as a function of the direction of the beam from the incident skin dose. For full-size radiographs, the skin dose per exposure is about 20 mrad; for photofluorography using 70- or 100-mm cameras, the skin dose is usually about 200-300 mrad; for photofluorography using 35-mm cameras, the skin dose is usually in the range 600-1000 mrad. In the Swedish study by Bengtsson *et al.* (17), the highest dose to the lung, 800 mrad, was found in examinations of the dorsal spine. Special examinations such as cardiac catheterization cause much higher lung doses (see paragraph 56).

(viii) *Doses in other organs*

73. *Eye.* Surveys (102, 103) have shown that the radiation dose to the cornea during extensive neurological x-ray examinations may be in the range 20-80 rad. Patients who have repeated examinations may have a considerably increased risk of a radiation-induced cataract. The introduction of new x-ray units using computerized axial tomography will tend to change the mode of examination of patients with head lesions. Dose distributions in the head have been reported by Perry and Bridges (165). Doses to various parts of the head in dental examinations have been calculated or measured by several authors (5, 187, 251, 260). Casebow (32) has reported the dose to the head during orthopantomographic dental examinations.

74. *Bone.* The frequent radiography of young children with orthopaedic handicaps may cause damage to the development of bone and, in particular, produce stunted growth when the epiphysis has received a high dose (67). It is not uncommon to observe that particular patients have had over 100 radiographs of one particular joint during childhood. Estimates of dose distributions are not yet available.

75. The application of nuclear-powered pace-makers introduces problems associated with the dose to the connective tissue surrounding the pace-maker itself (108). The dose rates vary from type to type, but Kowalewsky (122) has reported that the surface dose over 10 years may vary from 385 to 1150 rad of gamma rays and from 0 to 85 rad of neutrons. Smith and Munson (209) report a first-year dose of 70 rad at the surface of a generator with a beta cell containing ^{147}Pm and a similar dose with a ^{238}Pu power source. The rate of irradiation of a bystander in close proximity to a person with a nuclear-powered pace-maker has been estimated by Cross (41) to be about 1 mrad h^{-1} at the surface of the body. Data from Stieve (226) show that the average length of implantation has been between 3 and 4 y and that the dose rate at the surface of the generator evolves as shown in figure IX (122). In

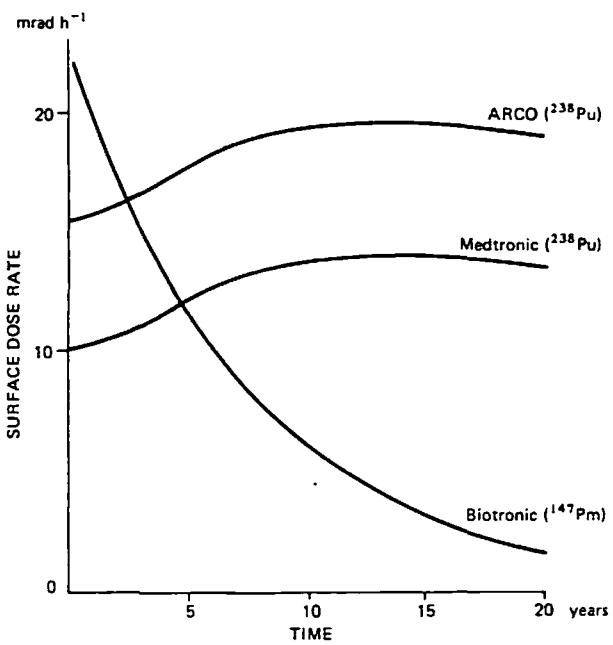


Figure IX. Dose rate at the surface of three brands of radioisotope-powered cardiac pace-makers (122)

interpreting the effect of the absorbed dose rate in figure IX, account should be taken of the relevant biological effectiveness of the neutron contribution.

(c) *Embryo and foetal exposures*

76. The surveys of pre-natally exposed children (134, 228) were summarized in the 1972 report. The practice of x-ray pelvimetry and obstetric abdomen examination has declined in frequency in a number of countries, even though recent statistical information on this is not readily available (see table 7, however). The introduction of ultrasonic scanning is probably reducing the need for x-ray and radionuclide investigations to localize the placenta (172). From the data given in the 1972 report, it can be deduced that the foetal whole-body dose is usually about 300 mrad in obstetric abdomen examinations and 620 mrad in pelvimetry examinations. The frequencies reported for the two examinations were about 2 and 1 per 1000 of population, respectively. These data give an annual collective dose to the foetus of about 1.2 man rad per 1000 of population from these two types of examination. A recent survey in Japan (1974) from Kitabatake *et al.* (119) reports, however, frequencies of 69 and 92 per 1000 pregnancies, respectively, for the two examinations.

77. Several reviews have been published (42, 150, 155, 223, 225) dealing with the levels of dose to women having child-bearing capacity at which subsequent action might be considered desirable, including termination of pregnancy. In the state of available human information on the risks of radiation during various stages of pregnancy (see Annex J, paragraphs 169-173), as well as on the normal incidence of congenital defects, it does not seem appropriate to make any absolute recommendation regarding the line of action following such medical radiation exposures. In any case, such recommendations could serve only as a guide that would have to be modified in specific instances according to the judgement of the patient's physician and consulting radiation experts and, of course according to the desires of the patient herself. The radiation dose itself, particularly from diagnostic radiologic procedures, is unlikely to be the sole determining factor in advising abortion. Decisions based on the generally small risks involved must require very careful consideration of the conditions applying in each individual case.

(d) *Comparison of procedures*

78. Tables showing mean organ doses from the various types of diagnostic x-ray procedures have frequently been published for gonad doses and mean marrow doses and for incident skin exposure (see tables 8 and 13). There has been less information on the overall exposure, including doses to a number of the most radiosensitive organs. In the Swedish survey by Bengtsson *et al.* (17), however, information is given on the doses in gonads, thyroid, active marrow, breast and lung, as well as on the energy imparted. This information is summarized in table 15.

TABLE 15. AVERAGE ORGAN DOSES IN VARIOUS DIAGNOSTIC X-RAY EXAMINATIONS IN SWEDEN

(mrad)

Examination	*Whole body*[a]	*Ovary*	*Testis*	*Active marrow*	*Thyroid*	*Breast*	*Lung*
Hip and femur	170	370[b]	1 500[b]	250	< 1[b]	< 5[b]	< 10[b]
Pelvis	125	190	310	190	< 1[b]	< 5[b]	< 10[b]
Pelvimetry	440	460	–	680[b]	< 10[b]	< 10[b]	< 50[b]
Lumbosacral region	150[b]	180[b]	100[b]	100[b]	< 1[b]	< 5[b]	< 10[b]
Lumbar spine	590	620	180	410	16	120	< 100
Urography	730	880	330	240	38	540	< 100
Retrograde pyelography	1 000[b]	800[b]	1 300[b]	300[b]	50[b]	500[b]	< 100[b]
Urethrocystography	600[b]	1 500[b]	2 000[b]	300[b]	5[b]	20[b]	20[b]
Stomach, upper GI tract	440	56	16	420	29	100	< 50
Small intestine	300	180	100	250	3	11	< 20
Colon	860	700	530	940	10	27	< 20
Abdomen	300[b]	200[b]	200[b]	300[b]	3[b]	11[b]	< 20[b]
Obstetrical abdomen	200[b]	150[b]	–	220[b]	2[b]	8[b]	< 15[b]
Hysterosalpingography	130	590	–	170	< 1[b]	< 5[b]	< 10
Cholecystography, cholangiography	130	24	6	150	3	15	< 10
Dorsal spine	300	< 100	< 20	470	1 300	170	800
Lung, ribs	30	< 3[b]	< 3[b]	29	17	55	80
Lung (photofluorography)	105	< 10[b]	< 10[b]	90	100	200	350
Lung plus heart	57	< 5[b]	< 5[b]	54	24	61	120
Cervical spine	26	< 1	< 1	38	140	< 10	< 10[b]
Shoulder, clavicle, sternum	60[b]	< 1[b]	< 1[b]	60[b]	50[b]	< 50[b]	< 10[b]
Head, sinus	97	< 1	< 1	122	790	< 10[b]	< 10[b]
Cerebral angiography	970	< 10	< 10	1 500	300	< 10[b]	< 10[b]
Femur (lower two thirds)	70[b]	50[b]	400[b]	< 1	< 1[b]	< 1[b]	< 1[b]
Lower leg, knee	30[b]	< 1	< 1	< 1	< 1	< 1	< 1
Arm	7[b]	< 1	< 1	< 1	< 1	< 1	< 1
Dental (single exposure)	2.9	0.01	0.01	1	3	0.5	0.1

Source: Reference 17.

[a] Assuming same mass as Reference Man (70 kg); not averaged over actual weight.

[b] Crude estimate.

79. The Swedish study involved measurements on about 1000 patients in 13 Swedish hospitals. The techniques employed at these hospitals were believed to be representative for the whole of Sweden since diagnostic techniques are quite uniform throughout the country. Image-intensifier television was generally used, the older fluoroscopic screen, rarely. Chest examinations were normally made without fluoroscopy. Automatic exposure control was generally used. The dominant screen-film combination would under optimum conditions require an exposure of 0.4-1 mR to give an adequate density. Examinations of gall bladder, stomach and colon, and special examinations were performed by doctors. Most other examinations were performed by specially trained nurses or x-ray technicians. The exposures were measured at various points on the patients using thermoluminescent lithium fluoride dosimeters. These were placed at the laryngeal prominence (to estimate the thyroid dose), the breast, the male gonad and the rectum (to estimate the ovary dose). For the other organs an estimate of the dose was made from the recorded exposure area product (see paragraph 48). The overall accuracy of the mean absorbed dose for a particular organ was ± 50 per cent.

80. It is seen from table 15 that the imparted energy (expressed in the table as mean whole body dose in Reference Man in mrad, but in the Swedish study reported in mJ is usually a good indicator of the significance of an exposure as regards high doses in radiosensitive organs. None of the examinations having an imparted energy of less than 200 mJ (280 mrad whole-body dose) caused an absorbed dose of more than 800 mrad in any of the organs listed, with the exception of a testis dose of 1500 mrad in examinations of hip and femur. However, some examinations simultaneously exposed several of the listed organs to the extent that the exposures might be considered more significant than indicated by the imparted energy alone. These examinations were the examinations of the lung and the dorsal spine. As can be expected, examinations of the pelvic region, e.g. pelvimetry, urethrocystography and examination of the hip and femur gave high gonad exposures in relation to the energy imparted.

3. Collective dose to various organs from different types of procedures

81. In this section, the population exposures from various procedures are reported in terms of the *per caput* dose, which, as explained in paragraph 26, is the collective dose to the population divided by the number of individuals in the population.

(a) *Accuracy of assessment*

82. Estimates of the overall error in the determination of the collective dose for a given organ may be exemplified by the case of the annual GSD. The overall error comprises the statistical error of the observations and the systematic errors incorporated in the organization of the inquiry. Statistical error estimates are available for three major studies: the 1958 United Kingdom survey (36), and the 1964 and 1970 United States surveys (27, 255). The estimated standard error in the United States surveys decreased from 37 per cent in 1964 to 15 per cent in 1970. For the United Kingdom study the error was estimated at 8 per cent. However, there have been no estimates of the systematic errors, which are difficult to assess.

(b) *Collective dose to various organs*

83. Bengtsson *et al.* (17) have calculated the *per caput* doses from the various types of diagnostic x-ray examinations in Sweden. Their data are shown in table 16. The *per caput* doses in the six listed organs are

TABLE 16. ANNUAL *PER CAPUT* DOSES TO ORGANS IN VARIOUS DIAGNOSTIC X-RAY EXAMINATIONS IN SWEDEN

(man rad per 1000 of population, or mrad per caput*)*

Examination	*Whole body*[a]	*Ovary*	*Testis*	*Active marrow*	*Thyroid*	*Breast*	*Lung*
Hip and femur	3.2	7.0[b]	28.0[b]	4.7	0.0	< 0.1[b]	< 0.2[b]
Pelvis	1.9	2.9	4.8	2.9	0.0	< 0.1[b]	< 0.2[b]
Pelvimetry	0.7	0.7	–	1.1[b]	0.0	0.0	< 0.1[b]
Lumbosacral region	0.4[b]	0.5[b]	0.3[b]	0.3[b]	0.0	0.0	0.0
Lumbar spine	13.2	14.0	4.0	9.1	0.4	2.6	< 2.2
Urography	17.2	21.0	7.8	5.6	0.9	13.0	< 2.4
Retrograde pyelography	0.3[b]	0.2[b]	0.4[b]	0.1[b]	0.0	0.2[b]	0.0
Urethrocystography	1.6[b]	4.1[b]	5.5[b]	0.8[b]	0.0	0.1[b]	0.1[b]
Stomach, upper GI tract	13.0	1.7	0.5	12.0	0.9	3.1	< 1.5
Small intestine	1.0	0.6	0.3	1.2	0.0	0.0	< 0.1
Colon	13.8	11.0	8.5	15.0	0.2	0.4	< 0.3
Abdomen	3.9[b]	2.6[b]	2.6[b]	3.9[b]	0.0	0.1[b]	< 0.3
Obstetrical abdomen	0.3[b]	0.2[b]	–	0.3[b]	0.0	0.0	0.0
Hysterosalpingography	0.1	0.5	–	0.1	0.0	0.0	0.0
Cholecystography, cholangiography	2.4	0.4	0.1	2.8	0.1	0.3	< 0.2
Dorsal spine	4.0	< 1.3	< 0.3	6.2	18.0	2.3	11.0
Lung, ribs	3.5	< 0.3[b]	< 0.3[b]	3.2	2.0	6.3	9.2
Lung (photofluorography)	11.6	< 1.1[b]	< 1.1[b]	9.9	11.0	22.0	39.0
Lung plus heart	2.7	< 0.2[b]	< 0.2[b]	2.5	1.1	2.8	5.6
Cervical spine	0.3	0.0	0.0	0.5	1.8	< 0.1	< 0.1[b]
Shoulder, clavicle, sternum	1.0[b]	0.0	0.0	1.0[b]	0.8[b]	< 0.8[b]	< 0.2[b]

Examination	Whole body[a]	Ovary	Testis	Active marrow	Thyroid	Breast	Lung
Head, sinus	4.2	0.0	0.0	5.3	34.0	< 0.4[b]	< 0.4[b]
Cerebral angiography	1.2	0.0	0.0	1.8	0.4	0.0	0.0
Femur (lower two thirds)	0.4[b]	0.3[b]	2.4[b]	0.0	0.0	0.0	0.0
Lower leg, knee	1.9[b]	< 0.1	< 0.1	0.0	< 0.1	< 0.1	< 0.1
Arm	0.4	0.0	0.0	0.0	0.0	0.0	0.0
Dental (single exposure)	4.4	0.0	0.0	1.5	4.5	0.8	0.2
Total (rounded)	110	70[c]	65[c]	90	75	55	65

Source: Reference 17.

[a]The authors estimated the *per caput* mean whole-body dose at about 100 mrad, based on actual patient weights instead of the 70 kg assumed in this table.

[b]Crude estimates.

[c]Not including foetal exposures.

between 55 and 90 mrad y^{-1}, whereas the annual *per caput* mean whole-body dose was estimated by the authors to be about 100 mrad.

(i) *Marrow collective doses*

84. The annual *per caput* mean marrow dose (CMD) as derived in three national surveys was reported in the 1972 report. The CMD totalled 30, 32 and 189 mrad y^{-1} for the Netherlands (259), United Kingdom (37) and Japanese (73) surveys, respectively. They were undertaken in 1960, 1957 and 1969, respectively. The recent Swedish survey (see table 16) gave 90 mrad for Sweden in 1974 and a repeat of the Japanese survey gave 132 mrad for the same year. A recent assessment (208) gives the CMD for the United States as 83 mrad for the 1964 survey and 103 mrad for the 1970 survey. In table 17, the examinations making

TABLE 17. ANNUAL *PER CAPUT* DOSE TO BONE MARROW

(mrad)

Type of examination	Japan (73, 79, 80, 81, 84, 138) 1969	Japan (73, 79, 80, 81, 84, 138) 1974	Netherlands (259)	Sweden (17)	United Kingdom (37)	United States (208) 1964	United States (208) 1970
Hip and femur	0.5	1.1	0.2	4.7	0.3	0.7	0.7
Pelvis	0.3	0.5	0.9	2.9	0.3	1.4	1.1
Lumbosacral joint	0.8	–	2.2	–	0.7	4.0	5.7
Lumbar spine	4.4	5.1	1.1	9.1	1.5	6.7	8.1
Urography	1.2	2.1	3.7	5.6	2.3	9.9	10.1
Stomach, upper GI tract	115	73.2	0.1	12.0	1.2	17.9	24.3
Small intestine	–	–	2.5	–	6.0	0.7	1.0
Barium meal (photofluorography)	–	16.5	–	–	–		
Colon	10.3	7.3	3.1	15.0	2.2	13.7	21.2
Abdomen	0.8	4.4	0.6	3.9	0.8	3.6	2.9
Obstetrical abdomen	0.2	0.2		–	1.1		
Cholecystography	7.0	2.1	0.5	2.8	0.5	3.2	3.7
Dorsal spine	1.0	0.8	0.3	6.2	0.6	2.0	2.5
Lung	10.1	6.1	8.1	–	1.8	2.0	3.2
Lung (photofluorography)	20.2	9.7	3.8	9.9	7.8	7.8	3.2
Head	0.7	–	1.1	5.3	0.5	1.0	1.6
Other	16.3	3.3	1.8	12.6	4.7	8.4	13.7
Total	189	132	30	90	32.3	83	103

the greatest contributions to the CMD in the seven national surveys are listed. The large contribution from stomach examinations in Japan is striking; it is caused by the very large frequency of these examinations. A recent survey by Hashizume *et al.* (83) gives the number of photofluorographic examinations of the stomach in 1975 as $2.38\ 10^6$ and $1.74\ 10^6$ in males and females, respectively. The mean marrow dose was 453 mrad and 392 mrad, respectively, and the CMD from this examination 16.5 mrad. A similar survey of mass chest screening in Japan (84) during 1975 gave a CMD of 9.7 mrad.

85. The 1970 United States survey (208) analysed the CMD for six different age groups; whereas the CMD for the whole population was 103 mrad, the CMD for the specific age groups were:

Age group	CMD (mrad)
15-24	52
25-34	81
35-44	107
45-54	120
55-64	143
⩾ 65	151

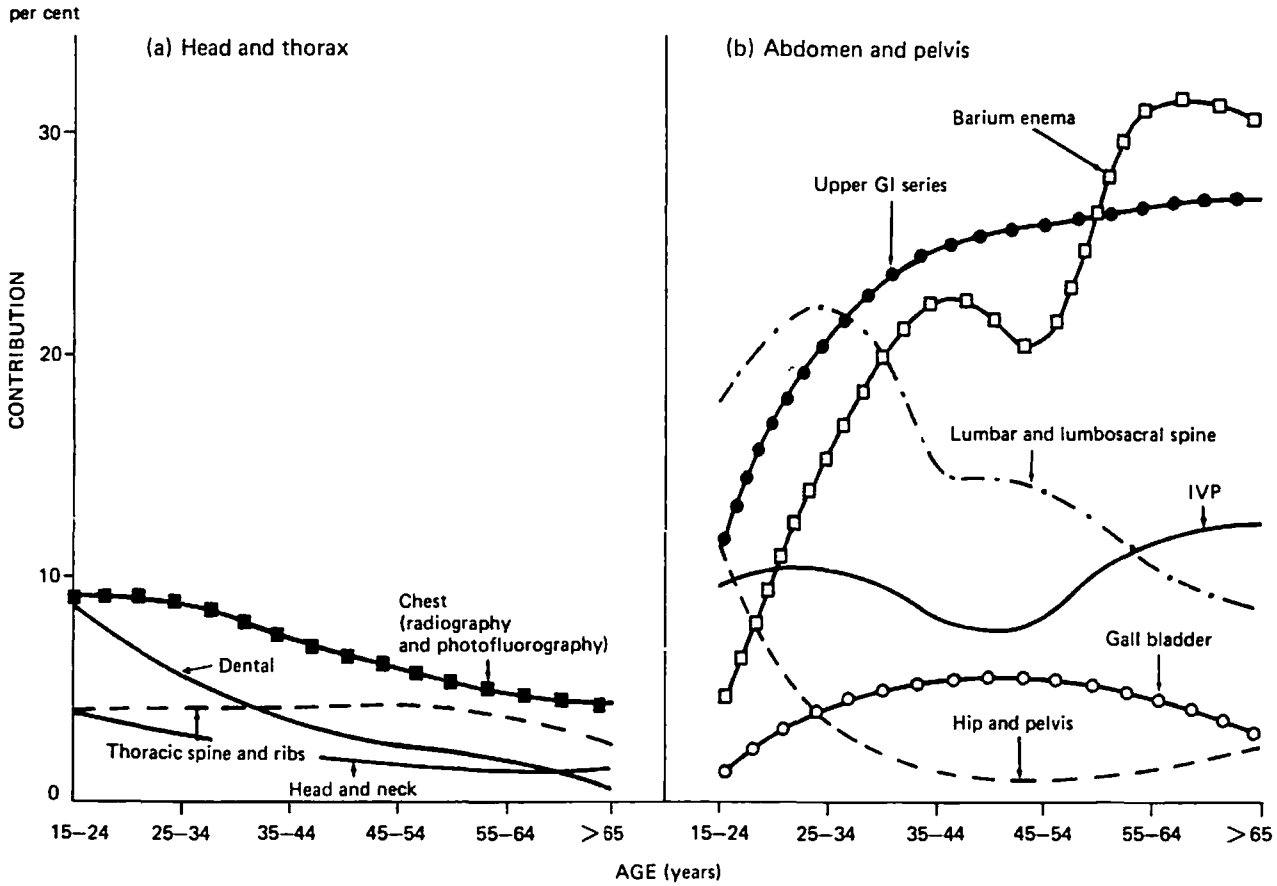


Figure X. Contribution of certain x-ray examinations to the age-specific *per caput* mean marrow dose (CMD) in the United States (208)

IVP = intravenous pyelography

The contributions made by the various examinations to these specific CMD are given in figure X. This demonstrates the variation in frequency with age of some of the major contributors to the CMD of the total population.

86. In the 1969 Japanese survey an attempt was also made to calculate a weighted mean marrow dose ("leukaemia significant dose") with weighting for reduced risk of leukaemia as a function of the age of exposure, considering the latency period for manifestation of the disease. This reduced the CMD from 189 to 169 mrad. The CMD for photofluorographic examinations of the stomach was reduced from 16.5 to 14.5 mrad by a similar weighting in the 1975 survey, and the mass chest screening CMD was reduced from 9.7 to 9.3 mrad (83).

87. An estimate of the CMD in Romania was made in 1970. The value derived was 382 mrad y^{-1}, but it would appear from the report that this value represents the dose to the marrow in the direct x-ray beam rather than the mean value in the whole active marrow.

(ii) *Breast collective doses*

88. As indicated in paragraph 71, health investigations with mammography may be expected to result in quite high breast collective doses if carried out at the level of 10 rad per examination. With 0.1 rad per examination, however, the individual breast doses would be about the same as the breast doses in photofluorographic examination of the lung (see table 15).

(iii) *Lung collective doses*

89. *Mass photofluorographic surveys of the chest.* The incidence of tuberculosis throughout the world is high; therefore, most countries have either mobile or fixed installations for taking 35-, 70- or 100-mm films of the chest as a screening or follow-up study. The radiation exposure incident on the back of patients is related to the size of the film and the optical system, and the skin exposure is usually in the range 0.5-2.0 R for 35-mm film and about 0.2-0.5 R for 70- or 100-mm film. Photofluorographic lung examinations give the highest contribution to the *per caput* lung dose in most countries (e.g., 60 per cent in Sweden). The median frequency of mass chest surveys among the countries for which data were reported to the Committee for the 1962 report was 130 per year and 1000 of population. Of the additional data presented in the 1972 report the median value was 267 examinations per year and 1000 of population. The frequency in Sweden in 1974 was 110 examinations per year and 1000 of population, a relatively low frequency. Nevertheless, the Swedish *per caput* annual lung dose from photofluorography of the lung was found to be about 40 mrad (table 16).

90. An assessment of the benefits and risks of mass chest radiography has been made by Kitabatake and his co-workers (114). In the 40 10^6 chest fluorographies carried out in 1968, about 44 500 cases of pulmonary tuberculosis were detected. Estimates were made of the number of lung cancers that might be detected and of how many of them were likely to benefit from early radical resection. An estimate of the deleterious effects produced by the irradiation was made for the next 25 years on the basis of current risk estimates. These included 46 leukaemias and 7 incurable lung cancers.

(iv) *Stomach collective doses*

91. An estimate of the collective dose to the stomach from the Japanese examinations may be deduced on the basis of the mean dose in the stomach of 4 rad per examination. This leads to an annual collective dose of 10^8 man rad. Such assessments have been made in attempts to estimate the risk of inducing cancer by the examination (113). During 2.2 10^6 fluoroscopic mass surveys, 2423 persons were found to have gastric cancers; 1042 of them were expected to survive more than five years. An estimate of the radiation-induced cancers indicated 30 leukaemias and 15 abdominal cancers during the following 25 years.

(v) *Foetal collective doses*

92. From the 1974 survey in Japan, Hashizume (82) has estimated an annual collective dose to the foetus of 0.86 man rad per 1000 of population from obstetric abdomen and pelvimetry examinations.

(c) *Annual genetically significant dose*

93. The details of the many GSD surveys have been given in the previous reports of the Committee. They are summarized in table 18.

TABLE 18. ANNUAL FREQUENCY OF X-RAY EXAMINATIONS AND GSD BY COUNTRY

Country or area	Period	Population 10^6	Annual number of x-ray examinations per 1 000 of total population: Diagnostic: Radiography	Diagnostic: Fluoroscopy	Mass surveys: Radiography	Mass surveys: Fluoroscopy	GSD (mrad): Diagnostic examinations	GSD (mrad): Mass surveys	Reference
(a) *Surveys reviewed in the 1962 report*									
Argentina									
Buenos Aires	1950-1959	6	270		80		37.0	1.90	166
Denmark	1956-1958	4.5	260		140		27.5	0.05	70
Egypt									
Alexandria	1956-1960	1.4	36		4		7.0	0.09	136
Cairo	1955-1961	.2.6	40		5		7.0	0.07	135
France	1957-1958	42	150		40	570	58.2[a]	0.02[b]	178-180
Germany, Federal Republic of									
Hamburg	1957-1958	1.8	560		130		17.7	0.05	94
Italy									
Rome	1957	1.9	500		80		43.4	0.93	21
Japan	1958-1960	90	410		320		39.0	0.08	181
Netherlands									
Leiden	1959-1960	0.1	350	200	130		6.8	0.02	15
Norway	1958	3.5	390		210		10.0	0.08	57
Sweden	1955-1957	7.3	290		140		37.8	0.40	128
Switzerland	1957	5.2	310	330	130	60	22.3	0.12	269
United Kingdom	1957-1958	50	280		95		14.1	0.01	37
(b) *Surveys reviewed in the 1972 report*									
Czechoslovakia									
Bohemia	1965-1966	4.3	517	79	331		37.0	0.44	126
Finland	1963-1964	4.5	334		266		16.8		104, 105
Germany, Federal Republic of									
Bavaria	1956-1958	9.6	601[c]		267		13.7 (15.1)[d]	0.05	203-206
Japan	1969	105	610	191	628		25.7	0.8	74
Netherlands	1967	12.6	810				20.0		16, 174
New Zealand	1963	2.5	366		113		13.1		266
	1969	2.8	400		113		13.7		152
Puerto Rico									
Southern region	1968	0.5	414				36.4		158
Western region	1968	0.4	512				48.6		157
Thailand	1970	34.7	39				5.2-1.3		142, 143
Union of Soviet Socialist Republics									
Russian SFSR	1964	82	171	439	183		27.0[f]		125
United Kingdom									
Sheffield	1964	4.5	310				8.6		139

TABLE 18 *(continued)*

Country or area	Period	Population 10^6	Annual number of x-ray examinations per 1000 of total population: Diagnostic: Radiography	Diagnostic: Fluoroscopy	Mass surveys: Radiography	Mass surveys: Fluoroscopy	GSD (mrad): Diagnostic examinations	GSD (mrad): Mass surveys	Reference
United States									
National surveys	1964	187	475	56	87		16.0[e]		63, 164
	1970	200	580	65	45		20.0[e]		247, 249, 28
Local surveys									
New York City	1962	8	630	100			50.0		161
New Orleans	1962-1963	0.9	825				75.3		106
Johns Hopkins University	1965						20.3		148
Texas	1963						16.0		38
Yugoslavia									
Slovenia	1960-1963	1.5	594	436			9.1		141

[a] From radiographic mass survey.
[b] Including fluoroscopic mass survey.
[c] In this case, one examination equals one radiograph.
[d] The figure in parentheses is a later figure that includes special children's clinics.
[e] Revised estimates (27, 255).
[f] Mean gonad dose per year rather than GSD.

94. Since the 1972 report a few further reports of investigations on the GSD in various countries and areas have become available. These may be usefully considered in two groups: countries or areas where there is an advanced technical medical service and those that only have these facilities in the largest towns and cities. A summary of these recent surveys is given in table 19 and below.

TABLE 19. ANNUAL FREQUENCY OF X-RAY EXAMINATIONS AND GSD BY COUNTRY

Recent surveys

Country or area	Period	Population (10^6)	Annual number of x-ray examinations per 1000 of total population: Diagnostic: Radiography	Diagnostic: Fluoroscopy	Mass survey: Radiography	Mass survey: Fluoroscopy	GSD (mrad): Diagnostic examinations	GSD (mrad): Mass surveys	Reference
Germany, Fed. Rep. of (Hamburg)	1974	1.8	1 530	–	128	–	41	–	129
India	1967-72	550	35	–	–	–	1.1	–	168
Iraq	1972	10	150[a]	–	88[a]	–	52	–	1
Japan	1974	105	676	134	–	–	16.5	–	74, 79, 80
Netherlands	1972	12.6	1 186	–	–	–	28	–	120
Puerto Rico	1973	3.0	502	40	56	–	46	–	61
Romania	1970	20.5	238	322	452	–	28.5	–	177
Sweden	1974-76	8.1	540	–	110	–	46	–	17
Switzerland	1971	6.3	1 350	–	–	–	42.9	–	170
Island of Taiwan (urban areas)	1972	5	43[a]	10[a]	–	–	3-4	–	261
United States	1970	195	669	–	–	–	20	–	27

[a] Estimate from data received.

(i) *France, 1976*

95. An estimate of the GSD in France, made by Reboul *et al.* (178-180) in 1959, was 58 mrad. Since then a large-scale study (163) was conducted in 1976 on the basis of 10^6 radiological examinations for the purpose of providing an estimate of the mean gonad dose received by the members of the public. The *per caput* gonad dose found in the study is about 7 estimated GSD of about 3 measures taken by the nationa suppression of obsolete fac quality of the examination authorized facilities, a decrea of the exposure received achieved.

United Sheffi

f. ose to be

(ii) *Federal Republic of Germany, 1972-1973*

96. An assessment of the GSD in the Federal Republic of Germany has been made by Stieve for 1972-1973 on the basis of reported average values of the doses from various procedures. The GSD has been estimated as 50 mrad from medical sources (25, 224). Surveys were conducted in the Hamburg region in 1958, 1972 and 1974 (94, 129). The GSD increased from 17.7 to 37 to 41 mrad, respectively while the average annual number of examinations per person increased from 0.61 to 1.16 to 1.33.

(iii) *India, 1967-1972*

97. Surveys in four representative areas of India were used to obtain data on the frequency of examination, dose per examination and child expectancy factors (228). From these data the GSD was calculated for each district in each area. The four GSDs derived were 1.89, 0.77, 0.88 and 0.93 mrad for the state of Maharashtra (1967-1968), the state of Tamil Nadu (1969-1970), the northern region (1970-1971) and the eastern region (1971-1972), respectively. In those districts where the larger x-ray facilities existed, considerably higher GSDs were obtained (table 20). The GSD was weighted

TABLE 20. CONTRIBUTION TO THE ANNUAL GSD DUE TO DIAGNOSTIC RADIOLOGY

India, 1967-1972

(mrad)

State or region and district	*Male*		*Female*		*Foetal dose*	*Annual GSD*	*District contribution to state or region annual GSD*
	Radiography	*Fluoroscopy*	*Radiography*	*Fluoroscopy*			
Maharashtra (1967-1968)							
Bombay	6.059	0.447	1.308	2.592	0.240	10.646	1.118
Poona	0.725	0.043	0.158	0.743	0.201	1.870	0.117
Nagpur	1.875	0.001	1.259	0.482	0.435	4.052	0.155
Nasik	0.822	0.006	0.083	0.009	0.037	0.957	0.152
Sangli	0.281	0.004	0.157	0.041	0.007	0.490	0.015
Nanded	0.212	0.014	0.032	0.081	0.023	0.362	0.043
Ratnagiri	0.023	0.013	0.018	0.081	0.006	0.141	0.016
Buldhana	0.014	0.003	0.001	0.001	0.002	0.021	0.003
Sholapur	0.110	0.147	0.036	2.619	0.014	2.926	0.138
Overall						1.894	
Tamil Nadu (1969-1970)							
Madras	4.1469	0.0048	1.4391	0.1646	0.2605	6.0159	0.3098
Madurai	0.3064	0.0003	0.4502	0.0418	0.0865	0.8852	0.0845
Coimbatore	0.6209	0.0005	0.2171	0.0714	0.0475	0.9574	0.1010
Thanjavur	0.1403	0.0004	0.0534	0.0022	0.0074	0.2037	0.0196
Kanya-kumari	0.1137	0.0023	0.1215	0.2185	0.0780	0.5340	0.0158
Overall						0.7664	
Northern region (1970-1971)							
Delhi	1.9751	0.0153	1.0166	0.1785	0.2590	3.4445	0.3257
Amritsar	0.7500	0.0031	0.2000	0.0037	0.0417	0.9985	0.0426
Patiala	1.0474	0.0156	0.5999	1.0706	0.3271	3.0606	0.0868
Chandigarh	7.1332	0.7060	3.0894	8.5605	3.5231	23.0122	0.1377
Himachal Pradesh	0.6457	0.0017	0.2240	0.0114	0.0359	0.9187	0.0739
Hissar	0.0533	0.0008	0.0426	0.0004	0.0077	0.1048	0.0052
Hoshiarpur	0.0064	0.0009	0.0003	0.0018	0.0003	0.0097	0.0002
Jullundar	0.4307	0.0224	0.1337	0.0017	0.0273	0.6158	0.0203
Overall						0.8772	
Eastern region (1971-1972)							
Calcutta	5.4412	0.0089	3.4016	0.6293	0.1908	9.6718	0.2478
Cuttack	1.2770	0.0080	0.5430	0.1184	0.0098	1.9562	0.0611
Patna	0.7365	0.0161	0.4203	0.0298	0.0257	1.2284	0.0356
Ranchi	0.2963	0.0038	0.0785	0.0018	0.0065	0.3869	0.0082
Shahabad	0.0254	0.0078	0.0101	0.0454	neg	0.0887	0.0028
Ganjam	0.7832	0.0008	0.1531	neg	neg	0.9371	0.0175
Sambalpur	1.2204	0.0004	0.4168	0.0012	neg	1.6388	0.0246
Saharsha	0.0006	neg	0.0103	neg	neg	0.0109	0.0002
Overall						0.9337	

Source: Reference 168.

according to the population, and an average of 1.11 mrad was obtained as representative of the country as a whole. The frequency of radiographic examinations (excluding dental and screening examinations) in India as a whole was estimated to be 35 per 1000 of population and in the four areas, 14, 25, 24 and 51, respectively. The numbers of males and females in various age groups and their child expectancy factors are given in table 21.

TABLE 21. AGE AND SEX DISTRIBUTION AND CHILD EXPECTANCY FACTORS OF THE POPULATION SURVEYED IN TABLE 20

Age (y)	*Maharashtra*		*Tamil Nadu*		*Northern region*		*Eastern region*	
	Male	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*
			(a) *Population by age and sex (10^3)*					
< 4	2 994	2 943	2 623	2 510	3 506	3 161	9 311	9 166
5-9	2 890	2 845	2 622	2 624	3 729	3 280	10 582	10 218
10-14	2 328	2 084	2 212	2 126	2 949	2 561	7 460	6 392
15-19	1 679	1 533	1 589	1 538	2 071	1 694	4 934	4 644
20-24	1 718	1 781	1 589	1 710	1 930	1 686	5 016	5 239
25-29	1 774	1 690	1 576	1 652	1 840	1 555	5 482	4 969
30-34	1 511	1 332	1 329	1 313	1 522	1 236	4 688	4 094
35-39	1 298	1 097	1 260	1 222	1 217	1 009	3 928	3 341
40-44	1 067	931	1 055	1 009	1 130	926	3 220	2 973
45-49	897	764	888	802	866	655	2 608	2 224
50-54	744	649	740	674	873	591	2 225	1 917
55-59	505	415	411	411	436	286	1 323	1 133
> 60	1 023	1 061	918	878	1 377	914	2 702	2 940
			(b) *Child expectancy factor*					
< 4	4.577	4.116	3.2785	3.3937	4.96	4.825	4.2465	4.1026
5-9	4.836	4.368	4.0837	4.1844	5.316	5.362	4.9274	4.8868
10-14	4.958	4.486	4.2967	4.3130	5.376	5.417	5.0118	4.9935
15-19	4.926	4.214	4.4539	4.0507	5.417	5.390	5.0653	4.8535
20-24	4.745	3.396	4.1797	3.1349	5.384	4.795	4.9127	4.1156
25-29	3.815	2.651	3.2548	1.9872	4.777	3.50	4.1391	2.9236
30-34	2.625	1.660	2.0487	1.0325	3.482	2.134	2.9155	1.7844
35-39	1.613	0.9016	1.351	0.3805	2.116	1.056	1.7630	0.8990
40-44	0.874	0.0874	0.3744	0.0639	1.048	0.368	0.8801	0.3593
45-49	0.342	0.0594	0.0627	0.0029	0.365	0.062	0.3517	0.0913
50-54	0.0579	0.0082	0.0028	0.0011	0.062	0.0	0.0903	0.0
55-59	0.0075	0.00	0.0011	0.0000	0.0	0.0	0.0	0.0
> 60	0.00	0.000	0.000	0.000	0.0	0.0	0.0	0.0

Source: Reference 168.

(iv) *Iraq, 1972*

98. A survey in Iraq during 1972 reported a total of 407 x-ray units and 146 dental x-ray units serving the population of 10^7 (1). The total radiographic exposures reported were 4.2 10^6 along with 1.5 10^5 dental x-ray exposures. The term "examination" is used in the reference to indicate exposures; thus, 2.2 "examinations" were reported per visit. A measurement survey using film badges determined the gonad dose per examination in a group of 70 patients. The age distribution and frequency of examination were derived from an analysis of 1000 patients. The GSD for 1972 was estimated to be 52 mrad, with a probable accuracy of 60 per cent. A dental survey estimated the GSD from dental radiography to be 0.3 mrad.

(v) *Japan, 1974*

99. Preliminary results are available for the GSD survey in Japan during 1974 (74, 79, 80). The GSD was estimated to be 16.5 mrad, compared with 25.7 mrad in the 1969 survey. The frequencies of the examinations were obtained from a sample of 8.5 per cent of the hospitals with >300 beds, with somewhat lower sampling fractions for the smaller hospitals. The frequency of examination for the major contributors and the resulting contributions to the GSD are given in table 22. The distribution of the GSD with age and the division between radiography and fluoroscopy are given in table 23. The values in parentheses indicate the contributions in the 1969 survey. The contribution from photofluorography for mass stomach screening was 0.15 mrad (83), and that from photofluorography for mass chest screening was 0.03 mrad (84).

(vi) *Netherlands, 1972*

100. New data on the male gonad dose per examination, the frequency of examination and child expectancy factors were used in conjunction with data from the 1967 survey to recalculate the GSD (120). It was assumed that the frequency of all examinations had increased by 10 per cent per year for each of the four years 1968-1971. The 1972 value of GSD obtained was 28 mrad, which was not significantly different from the 1967 estimate of 19-40 mrad. The measurement survey was extended and by mid-1974, 6600 measurements had been made on patients. The GSD for 1974 was estimated to be about 20 mrad (121). Further studies have also been reported on the contributions to the GSD due to various x-ray diagnostic examinations.

TABLE 22. FREQUENCY OF X-RAY EXAMINATIONS AND GSD BY SEX AND TYPE OF EXAMINATION

Japan, 1974

(Units: frequency, number of examinations per 1000 of population group; GSD, mrad)

Type of examination	Radiography				Fluoroscopy				Total		
	Male		Female		Male		Female				
	Frequency	GSD	Frequency	GSD	Frequency	GSD	Frequency	GSD	Frequency	GSD	Fraction of total GSD (%)
Chest	145	–	136	–	7	–	6	–	294	0.1	0.6
Stomach	59	0.2	46	1.1	56	0.3	43	2.0	204	3.6	22
Abdomen	12	0.3	10	0.3	2	0.2	2	0.5	26	1.3	7.9
Intestine	3	1.5	3	0.3	2	0.5	2	0.5	10	2.8	17
Lumbar, lumbosacral	23	0.7	17	0.8	0.5	–	0.3	0.2	41	1.7	10
Pelvis	2	0.4	3	0.2	0.1	–	0.1	–	5.2	0.7	4.3
Urography	3	0.1	3	0.4	0.7	0.1	0.5	0.2	7.2	0.8	4.9
Bladder	2	0.4	0.9	–	0.3	0.1	0.2	0.1	3.4	0.6	3.7
Hystero			0.7	0.1			0.1	0.1	0.8	0.2	1.2
Obstetric			1.9	0.5					1.9	0.5	3.0
Hip joint	9	2.2	10	0.9	0.1	0.1	0.1	0.2	18	3.4	21
Lower leg	34	0.5	20	–	0.5	–	0.3	–	55	0.6	3.7
Other	75.1	–	57.9	–	5.6	–	4.4	–	143	0.1	0.6
Total	367.1	6.4	309.4	4.7	74.8	1.5	59	3.9	809.5	16.4	100

Sources: References 74, 79, 80.

Note: A dash (–) signifies that the GSD was less than 0.05 mrad.

TABLE 23. GSD FROM X-RAY EXAMINATIONS BY AGE AND SEX

Japan, 1974

(mrad)

Type of examination	0-14 y		15-29 y		30-44 y		⩾ 45 y		Total
	Male	Female	Male	Female	Male	Female	Male	Female	
Radiography	1.51 (1.32)	1.16 (0.61)	4.22 (7.23)	3.24 (4.31)	0.63 (1.45)	0.32 (0.30)	0.02 (0.02)	0.0	11.1 (15.2)
Fluoroscopy	0.20 (0.41)	0.53 (0.64)	1.04 (2.64)	3.00 (5.62)	0.22 (0.54)	0.39 (0.61)	0.01 (0.01)	0.002	5.4 (10.5)
Total	1.71 (1.73)	1.69 (1.25)	5.26 (9.87)	6.24 (9.93)	0.85 (1.99)	0.71 (0.91)	0.03 (0.03)	0.002	16.5 (25.7)

Sources: References 74, 80

Note: Values in parentheses are the 1969 dose values (74).

(vii) *Puerto Rico*

101. In Puerto Rico a repeat in 1973 on the same basis as the 1968 survey included new frequency data derived from questionnaires about one week's work in all the hospitals (61). The new gonad doses per examination that are reported show apparent decreases compared with those in the 1968 survey, but these recent values would appear to be based on very few measurements. The frequency of lumbar spine and abdominal examinations, particularly in females, has increased the contribution to the GSD from these examinations by factors of three and two respectively. There was however no significant change in the overall GSD, which was estimated to be 46 mrad, compared with 43 mrad in the 1968 survey.

(viii) *Romania, 1970*

102. The frequency of the use of x rays in Romania during the period 1953 to 1970 increased from 429 to 1012 examinations per 1000 of population. This increase has predominantly been in radiography (37 to 238) and photofluorography (54 to 452), with a slight decrease in fluoroscopic examinations (338 to 322). A measurement survey has been conducted in which direct patient measurements using thermoluminescent detectors have been made during 5370 radiological, 8750 fluoroscopic and 9370 photofluorography examinations. The GSD has been estimated for the first time and a value of 28.5 mrad obtained (177).

(ix) *Sweden, 1974*

103. From preliminary data reported by Bengtsson *et al.* (17), it is possible to analyze the changes that have occurred in the factors from which the GSD in Sweden was derived in the 1962 report by the Committee. The results of this analysis are shown in table 24.

TABLE 24. ANALYSIS OF THE INCREASE IN THE GSD

Sweden, 1955-1974

Type of examination	Ratio of examination frequency 1974/1955	Ratio of gonad doses 1974/1955		GSD (mrad)					
				1955			1974		
		Male	Female	Male	Female	Foetus	Male	Female	Foetus
Lumbosacral region	1.55	0.18	1.16	6.30	1.36	0.14	1.75	2.44	0.25
Pelvimetry	2.59	–	0.46[a]	–	0.28	6.40	–	0.33	1.35
Urography	2.59	0.27	0.95	3.48	1.77	0.16	2.43	4.36	0.39
Pelvis	1.86	0.36	0.95	2.70	0.40	0.03	1.80	0.71	0.05
Abdomen	2.63	0.15	0.17	1.78	0.93	0.11	0.70	0.42	0.05
Colon	1.76	1.71	0.46	0.56	2.03	0.21	1.68	1.64	0.17
Hip and femur	2.70	1.38	1.42	2.19	0.25	0.01	8.16	0.96	0.04
Urethrocystography	2.25	0.54	0.77	1.57	0.14	0.02	1.90	0.24	0.03
Femur[b]	–	–	–	1.40	0.02	0.01	–	–	–
Obstetrical abdomen	2.33	–	0.57	–	0.06	1.20	–	0.08	1.59
Subtotal				20.0	7.2	8.3	18.4	11.2	3.9
Other	1.42	(No change assumed)		0.3	1.8	0.2	0.4	2.6	0.3
Total				20.3	9.0	8.5	18.8	13.8	4.2
Total of male, female and foetus totals for the year				37.8			36.8		
Enhanced 1974 totals due to an assumed shift in age distribution							24.4	16.5	5.0
Total of enhanced totals							46		

Source: Reference 131.

[a] For the mother; the ratio for the foetus is 0.03.

[b] Not included in comparison; no data for 1974.

104. It can be seen from table 7 that the total frequency of examinations (excluding dental exposures) increased by 50 per cent from 1955 to 1974. Table 24 shows that the increase in the types of examination which give the highest contributions to the GSD has been higher, nearly 100 per cent. The mean gonad doses in the various types of examinations have sometimes, but not always, been substantially reduced. The result is that the male contribution to the GSD has not changed despite the increased number of examinations. The female contribution, however, has increased approximately in proportion to the higher number of examinations, since there has been no apparent dose reduction in the types of examinations which give the highest contributions (e.g., urography and examinations of the lumbar spine). Due to improved techniques, the foetal contribution has decreased despite an increase in the number of pelvimetries. In total, the annual genetically significant dose from x-ray diagnostic procedures in Sweden has not changed significantly from the value of 38 mrad assessed for 1956, assuming no shift in the age distribution within the types of examinations giving the highest contributions. Bengtsson *et al.* (17), however, take into account an enhancement due to shift towards younger patients, corresponding to a factor of 1.2 for females and 1.3 for males. If this correction is made on the results in table 24, the annual GSD will be assessed at about 46 mrad.

(x) *Switzerland, 1971*

105. A radiological survey of the frequency of 60 types of x-ray examinations was carried out during two weeks of September 1971 and information recorded on 60 000 patients in 1567 hospitals (170). The total number of films used in 1971 was estimated to be $15\ 10^6$, compared with $5\ 10^6$ in 1957. The total number of examinations in 1971 was estimated to be $8.55\ 10^6$, increasing annually at the rate of 3-4 per cent. The number of examinations *per caput* of the population increased from 0.96 in 1957 to 1.35 in 1971. The GSD for 1971 was estimated to be 42.9 mrad; the breakdown by type of examination is given in table 25. A calculation shows that by using suitable gonad shielding the GSD could be reduced by 20 per cent to 34.9 mrad.

TABLE 25. BREAKDOWN OF GSD BY TYPE OF EXAMINATION

Switzerland, 1971

Type of examination	Contribution to GSD	
	(mrad)	(%)
Pelvis without pregnancies	9.24	21.5
Descending urography	8.74	20.4
Hip and femur	6.24	14.5
Lumbar vertebrae	3.81	8.9
Barium meal	2.19	5.1
Barium enema	1.91	4.5
Urography	1.29	3.0
Obstetric abdomen	1.06	2.5
Abdomen without pregnancies	1.01	2.3
Pelvimetry	0.52	1.2
Other	6.89	16.1
Total	42.90	100

Source: Reference 170.

(xi) *Island of Taiwan, 1972*

106. A survey was conducted over eight months of 1972 in five hospitals in the city of Hsineku, considered

to be representative of the five major cities on the island of Taiwan, where the urban population is 5 10^6 (261), about one half of the total population. The method of estimating the frequency of examination and the gonad dose per examination was simplified. It would appear from the reference that the radiation dose incident to the gonad region was integrated, using a thermoluminescent detector, for all patients examined radiographically over a period of one month on five x-ray units at the five chosen hospitals. A separate detector was used for those patients having fluoroscopic examinations. A mean gonad dose was used for all examination types, and the age distribution of those examined was used in the calculation of the GSD for 1972, which was found to be 3-4 mrad.

(xii) *United States surveys in 1964 and 1970*

107. The dosimetry of the United States surveys in 1964 and 1970 has been revised, and the new national estimates of the GSD in those years from radiographic examinations only are 16 and 20 mrad, respectively (251, 255). The contribution from screening examinations was not included. The main examinations and their contributions (per cent) to the 1970 total were as follows: lumbar spine, 18; urography, 16; pelvis, 12; abdomen KUB and flat plate, 10; other abdominal examinations, 20; barium enema, 10; hip, 5. The frequency of x-ray examinations is given in table 26.

TABLE 26. FREQUENCY OF X-RAY EXAMINATIONS BY TYPE OF EXAMINATION

United States, 1970

Type of examination	*Frequency (number of examinations per 1000 of population)*
Head and neck	49.8
Chest	
Radiography	251.7
Photofluorography	53.7
Not categorized	32.5
Cholecystography, and cholangiography	20.7
Lumbar and dorso-lumbar spine	18.7
Upper GI tract	29.1
Upper abdomen not categorized	8.0
Abdomen KUB and flat plate	17.5
Urography	20.7
Barium enema	17.8
Pelvis, lumbo-pelvis	10.6
Lower abdomen not categorized	22.7
Upper extremities	50.9
Lower extremities	62.6
Two-area examinations	1.8
Total	668.8

Source: Reference 251.

(xiii) *Projections of GSD for other countries*

108. Three new estimates of GSD (India, Iraq and Taiwan) have been reported for populations that have limited radiological facilities. Low frequencies of radiological examinations correlate in principle with small GSD, unless very high individual doses are involved. A WHO staff report (64) describes the present status of radiological services in several countries of the eastern Mediterranean area. The report compared the average of one diagnostic x-ray unit per 72 000 people with the United States situation of one unit per 1000 people, and the film consumption of 0.063 film per person-year with the United States value of 2.46 films per person-year.

4. Groups of epidemiological interest

109. Collective doses to special patient groups are of particular interest when they can be used for epidemiological studies. Annex G describes in detail the use of such information, from past medical practices, for the assessment of carcinogenesis risks.

110. The organs of special interest in these investigations, for which dose information are required, are:

Public health investigations:

Dental	Skin, thyroid, hypothalamus, lens of the eye; particularly for patients having regular whole-mouth x-ray examinations
Mass surveys of the chest	Lung, heart, thyroid, bone marrow; particularly for patients with a history of chronic chest disease
Mammography	Breast; particularly for groups of high breast-cancer risk

Clinical investigations:

Barium meal	Stomach, bone marrow, small intestine, pancreas; particularly for patients having multiple fluoroscopic examinations
Barium enema	Large intestine, particularly for patients with chronic diseases such as ulcerative colitis
Urography	Kidney, particularly in patients with chronic disease or kidney failure
Children with orthopaedic handicaps	Epiphyses of bones, gonads, bone marrow
Foetal irradiation	Whole body of foetus
Cardiac catheterization	Heart, lung, bone marrow; particularly in children
Pace-maker insertions	Heart, lung, bone marrow and connective tissues in vicinity of nuclear-powered pace-makers; particularly in patients under 40 years of age
Dynamic investigations	Organs in the chest for cardiac investigations and the kidneys, large intestine, bladder and gonads for pelvic examinations
Neurological examinations	Eye, thyroid, hypothalamus

5. Potential means of dose reduction

111. ICRP publications 15, 16 and 21 (97, 98) and certain WHO publications (112, 216) indicate general ways in which the patient dose in diagnostic radiology may be reduced without loss of useful information. In addition to these, there are a number of national publications giving general guidance on procedures likely to reduce patient doses. These may be summarized as follows: implementation of the "ten-day rule" in the United Kingdom (193), guidelines on use of gonad shielding in the United States (252, 253), radiological protection in dental practice in France, the United Kingdom and United States (162, 241, 149, respectively), and general radiation dose reductions (26, 40, 144, 154, 201, 218, 233, 256).

112. Useful surveys have been carried out on aspects of dose reduction, such as the rate of retakes of x-ray examinations in hospitals in Japan (117) and in two large hospitals in the United States (29).

113. Investigations have been made on the effect of positioning for radiographic examinations and the resulting gonad dose (62), and on the design and effectiveness of gonad shields (33). Absorbed dose measurements of male gonad doses have been made in phantoms representing various age groups by Warner (257). Studies of the range of gonad doses for particular examinations in the German Democratic Republic indicate that the maximum tends to be about twice the mean value (202). The reduction in gonad dose during mass chest screening by appropriate use of shields, particularly when examining children, has been demonstrated by Hashizume in the Japanese 1975 survey report (84).

114. Comparisons of the radiation exposure of patients using various types of apparatus have also been studied, e.g., on the exposure reduction obtained by using image intensifiers instead of fluoroscopy (87).

115. Questionnaires aimed at determining how much the public knows about radiation-dose reduction have produced answers that indicate that further education, not only of radiological personnel, but also of the general public is required (195, 240). General descriptions of examination techniques, such as those produced in the German Democratic Republic (200, 217), may help.

116. The introduction of new techniques, such as pulsed fluoroscopy and electronic retention of the resultant image, should reduce the radiation dose by a factor of five in the case of stomach examinations (156). However, Gustafsson (69) has reported that, in a comparison of 1974 techniques with those used in 1960, the mean energy imparted (integral dose) for stomach examinations has remained the same despite the advances in techniques (figure XI). In barium enema examinations, the mean energy imparted has increased by 50 per cent from 1960 to 1974 (69).

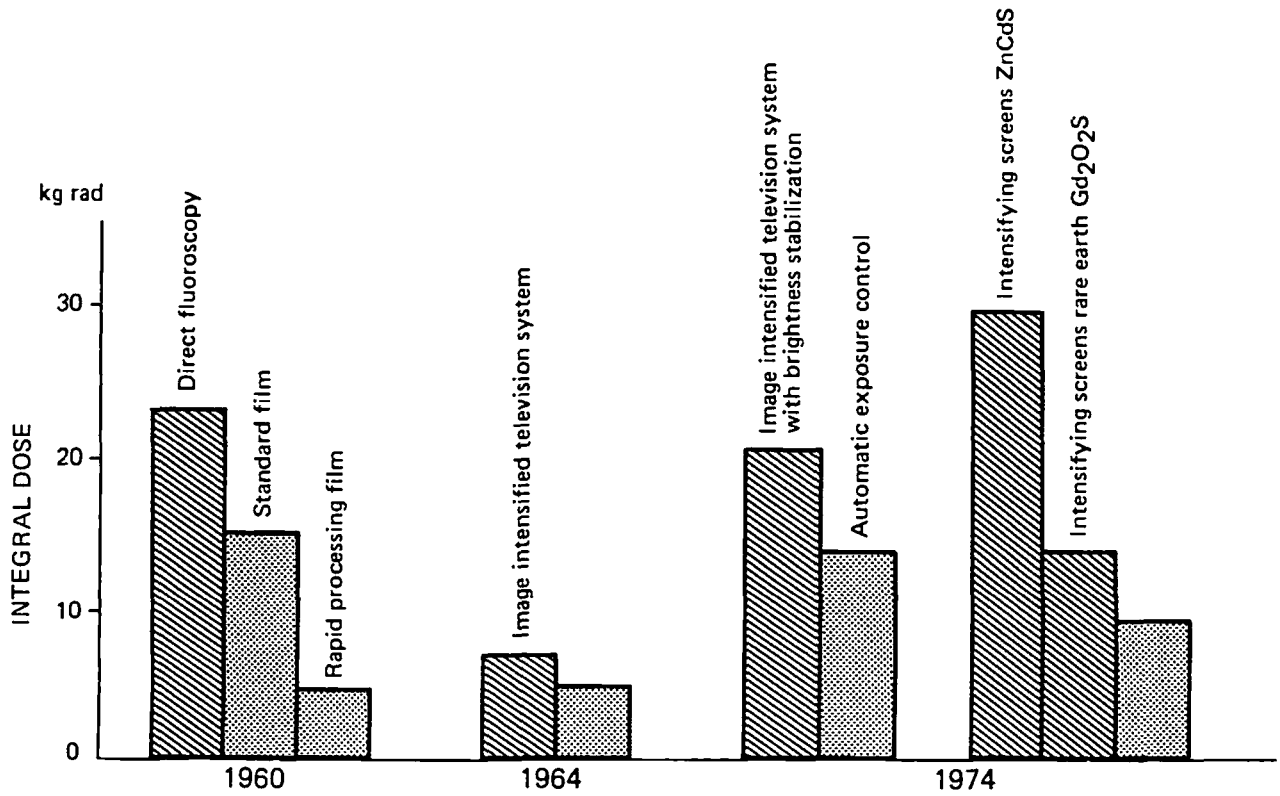


Figure XI. Comparison of mean energy imparted in stomach examinations by various techniques, 1960-1974

B. DIAGNOSTIC USES OF RADIOPHARMACEUTICALS

1. Trends in frequencies and techniques

117. In the 1972 report attention was drawn to the fact that in certain countries the number of diagnostic examinations using radiopharmaceuticals was doubling approximately every three years. This trend is continuing, and therefore it is important that more data should be presented so that estimates of organ dose and GSD may be calculated. Most examinations using radiopharmaceuticals give organ doses of about the same order as or less than complementary x-ray examinations (99, 238). Examination of the thyroid using ^{131}I is the main exception, but with the introduction of alternative *in vitro* techniques, the number of *in vivo* tests using ^{131}I is likely to decline (172). The growth of radioisotope uses in developing countries is being monitored by IAEA (96); from their data it may be possible to assess the effect of the introduction and general availability of short-lived radiopharmaceuticals and the changes in demand resulting from new x-ray facilities, such as computerized axial tomography.

118. The annual frequency of radionuclide examinations was given in the 1972 report for a number of countries for the late 1960s as 2-10 per 1000 of population. With a doubling time of three years, it is now, in several places, approaching and even exceeding 10 per 1000 of population as can be seen in figure XII and in table 27 (93), which show the increase in the annual number and frequency of application of radiopharmaceuticals in West Berlin (91, 92, 93 186), and in table 28, which show similar data for the German Democratic Republic (202). Table 29 shows the reduction in the frequency of ^{131}I-uptake tests in the German Democratic Republic in the last few years due to the introduction of *in vitro* techniques.

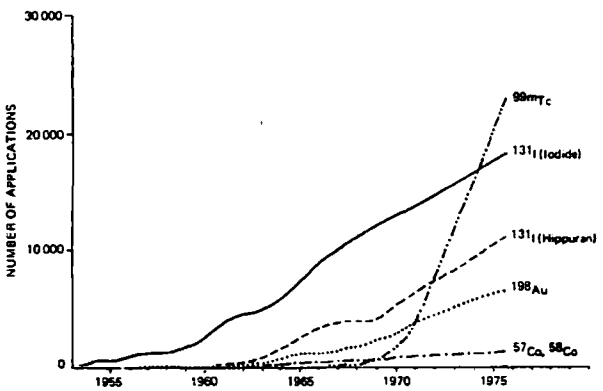


Figure XII. Trend in the annual number of applications of certain radionuclides in West Berlin, 1953-1975 (93)

TABLE 27. SURVEY OF THE DEVELOPMENT OF NUCLEAR MEDICINE IN WEST BERLIN, 1955-1975

(1975 population approximately 2.2 10^6)

Year	Number of all radionuclide applications	Frequency (per 1000 of population)	Distribution by purpose of application (%)	
			Diagnostic	Therapeutic
1955	729	0.32	90.5	9.5
1960	4 220	1.92	91.0	9.0
1965	15 228	6.92	97,1	2.9
1970	30 236	13.87	98.1	1.9
1975	64 720	32.29	99.2	0.8

Source: Reference 93.

TABLE 28. SURVEY OF THE DEVELOPMENT OF NUCLEAR MEDICINE IN THE GERMAN DEMOCRATIC REPUBLIC, 1965-1974

(1974 population approximately 17 10^6)

Year	Number of all radionuclide applications	Frequency (per 1000 of population)	Distribution by purpose of application (%)	
			Diagnostic	Therapeutic
1965	25 913	1.5	96.96	3.04
1966	31 895	1.9	97.06	2.94
1967	42 461	2.5	97.67	2.33
1970	71 378	4.2	98.79	1.21
1971	77 172	4.5	98.75	1.25
1972	131 021	7.7	99.20	0.80
1973	137 128	8.0	98.94	1.06
1974	167 483	9.9	99.16	0.84

Source: Reference 202.

TABLE 29. TRENDS IN THE ^{131}I-UPTAKE TESTS IN THE GERMAN DEMOCRATIC REPUBLIC, 1958-1974

(Administered activity 25-30 μCi)

Year	Number of tests	Fraction of all radionuclide diagnostic examinations (%)	Frequency of test (per 1000 of population)	Number of performing facilities
1958	729			2
1960	2 818			6
1965	10 192	40.6		11
1970	20 092	28.5		14
1971	21 902	27.8		15
1972	26 326	21.6		16
1973	25 170	18.5		16
1974	24 969	15.0	1.47	17

Source: Reference 202.

119. The introduction of new nuclides in radiopharmaceuticals giving lower doses for some types of examinations has to some extent minimized the increase in dose that would be expected from the rapid increase in the number of radiopharmaceutical examinations. This is illustrated in figure XIII, which shows how the change from ^{198}Au to ^{99m}Tc in liver scans has reduced the gonad dose per examination by a factor of three so that the collective dose has increased but little, even though the total number of examinations has increased substantially (151). Roedler *et al.* (186) have calculated the achievable dose reduction for examined or critical organs and gonads by selection of suitable radiopharmaceuticals (see table 30). The most promising dose reductions have been made possible by the introduction in the mid 1960s of ^{99m}Tc, which is now in increasing use all over the world.

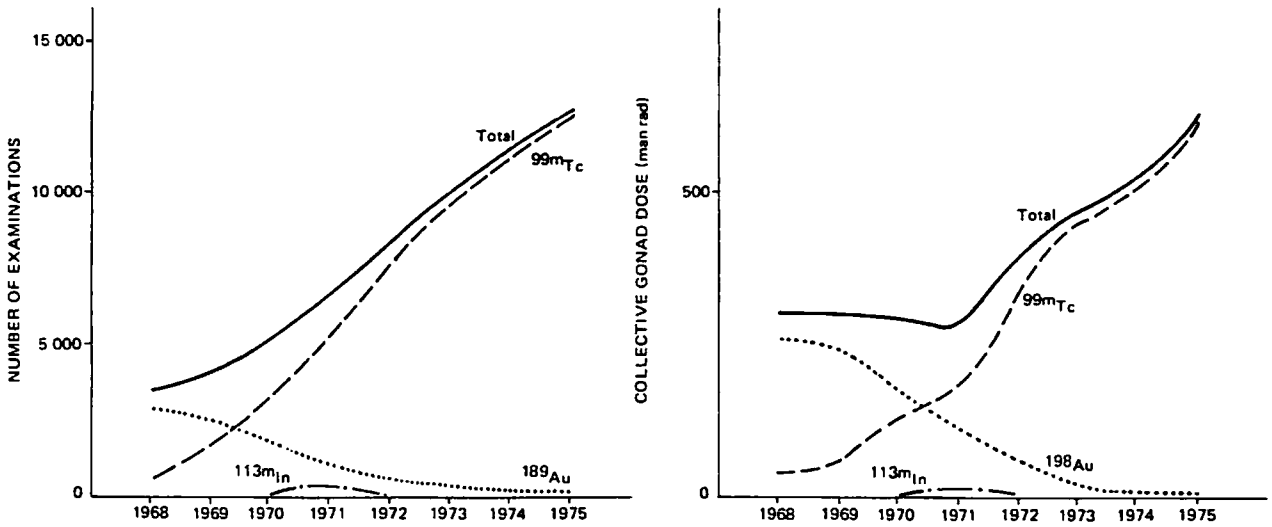


Figure XIII. Trend in the annual number of examinations and collective gonad dose for liver scans in Sweden 1968-1975 (151)

TABLE 30. DOSE REDUCTION FOR EXAMINED OR CRITICAL ORGAN AND GONADS BY REPLACEMENT OF CONVENTIONAL RADIOPHARMACEUTICALS

Radiopharmaceutical[a]			*Dose reduction coefficient*		
Conventional	*Replacement*	*Diagnostic method*	*Examined or critical organ*		*Gonads*
^{131}I iodide (43)	^{99m}Tc pertechnetate (1 000)	Thyroid scanning	Thyroid	0.013	2.6
	^{132}I iodide (25)	Function test (30%)	Thyroid		
^{198}Au colloid (240)	^{99m}Tc S-colloid (1 500)	Liver scanning	Liver	0.063	0.13
^{58}Co vitamin B_{12} (0.9)	^{57}Co vitamin B_{12} (0.5)	Schilling test	Liver	0.12	0.11
^{131}I MAA (220)	^{99m}Tc MAA (3 000)	Lung scanning (66%)	Lung	1.1	0.071
	^{133}Xe (15 000)	Lung scanning (34%)	Lung		
^{131}I HSA (10$^+$)	^{99m}Tc HSA (100)	Blood volume	Total body	0.088	0.1
^{131}I HSA (10$^+$)	^{99m}Tc HSA (500)	Placental localization	Total body	0.44	0.5
^{131}I HSA (100$^+$)	^{99m}Tc HSA (1500)	Myelography	Total body	0.13	0.15
^{197}Hg BMHP (360)	^{99m}Tc S-colloid (1500)	Spleen scanning	Spleen	0.15	0.069
^{85}Sr nitrate (330)	^{99m}Tc polyphosphate (10 000)	Bone scanning	Skeleton	0.11	0.2
^{203}Hg BMHP (400)	^{99m}Tc DTPA (3 000)	Kidney scanning	Kidney	0.0009	0.0096
^{203}Hg chlormerodrine (180)	^{99m}Tc DTPA (3 000)	Kidney scanning	Kidney	0.017	0.053

Source: Reference 186.

[a] The mean administered activity in microcuries is given in parentheses.

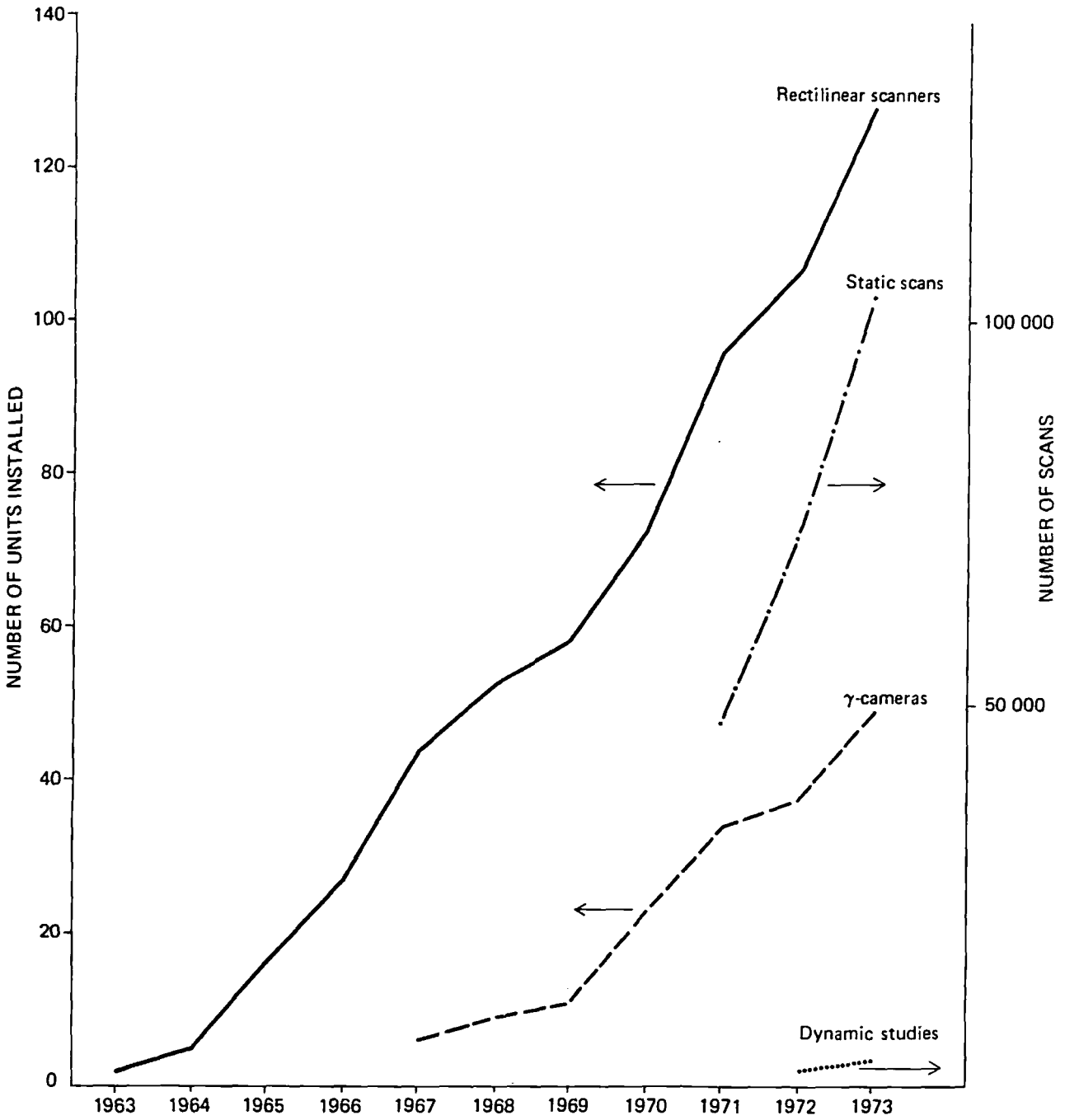


Figure XIV. Number of scanners and γ-cameras installed in the United Kingdom, 1963-1973, and total number of static scans and dynamic studies carried out, 1971-1973 (172, 188, 189)

120. Part of the increase in frequency of examinations in the United Kingdom is due to the increased availability of imaging equipment; the increase in scanners and cameras in England and Wales is shown for the period 1963-1973 in figure XIV (172, 188, 189). In a population of 50 10^6, the number of scans, also shown in figure XIV, doubled every two years and by 1973 amounted to 2 per 1000 of population.

121. The most common single type of radionuclide examination is the thyroid function (uptake) test with ^{131}I. In many countries it accounts for about one third of all radionuclide examinations, while in technologically advanced countries this proportion has declined to about 10 per cent of the total, as can be seen from Table 31 (96). The use of *in vitro* T3 and T4 tests to replace *in vivo* uptake studies is significantly reducing

TABLE 31. RELATIVE PROPORTION OF IODINE-131 THYROID UPTAKE STUDIES IN VARIOUS COUNTRIES

Country	*Fraction of all radionuclide investigations (%)*
Argentina	40
Brazil	47
Denmark (1973/74)	9
Hungary	27
India	38
Israel	18
Mexico	23
Poland	30
Sweden (1968)	19
Sweden (1974)	12
United States[a]	8
Yugoslavia	22

Source: Reference 96.

[a]Data from 65 academic divisions of nuclear medicine (231).

TABLE 32. FREQUENCY OF ^{131}I-UPTAKE STUDIES AND THE ACTIVITY ADMINISTERED IN VARIOUS COUNTRIES

Country	*Population (10^6)*	*Frequency (per 1000 of population)*	*Administered activity (μCi)*	
			Range	*Mean (population weighted)*
Argentina	24.0	0.66	5-100	44
Brazil	91.3	0.18	20-70	41
Denmark (1973)	5.06	0.89	–	20
Hungary	10.3	1.40	0.5-50	16
India	537.0	0.013	7-40	16
Israel	2.82	2.29	6-35	21
Sweden	7.9	1.14	2.5-35	9
Mexico	48.9	0.12	5-50	14
Poland	32.5	0.46	5-60	13
United States (1966)	195.0	1.54	2.5-100	37
Yugoslavia	20.4	0.66	5-100	31

Source: Reference 96.

TABLE 33. FREQUENCY OF ^{131}I THYROID SCANS AND THE ACTIVITY ADMINISTERED IN VARIOUS COUNTRIES

Country	*Population (10^6)*	*Frequency (per 1000 of population)*	*Administered activity (μCi)*	
			Range	*Mean (population weighted)*
Argentina	24.0	0.23	50-100	80
Brazil	91.3	0.093	15-300	71
Denmark	5.06	0.23	–	78
Hungary	10.3	0.36	15-50	32
India	537.0	0.003	20-100	41
Israel	2.82	1.38	10-50	31
Sweden	7.9	1.53	4-100	41
Mexico	48.9	0.077	50-180	116
Poland	32.5	0.14	10-100	50
United States (1966)	195.0	0.78	10-150	57
Yugoslavia	20.4	0.63	20-100	45

Source: Reference 96.

the radiation dose to this group of patients in the United Kingdom (172). The introduction of the use of ^{123}I for thyroid imaging would reduce the dose by a factor of about 10 compared with ^{131}I (254).

122. It is possible to complete the picture of the use of ^{131}I by presenting some data compiled by IAEA (96) on the use of radionuclides in 11 countries for periods around 1970. Tables 32 and 33 give the frequencies, the average administered activities and the range of activities in these countries for thyroid uptake studies and thyroid scans with ^{131}I. It has already been shown (table 31) that thyroid uptake studies dominate the number of radionuclide examinations in many countries. It can be seen from table 32 that, with the exception of India, there is relatively little variation in the frequency of uptake studies, the range being 0.12-2.29 per 1000 of population. Table 33 shows that there is on the average one ^{131}I thyroid scan for every two uptake tests. The administered activities range between 9 and 44 μCi for the uptake studies and between 31 and 116 μCi for the scans. It is important to obtain more recent information on these aspects, as the situation is likely to have changed significantly in the last eight years.

2. Individual dose per unit procedure

(a) *Administered activity*

123. As with x-ray examinations, the doses received during radiopharmaceutical examinations vary from hospital to hospital. In this case, however, comparisons are somewhat easier because the choice of nuclide, chemical substance, mode of administration and administered activity define the dose for any particular investigation of disease. Interesting comparisons may therefore be made on the basis of the administered activity, once the other factors are kept constant, which is usually the case within each type of examination and for each nuclide.

124. Data are available from Sweden on the average activity used in each type of examination and on the lowest and highest average activities used in particular clinics. On the basis of the reported average activity, the highest organ dose (in the average procedure) has been calculated, together with the gonad dose. The results are shown in tables 34 and 35 for 1968 and 1974 (151). The doses have been calculated using data from Swedish compilations (59).

125. Tables 34 and 35 may be compared with tables 36 and 37, where similar information is presented for Denmark (1973-1974) and the United States (1966) (219, 248). There is a great degree of similarity in the practices for the corresponding years. These recent data give a relatively clear picture of the magnitude of radionuclide examinations in technologically developed countries for the year 1974. The variation in administered activities in three of the most common types of examinations is shown in table 38.

TABLE 34. DATA ON THE USE OF RADIONUCLIDES FOR DIAGNOSTIC PURPOSES

Sweden, 1968

Type of examination	Radionuclide	Chemical form	Administration method	Administered activity per examination (μCi)			Critical organ dose per examination (mrad)	Critical organ	Number of examinations	Frequency (per 1000 of population)	Gonad dose	
				Average	Lowest	Highest					Per examination (mrad)	Per 1000 of population (man rad)
Thyroid scan	^{131}I,	Iodide	PO	41	4	100	73 000	Thyroid	12 091	1.53	96	0.147
	^{125}I	Iodide	PO	42	30	50	31 000	Thyroid	766	0.097	16	0.002
	^{99m}Tc	Pertechnetate	PO	1 700	1 000	2 100	430	Thyroid	610	0.077	14	0.001
Thyroid[a]	^{131}I	Iodide	PO	980	750	1 000			89	0.011	2 300	0.026
Brain scan	^{131}I	RIHSA	IV	353	94	500	12 000	Thyroid	40	0.005	1 600	0.008
	^{99m}Tc	Pertechnetate	IV	10 000	3 720	14 000	1 700	Lower intestine	1 033	0.130	170	0.022
Lung scan	^{131}I	MAA	IV	235	130	325	1 200	Lung	391	0.049	150	0.007
Skeleton scan	^{85}Sr	Chloride	IV	53	30	200	1 500	Skeleton	545	0.069	400	0.028
Liver scan	^{198}Au	Colloid	IV	182	100	300	7 800	Spleen	2 894	0.365	90	0.033
	^{99m}Tc	S-colloid	IV	2 800	600	3 000	800	Liver	590	0.075	64	0.005
	^{131}I	Rose Bengal	IV	128	100	300	240	Liver	96	0.012	92	0.001
Marrow scan	^{198}Au	Colloid	IV	921	300	2 000	39 000	Spleen	193	0.024	450	0.011
Pancreas scan	^{75}Se	Methionine	IV	210	200	250	12 000	Kidney	38	0.005	2 200	0.011
Profile scan	^{131}I	Iodide	PO	220	50	241	430 000	Thyroid	138	0.017	510	0.009
Thyroid function	^{131}I	Iodide	PO	9	2.5	35	16 000	Thyroid	9 002	1.14	21	0.024
	^{125}I	Iodide	PO	16	6	127	12 000	Thyroid	251	0.032	6	0.000
Brain circulation	^{131}I	RIHSA	IA	156	50	263	5 300	Thyroid	99	0.013	720	0.009
Circulation test	^{133}Xe	Sol	IM	109	20	300	2 800	Adipose tissue	1 231	0.155	(100)	0.016
Lung function	^{133}Xe	Sol	IV	1 720	500	4 900	34	Trachea	811	0.102	1	0.000
Blood volume	^{131}I	RIHSA	IV	11	1	115	380	Thyroid	954	0.120	50	0.006
	^{125}I	RIHSA	IV	3	1	8	8	Blood	818	0.103	2	0.000
Potassium determination	^{42}K	Chloride	PO	150	50	107	950	GI tract	292	0.037	200	0.007
Iron metabolism	^{59}Fe	Citrate	PO	5	3	40	760	Spleen	377	0.048	72	0.003
Schilling test	^{60}Co	Vitamin B_{12}	PO	0.4	0.24	0.5	730	Liver	523	0.066	260	0.017
	^{58}Co	Vitamin B_{12}	PO	0.4	0.05	0.7	150	Liver	1 430	0.181	57	0.010
	^{57}Co	Vitamin B_{12}	PO	0.4	0.16	0.75	35	Liver	1 436	0.181	2	0.000
Renography	^{131}I	Iodide	IV	50	50	50	120	Gonads	121	0.015	120	0.002
	^{131}I	Hippurate	IV	23	10	200	40	Bladder	5 176	0.654	1	0.000
	^{125}I	Hippurate	IV	14	1	100	3	Kidney	2 849	0.360	1	0.000
Other	–	–	–	–	–	–	–	–	2 728	0.345	(50)	0.017
Total									47 616	6.02	70	0.422

Source: Reference 151.

[a]Cancer patients.

TABLE 35. DATA ON THE USE OF RADIONUCLIDES FOR DIAGNOSTIC PURPOSES

Sweden, 1974

Type of examination	Radionuclide	Chemical form	Administration method	Administered activity per examination (μCi)			Critical organ dose per examination (mrad)	Critical organ	Number of examinations	Frequency (per 1000 of population)	Gonad dose	
				Average	Lowest	Highest					Per examination (mrad)	Per 1000 of population (man rad)
Thyroid scan	^{131}I	Iodide	PO	86	4	1 000	153 000	Thyroid	10 101	1.22	202	0.246
	^{125}I	Iodide	PO	25	11	40	18 500	Thyroid	265	0.032	10	0.000
	^{99m}Tc	Pertechnetate	IV	1 810	600	5 000	920	Thyroid	3 647	0.439	30	0.013
Brain scan	^{99m}Tc	Pertechnetate	IV	10 950	5 000	15 000	1 860	Lower intestine	10 894	1.31	185	0.242
	^{99m}Tc	DTPA	IV	14 360	14 000	14 700	5 600	Bladder	1 382	0.166	280	0.047
Lung scan	^{131}I	MAA	IV	767	300	1 500	3 900	Lung	200	0.024	490	0.012
	^{99m}Tc	MAA	IV	1 780	1 000	3 000	90	Blood	2 084	0.251	20	0.005
Skeleton scan	^{85}Sr	Chloride	IV	66	40	100	1 900	Skeleton	831	0.100	500	0.050
	^{99m}Tc	Phosphate	IV	8 670	4 000	15 000	1 765	Bladder	3 926	0.473	135	0.064
Liver scan	^{198}Au	Colloid	IV	138	120	175	5 900	Spleen	162	0.020	68	0.001
	^{99m}Tc	S-colloid	IV	2 050	500	5 000	585	Liver	10 600	1.28	47	0.060
Marrow scan	^{198}Au	Colloid	IV	833	500	1 000	35 000	Spleen	97	0.012	410	0.005
Pancreas scan	^{75}Se	Metionine	IV	240	200	250	13 500	Kidney	328	0.039	2 500	0.098
	^{99m}Tc	S-colloid	IV	2 000	2 000	2 000	570	Liver	236	0.028	46	0.001
Profile scan	^{131}I	Iodide	PO	479	100	950	936 000	Thyroid	155	0.019	1 100	0.021
Thyroid function	^{131}I	Iodide	PO	12	2	30	21 000	Thyroid	11 796	1.42	28	0.040
Thyroid[a]	^{131}I	Iodide	PO	279	200	357			346	0.042	640	0.027
Circulation test	^{133}Xe	Sol	IM	319	8	1 400	8 200	Adipose tissues	259	0.031	(300)	0.009
Lung function	^{133}Xe	Sol	IV	2 517	263	10 500	50	Trachea	2 652	0.319	1	0.000
Blood volume	^{131}I	RIHSA	IV	4.4	1.5	6	150	Thyroid	1 546	0.186	20	0.004
	^{125}I	RIHSA	IV	4.6	0.7	10	12	Blood	695	0.084	3	0.000
Iron metabolism	^{59}Fe	Chloride	PO	6.9	0.6	20	1 050	Spleen	484	0.058	100	0.006
Schilling test	^{58}Co	Vitamin B_{12}	PO	0.57	0.05	0.8	210	Liver	727	0.088	80	0.007
	^{57}Co	Vitamin B_{12}	PO	0.44	0.05	0.5	38	Liver	1 682	0.203	2	0.000
Renography	^{131}I	Hippurate	IV	32	6	200	56	Bladder	11 475	1.38	1	0.001
	^{125}I	Hippurate	IV	17	6	40	4	Kidney	8 311	1.00	1	0.001
	^{131}I	RIHSA	IV	10	10	10	340	Thyroid	110	0.013	45	0.001
Other	–	–	–	–	–	–	–	–	10 774	1.30	(50)	0.065
Total									95 765	11.5	80	0.922

Source: Reference 151.

[a] Cancer patients.

TABLE 36. DATA ON THE USE OF RADIONUCLIDES FOR DIAGNOSTIC PURPOSES

Denmark, 1973/74

Type of examination	*Radio-nuclide*	*Chemical form*	*Number of examin-ations*	*Frequency (per 1000 of popu-lation)*	*Administered activity per examination (μCi)*	*Gonad dose*	
						Per examin-ation (mrad)	*Per 1000 of population (man rad)*
Thyroid scan	^{131}I	Iodide	1 187	0.235	78	183	0.043
	^{99m}Tc	Pertechnetate	2 605	0.515	1 493	25	0.013
Brain scan	^{99m}Tc	Pertechnetate	8 624	1.70	11 890	200	0.340
Lung scan	^{133}I	MAA	334	0.066	293	187	0.012
	^{99m}Tc	Microspheres	714	0.141	1 467	19	0.003
Skeleton scan	^{99m}Tc	Phosphate	1 409	0.278	10 250	154	0.043
Liver scan	^{99m}Tc	S-colloid	2 463	0.487	1 689	56	0.027
Pancreas scan	^{75}Se	Methionine	46	0.009	263	2 740	0.025
Thyroid function	^{131}I	Iodide	4 525	0.894	20	47	0.042
	^{99m}Tc	Pertechnetate	447	0.088	1 000	17	0.001
Circulation test	^{133}Xe	Sol	2 112	0.417	90	(100)	0.042
Lung function	^{133}Xe	Sol	123	0.024	2 852	1	0.000
Iron metabolism	^{59}Fe	Citrate	140	0.028	10	145	0.004
Schilling test	^{58}Co	Vitamin B_{12}	1 101	0.218	0.54	80	0.017
	^{57}Co	Vitamin B_{12}	932	0.184	0.44	2	0.000
Renography	^{131}I	Hippuran	7 539	1.49	36	1	0.001
	^{125}I	Hippuran	2 638	0.521	26	1	0.000
Kidney clearance	^{51}Cr	EDTA	1 019	0.201	82	1	0.000
Other	–	–	10 741	2.12	–	(50)	0.106
Total			48 699	9.62		75	0.719

Source: Reference 219.

TABLE 37. DATA ON THE USE OF

United

Type of examination	*Radio-nuclide*	*Chemical form*	*Adminis-tration method*	*Administered activity per examination (μCi)*		
				Average	*Lowest*	*Highest*
Thyroid scan	^{131}I	Iodide	PO	57	10	150
Brain scan	^{99m}Tc	Pertechnetate	IV	7 937	600	15 000
Liver scan	^{198}Au	Colloid	IV	175	60	500
	^{131}I	Rose Bengal	IV	158	55	400
Lung scan	^{131}I	Albumin	IV	260	100	350
Skeleton scan	^{85}Sr	Chloride	IV	105	50	300
Thyroid function	^{131}I	Iodide	PO	37	2.5	100
Blood volume	^{131}I	RIHSA	IV	5.5	0.5	22.5
Vitamin B_{12} absorption	^{60}Co	Vitamin B_{12}	PO	0.5	0.1	1.4

Source: Reference 248.

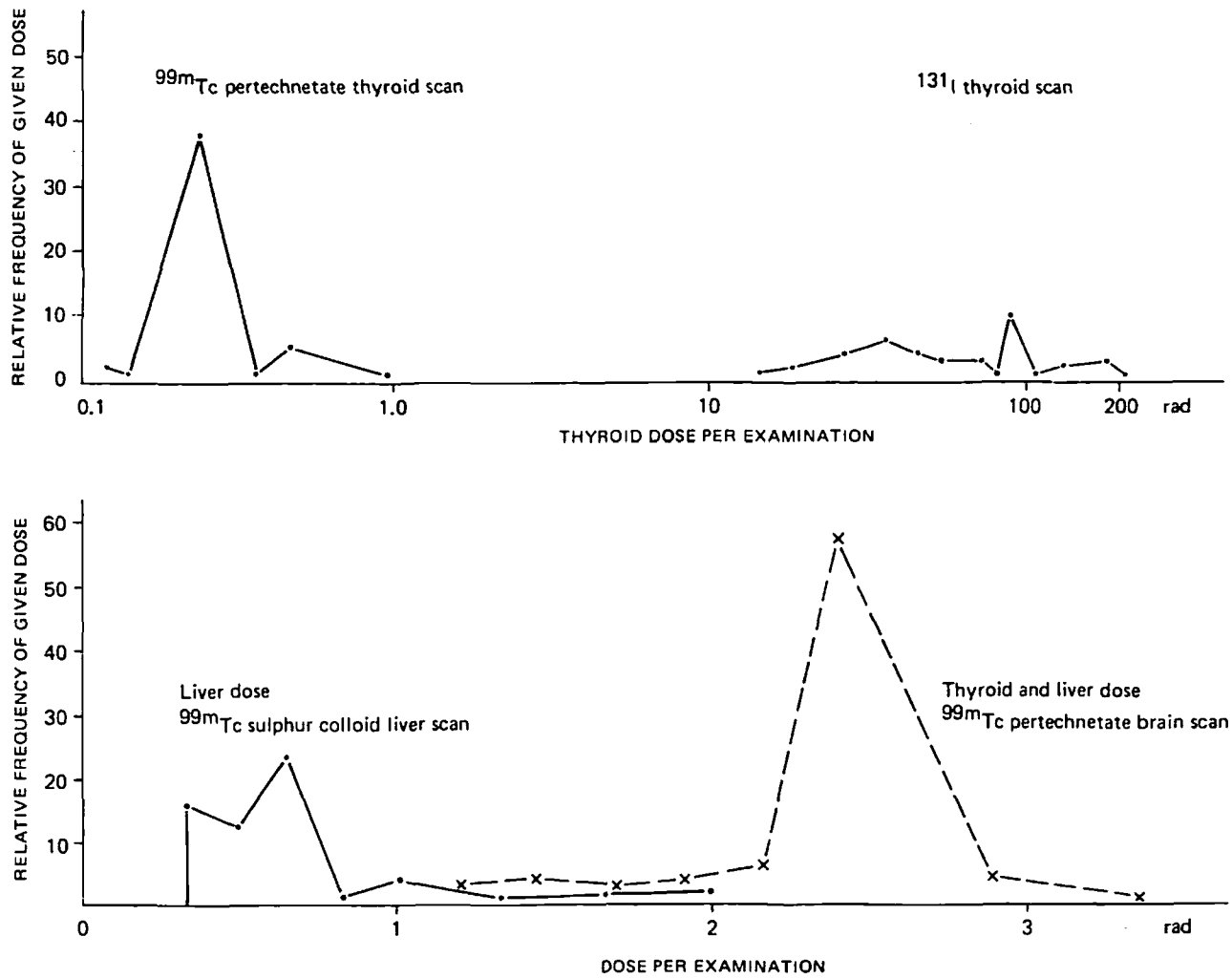


Figure XV. Frequency distribution of doses to thyroid and liver in radiopharmaceutical examinations given in England and Wales (172)

(b) *Dose per examination*

126. A number of publications give estimates of organ doses per unit of administered activity (18, 24, 43, 44, 59, 85, 90, 95, 99, 110, 124, 125, 132, 133, 140, 183, 184, 185, 211, 213, 245, 246). The estimates are given for normal individuals as well as for patients who, because of metabolic changes caused by the disease, may receive somewhat different organ doses. In a number of examinations with ^{131}I or with other radionuclides, such as ^{99m}Tc, which are readily taken up by the thyroid, it is customary to reduce the thyroid dose by blocking the thyroid (51). The dose estimates then critically depend upon the assumptions about thyroid blocking. The biokinetic data compiled by Kaul *et al.* (109) are particularly useful in calculating the absorbed doses from various radiopharmaceuticals when differences from the normal have to be taken into account.

States, 1966

Critical organ dose (mrad)	Critical organ	Number of examinations	Frequency (per 1000 of population)	Gonad dose	
				Per examination (mrad)	Per 1000 of population (man rad)
101 500	Thyroid	153 089	0.78	133	0.104
1 350	Lower intestine	63 078	0.32	135	0.043
7 500	Spleen	41 855	0.21	87	0.018
296	Liver	19 721	0.10	114	0.012
1 330	Lung	22 840	0.120	166	0.020
2 970	Bone	6 232	0.032	792	0.025
65 000	Thyroid	301 052	1.54	86	0.132
190	Thyroid	101 994	0.52	25	0.013
913	Liver	16 486	0.085	325	0.028

TABLE 38. ADMINISTERED ACTIVITY IN THREE COMMON RADIOPHARMACEUTICAL EXAMINATIONS

(μCi per examination)

Country	Examination			
	Thyroid scan		Thyroid uptake	Brain scan
	^{131}I	^{99m}Tc	^{131}I	^{99m}Tc
Denmark (1973/74)	78	1 490	20	11 890
West Berlin (1975)	–	1 035	–	9 380
Sweden (1968)	41	1 700	9	10 000
Sweden (1975)	57	1 840	9	10 990
United Kingdom (1973)	41	900	–	9 500
United States (1966)	57	–	37	7 940

Sources: References 93, 151, 172, 219, 248.

127. Typical radiation doses received from radiopharmaceutical examinations are given in the eighth column of table 34 for the organs listed in the ninth column. The distribution of typical doses in all the centres in England and Wales have been reported by Potter (172), and are given in figure XV. It is important to note that the dose to the thyroid is two orders of magnitude lower when ^{99m}Tc pertechnetate is used instead of ^{131}I.

128. Roedler *et al.* (186) have made a critical review of the dose factors reported in the literature. Because of the high frequency of thyroid examinations with ^{131}I, the dose factors for this nuclide are of particular interest. A number of authors have assessed the gonadal dose per unit administered activity of ^{131}I at more than 2 mrad μCi^{-1}. Roedler *et al.* suggest that the dose factor is only 0.2 mrad μCi^{-1}. A comparison of some current estimates of the dose factor to organs for a number of examinations is made in table 39 and the corresponding dose per examination given in table 40.

TABLE 39. RANGE AND NOMINAL VALUE OF ABSORBED DOSE PER UNIT ADMINISTERED ACTIVITY IN THE MOST FREQUENTLY PERFORMED RADIOPHARMACEUTICAL EXAMINATIONS

(mrad μCi^{-1})

Type of examination	Radionuclide	Chemical form	Organ	Range		Nominal value
				From literature	Recalculated	
Thyroid scan or function	^{131}I	Iodide	Thyroid	68-3 400	840-3 700	2 000
			Gonads	0.024-8.5	0.10-0.33	0.2
			Skeleton	0.3-1.4	0.20-0.59	0.4
Thyroid scan Brain scan	^{99m}Tc	Pertechnetate	Thyroid	0.1-0.6	0.56	0.6
			Gonads	0.01-0.04	0.019	0.02
			Skeleton		0.018	0.02
Thyroid function	^{132}I	Iodide	Thyroid	0.37-50	4-90	30
			Gonads	0.18-0.20	0.061-0.14	0.1
			Skeleton		0.068-0.11	0.1
Kidney function	^{131}I	*o*-Iodohippurate	Kidney	0.07-1	0.22-0.65	0.5
			Gonads	0.016-0.25	0.0053-0.0087	0.01
			Skeleton		0.0057-0.0076	0.007
Bone scan	^{85}Sr	Nitrate/chloride	Gonads	2.9-40	2.8-3.3	3
			Skeleton	2.9-52	11	10
	^{87m}Sr	Nitrate/chloride	Gonads		0.02	0.02
			Skeleton	0.071-0.6	0.05	0.05
	^{99m}Tc	Polyphosphate	Gonads		0.02	0.02
			Skeleton		0.04	0.04

TABLE 39 *(continued)*

Type of examination	*Radio-nuclide*	*Chemical form*	*Organ*	*Range*		*Nominal value*
				From literature	*Recalculated*	
Kidney scan	^{203}Hg	BMHP	Kidney	690-760		(500)
			Gonads			(10)
			Skeleton			(10)
	^{203}Hg	Chlor-merodrine	Kidney	0.66-580	87	90
			Gonads	0.02-1.9	1.7-1.9	2
			Skeleton		1.7	2
	^{99m}Tc	DTPA	Kidney	0.042		(0.04)
			Gonads	0.01-0.02		(0.02)
			Skeleton			(0.02)
Spleen scan	^{197}Hg	BMHP	Spleen	0.17-30		(10)
			Gonads	0.05-0.4		(0.5)
			Skeleton			(0.5)
	^{99m}Tc	S-colloid	Spleen	0.02-0.45	0.053	0.1
			Gonads	0.012-0.023	0.0021-0.0061	0.005
			Skeleton	0.026-0.034	0.011	0.01
Liver scan	^{198}Au	Colloid	Liver	20-1 000	30-39	40
			Gonads	0.11-1.4	0.035-0.38	0.3
			Skeleton	2.7-50	0.28-0.49	0.5
	^{99m}Tc	S-colloid	Liver	0.002-0.53	0.35	0.4
			Gonads	0.012-0.023	0.002-0.006	0.005
			Skeleton	0.02-0.14	0.011	0.01
	^{113m}In	Colloid	Liver	0.05-0.6	0.44	0.5
			Gonads		0.001-0.003	0.002
			Skeleton	0.02-0.5	0.007	0.01
Pancreas scan	^{75}Se	Methionine	Pancreas	0.24-12	13	15
			Gonads	1-11	10	10
			Skeleton		8.3	10
Blood (plasma) volume	^{131}I	HSA	Total body	0.25-12.3	1.7	2
			Gonads	1.7-4	2.0	2
			Skeleton		1.7	2
	^{99m}Tc	HSA	Total body	0.002-0.02	0.014-0.016	0.02
			Gonads	0.005-0.08	0.019-0.022	0.02
			Skeleton		0.018-0.021	0.02
Erythrocyte volume or survival time	^{51}Cr	Chromate	Total body	0.25-3	0.34	0.4
			Gonads	0.03-3	0.43	0.4
			Skeleton	2	0.35	0.4
Lung scan	^{131}I	MAA	Lung	0.67-9.8	4.0	4
			Gonads	0.074-2	0.29	0.3
			Skeleton		0.28	0.3
	^{99m}Tc	MAA	Lung	0.047-0.4	0.2-0.36	0.3
			Gonads		0.012-0.057	0.002
			Skeleton		0.01-0.012	0.01
Iron kinetics	^{59}Fe	Citrate	Spleen	14-230	130	150
			Gonads	3-350	50	50
			Skeleton	1.3-18	16	15

Source: Reference 185.

TABLE 40. ABSORBED DOSE PER EXAMINATION IN THE MOST FREQUENTLY PERFORMED RADIOPHARMACEUTICAL EXAMINATIONS

Type of examination	*Radio-nuclide*	*Chemical form*	*Average administered activity (μCi)*	*Absorbed dose per examination (mrad)*			
				Examined and/or critical organ		*Gonads*	*Skeleton*
Thyroid scan or function	^{131}I	Iodide	25	Thyroid	50 000	5	10
Thyroid scan	^{99m}Tc	Pertechnetate	1 000	Thyroid	600	20	20
Thyroid function	^{132}I	Iodide	25	Thyroid	750	2.5	2.5
Kidney function	^{131}I	*o*-Iodohippurate	20	Kidney	10	0.2	0.14
Bone scan	^{85}Sr	Nitrate/chloride	100	Skeleton	1 000	300	1 000
	^{87m}Sr	Nitrate/chloride	1 000	Skeleton	50	20	50
	^{99m}Tc	Polyphosphate	10 000	Skeleton	400	400	200

Type of examination	Radio-nuclide	Chemical form	Average administered activity (μCi)	Absorbed dose per examination (mrad)			
				Examined and/or critical organ		Gonads	Skeleton
Kidney scan	^{203}Hg	BMHP	100	Kidney	50 000	1 000	1 000
	^{203}Hg	Chlormerodrine	150	Kidney	13 500	300	300
	^{99m}Tc	DTPA	3 000	Kidney	120	60	60
Brain scan	^{99m}Tc	Pertechnetate	10 000	Thyroid	6 000	200	200
Spleen scan	^{197}Hg	BMHP	300	Spleen	3 000	150	150
	^{99m}Tc	S-colloid	1 500	Spleen	150	7.5	15
Liver scan	^{198}Au	Colloid	150	Liver	6 000	45	75
	^{99m}Tc	S-colloid	1 500	Liver	600	7.5	15
	^{113m}In	Colloid	1 000	Liver	500	2	10
Pancreas scan	^{75}Se	Methionine	200	Pancreas	3 000	2 000	2 000
Blood (plasma) volume	^{131}I	HSA	10	Total body	20	20	20
	^{99m}Tc	HSA	100	Total body	2	2	2
Erythrocyte volume or survival time	^{51}Cr	Chromate	100	Total body	40	40	40
Lung scan	^{131}I	MAA	200	Lung	800	60	60
	^{99m}Tc	MAA	3 000	Lung	900	6	30
Iron kinetics	^{59}Fe	Citrate	15	Spleen	2 250	750	225

Source: Reference 185.

129. To calculate an approximate value for the annual collective dose, the data from England and Wales (population 50 10^6) for 1973 may be averaged and combined with the number of examinations carried out. The collective doses for five examinations are given in table 41.

TABLE 41. COLLECTIVE DOSE FROM RADIOPHARMACEUTICAL EXAMINATIONS IN ENGLAND AND WALES

Type of examination	Radio-nuclide	Chemical form	Average administered activity (μCi)	Organ	Collective dose (10^3 man rad)	Annual number of examinations
Brain scan	^{99m}Tc	Pertechnetate	9 500	Stomach	101	44 000
				Thyroid	101	44 000
Liver scan	^{99m}Tc	S-colloid	2 000	Liver	14	20 000
Thyroid scan	^{99m}Tc	Pertechnetate	900	Thyroid	2	10 000
				Stomach	2	10 000
	^{131}I		41	Thyroid	467	4 600
Lung scan	^{99m}Tc	MAA	1 800	Lung	4	8 600
Placental localization	^{113m}In	Chloride	700	Foetus	.040	2 900

Source: Reference 172.

130. Only very little new information is available since the 1972 report on the GSD from radionuclide examinations. The survey in West Berlin has been updated (186) and the GSD in 1970 was estimated to be 0.2 mrad, compared with 0.1 mrad in 1968. The change is primarily due to the increased number of examinations. This is in line with the GSDs reported in 1972 by the Committee, which were in the range 0.01-0.4 mrad.

III. THERAPEUTIC USES OF RADIATION

A. TREATMENT WITH EXTERNAL BEAMS AND SEALED SOURCES

1. General

131. High radiation doses have been used in radiotherapy for the treatment of two major classes of disease, the first being skin and other non-neoplastic diseases, for which radiation doses of up to 1000-2000 rad have been given. The majority of these treatments are for skin diseases, for which a low-energy, fairly non-penetrating radiation has been used.

132. The second class of disease treated by irradiation has been neoplastic disease, which includes all the various forms of cancer and other invasive and malignant diseases. For the treatment of these diseases, radiation doses of up to 6000-7000 rad are given to localized tumours; in the ease of more generalized neoplastic diseases, such as leukaemia, extra corporeal irradiation may be given. These high doses are necessary to cause a destructive effect on the tumour cells. It is inevitable in these treatments thatlarge radiation doses will also be received by some of the healthy tissues lying within the treatment volume or in the path of any of the treatment beams. The seriousness of the primary disease, however, necessitates that little consideration be given to any

deleterious late effects of radiation that might occur many years after a successful treatment. Nevertheless, it is important to obtain estimates of the radiation dose within healthy organs and tissues irradiated in the treatment régime, so that estimates of the frequency of such late effects may be made.

2. Trends in radiotherapy practice

133. In the 1972 report of the Committee it was estimated that in many industrialized countries about one half of the new cancer cases arising each year are treated with radiotherapy and that this proportion does not seem to change appreciably even with the increased use of chemotherapy. Elsewhere, the treatment of cancer will rise in importance as other causes of death such as malnutrition, malaria and tuberculosis are gradually eliminated by the improvement of living conditions and the availability of medical care. These estimates seem to remain valid.

134. For the treatment of non-neoplastic disease, alternative treatment forms not involving radiation have been recommended, and a drastic decrease in the number of such treatments took place in the 1960s (118, 232), which is illustrated by table 42. X rays were regularly used for the treatment of skin lesions, particularly dermatological conditions, in the years 1930 to 1960. Since that time a great reduction in the number of patients treated has occurred and lower tube voltages have been used, meaning less penetration of the beam.

TABLE 42. PERCENTAGE OF THERAPEUTIC IRRADIATIONS PERFORMED IN CONNECTION WITH NON-NEOPLASTIC DISEASE IN JAPAN AND SWEDEN, 1956-1972

Country	*1956*	*1965*	*1970*	*1972*
Japan (118)	72	22	12[a]	10
Sweden (171)	88	49	14	10

[a] Representing 1722 patients.

135. The technological development in radiotherapy equipment over the last 25 years has been aimed at providing radiation beams capable of penetrating adequately to deep-seated tumours and of producing higher dose rates. Thus, orthovoltage x-ray units operating at 250 kV and ^{226}Ra sources used in brachytherapy have been replaced by electron accelerators (4-20 MeV) and telecurie units containing gamma-ray emitting sources such as ^{60}Co with activities of up to 10 kCi. This trend is illustrated by the installation in Sweden of cancer therapy machines (table 43).

TABLE 43. CHANGE IN USE OF RADIOTHERAPHY EQUIPMENT AT ONE LARGE SWEDISH CANCER CLINIC, 1956-1970

	Annual number of treatments	
Year	*Using 250-kV and short-distance ^{226}Ra and ^{60}Co units*	*Using accelerators and telecurie units*
1956	49 582	0
1965	30 145	21 633
1970	11 281	46 941

Source: Reference 151.

3. Dose data in radiotherapy

136. Radiotherapy of non-neoplastic diseases has been reasonably well controlled and recorded. The radiation doses received by the skin of such patients are therefore reliably known. Information about the filters and tube voltages employed is less likely to be available. This is exactly the information required for deducing the penetration of the beam and hence the dose to organs below the irradiated skin surface. These doses will usually be less well known than the dose to the irradiated skin surface. Calculations of doses to an organ outside the direct beam will be less accurate, particularly if there is a possibility that the organ might on occasions be just outside or just inside the main beam. These variations may occur due to slightly different positions of the patient when the treatment is undertaken; for example, irradiation of children for thymic enlargement may have been carried out with the thyroid just in or just out of the beam (88) (see Annex G).

137. The complexity of the treatments and the generally somewhat higher doses delivered for neoplastic disease make careful dosimetric control a necessity, and,

TABLE 44. RADIOTHERAPY OF NON-NEOPLASTIC DISEASE:

	Head and trunk only							
	Children				*Adults*			
	Males		*Females*		*Males*		*Females*	
Condition treated	*Number*	*Mean dose (rad)*	*Number*	*Mean dose (rad)*	*Number*	*Mean dose (rad)*	*Number*	*Mean dose (rad)*
Skin conditions								
Growths	27	14.6	21	10.0	52	4.8	80	7.6
Allergic and inflammatory	10	10.8	13	23.3	201	10.4	230	7.9
Ringworm	5	92.0	1	62.5	2	36.0	–	–
Other	1	49.0	1	5.6	38	6.9	38	4.3
Glandular enlargements	–	–	2	6.2	7	5.5	1	5.9
Ankylosing spondylitis	–	–	–	–	70	83.6	14	59.5
Arthritic and rheumatic	–	–	–	–	23	27.1	29	22.0
Artificial menopause	–	–	–	–	–	–	74	51.5
Deafness	5	9.4	2	8.6	7	3.5	10	3.7
Other non-neoplastic	1	2.6	2	282.0	15	20.9	35	27.6

Source: Reference 37.

Note: The data in this table were produced by a computer programme that was adapted to make an approximate estimate of the bone-marrow dose from small treatment areas which receive high doses.

because of the need to provide a follow-up service, the records of such patients are generally well kept. It is, therefore, reasonably easy to determine the radiation doses to particular organs retrospectively. The potential groups of interest would be composed of patients with long survival after treatment.

4. Information of epidemiological interest

138. The following determinations of dose to given organs have been carried out for epidemiological surveys:

Bone-marrow dose and whole-body integral dose in the treatment of ankylosing spondylitis (39, 107, 269)

Dose to the stomach and pancreas in the treatment of ankylosing spondylitis (14)

Dose to the kidney in patients treated for stomach ulcers (35, 236)

Dose distribution through the head and neck for children treated for tinea capitis (2, 3, 4, 72, 159, 160, 199, 263, 264)

Thyroid dose for children treated for thymic enlargement (88)

Skin dose in patients treated for skin disease and neoplastic disease with rodent ulcers and basal cell carcinoma occurring in the treatment area (9, 237)

Bone-marrow dose in the treatment of metropathia haemorrhagica (45, 210).

139. As leukaemia has been associated with the irradiation of the bone marrow and a number of surveys of patients treated for non-neoplastic disease have reported an increase in the incidence of leukaemia, considerable effort has been made to derive bone-marrow doses. In its 1972 report, the Committee reproduced data from the British survey (37) on bone-marrow doses from treatment of non-neoplastic disease in the years 1957-1958, assessed by measurements and a computer programme (50). Since further information is lacking, these data are again presented in table 44 to illustrate the fact that the mean marrow doses may range from less than 1 to nearly 300 rad per treatment course, with values of about 10 rad not being infrequent. Recent measurements and calculations based on depth-dose studies published by Hashizume (76) provide tabular information from which the bone-marrow dose may be calculated for any particular radiotherapeutic treatment. Figure XVI shows the grid reference system used to indicate the particular part of the body that is irradiated. By selecting a particular pair of grid reference numbers in the first two columns of table 45 one can find, for the particular types of radiation given in the other column headings the values of direct plus scatter radiation $M + S$ and of the marrow dose T from the generalized leakage radiation from the source per unit of dose at the skin. These data are useful in that they give the values for 250-kV x rays, ^{60}Co gamma rays, 6-MV x rays and 15-MeV electrons. As predicted in earlier United Kingdom work, the marrow dose per treatment course calculated for 250-kV x rays tends to exceed the bone-marrow dose from any other energy source.

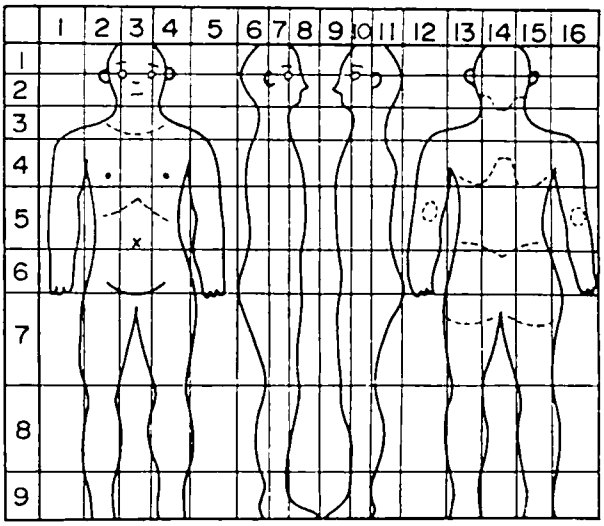


Figure XVI. Grid reference system for defining irradiation position (see tables 45 and 48) (76)

MEAN BONE-MARROW DOSE PER TREATMENT COURSE

All cases							
Children				*Adults*			
Males		*Females*		*Males*		*Females*	
Number	*Mean dose (rad)*	*Number*	*Mean dose (rad)*	*Number*	*Mean dose (rad)*	*Number*	*Mean dose (rad)*
91	4.3	125	1.7	110	2.3	185	3.3
26	4.2	18	16.8	600	3.5	578	3.2
6	76.0	2	31.3	4	18.0	3	18.0[a]
1	49.0	1	5.6	65	4.0	115	1.4
–	–	2	6.2	7	5.5	1	5.9
–	–	–	–	70	83.6	14	59.5
–	–	–	–	33	18.9	42	15.1
–	–	–	–	–	–	74	51.5
5	9.4	2	8.6	7	3.5	10	3.7
1	2.6	2	282.0	23	13.6	37	26.2

[a] Assumed male value in absence of data

TABLE 45. ACTIVE BONE-MARROW DOSE IN ADULTS IN DIFFERENT IRRADIATION CONDITIONS

(mrad per rad at the skin)

Irradiation position[a]		^{60}Co gamma rays		X rays				15-MeV electrons	
				Conventional		6-MV			
Vertical number	Lateral number	M + S	T	M + S	T	M + S	T	M + S	T
1	2, 4	290	250	280	30	295	150	200	175
	13, 15	300	370	350	35	305	250	200	180
	14	320	360	370	35	330	250	230	180
	3, 7, 10	295	240	360	30	320	170	230	135
2	2, 4	70	265	95	30	75	180	25	130
	13, 15	70	380	95	40	75	260	25	195
	3	140	305	180	45	150	300	0	105
	7, 10, 14	180	360	220	45	175	340	30	220
3	3, 7, 10, 14	120	385	170	40	125	260	0	195
	1, 5, 12, 16,	25	340	35	30	30	235	0	175
	13, 15	45	450	70	45	50	300	25	220
	2, 4	40	380	55	35	45	265	25	190
4	2, 4	230	505	315	40	235	340	100	260
	13,15	250	560	320	50	255	380	100	300
	3	500	475	710	50	510	315	200	250
	14	750	530	1 200	55	760	350	650	285
	12, 15, 16	120	380	170	40	120	255	20	200
	6, 7, 10, 11	200	300	240	30	205	210	220	170
5	6, 7, 10, 11	260	285	380	30	270	195	0	145
	14	830	345	1 350	55	840	380	105	290
	3	480	425	700	40	485	285	0	220
	13, 15	60	340	85	50	60	365	0	265
	2, 4	65	415	90	40	70	285	0	210
	1, 5, 12, 16	50	385	70	40	55	260	0	190
6	6, 7, 10, 11	330	345	430	30	335	235	230	175
	14	720	595	1 150	60	730	400	95	300
	3	370	475	520	45	375	320	0	230
	13, 15	340	680	490	60	345	320	300	340
	2, 4	160	440	220	40	165	160	30	220
	1, 5, 12, 16	50	385	70	35	50	300	0	170
7	3, 14	70	395	95	40	70	195	0	210
	2, 4, 7, 10, 13, 15	70	290	95	30	70	160	30	150
8	2, 4, 7, 10, 13, 15	1	235	5	25	1	26	0	115
9	2, 4, 7, 10, 13, 15	0	40	0	10	0	0	0	26

Source: Reference 76.

Note: See paragraph 139 for an explanation of the use of this table.

[a] As defined by the grid reference system in figure XVI.

140. The *per caput* marrow dose (CMD) and dose weighted for the incidence of leukaemia (LSD) in the remainder of the patient's life were 206 and 37 mrad, respectively, for the practice in Japan during 1971. Table 46 shows that the contributions to the CMD were about 60 per cent from ^{60}Co units, 30 per cent from accelerators and 10 per cent from conventional x-ray machines. The skin treatment of non-neoplastic disease gives only 1.3 per cent of the total CMD (table 46). The use of the product of the average dose and the number of patients treated is a better measure of the possible detriment to the irradiated group than the *per caput* dose to the whole population. The average bone-marrow dose was 120 rad to the 177 000 patients treated for neoplastic disease and 0.15 rad to the 1 965 000 patients treated for non-neoplastic disease. This latter dose may be compared with the average dose from the treatment of non-neoplastic disease in the United Kingdom in 1957-1958 of 103 rad to the 6000 persons treated (37).

141. The number of patients treated by brachytherapy in Japan (78) in 1974 was 21 650 (table 47a). The population doses are given in table 47b, the CMD and LSD being 43 and 7.7 mrad, respectively.

142. The average doses and the sizes of the patient populations studied in some epidemiological surveys are to be found in Annex G.

5. Genetically significant dose

143. The gonad dose and GSD received from radiotherapeutic practice was given in the 1962 and 1972 reports for a few countries. The GSD from the treatment of non-neoplastic disease ranged from 0.9 to 12.1 mrad; of neoplastic disease, from 0.5 to 2.5 mrad. Recent data by Hashizume (75, 77) are in the form of a tabulation of the gonad dose for different kinds of radiotherapeutic irradiation (table 48). The doses are given in terms of the leakage radiation L and the scattered radiation S per field area of 100 cm^2, and in some cases in terms of the primary beam.

144. The GSD in Japan for 1971 from the treatment of non-neoplastic disease was 0.7 mrad; of neoplastic disease, suitably corrected for the expected number of children in these ill patients, 0.26 mrad. The GSD

TABLE 46. *PER CAPUT* MARROW DOSE (CMD) AND LEUKAEMIA SIGNIFICANT DOSE (LSD) IN JAPAN, 1971

(mrad)

Source	Age (y)	Male		Female	
		CMD	LSD	CMD	LSD
^{60}Co gamma rays	⩽ 14	1.5	0.71	0.93	0.30
	15-29	1.1	0.33	3.2	0.80
	30-44	4.2	0.87	28	5.0
	⩾ 45	20	2.0	70	11.5
	Subtotal	27	3.9	102	18
Conventional x rays (HVL Cu 0.5-2 mm)	⩽ 14	0	0	0.12	0.03
	15-29	0.42	0.10	0.30	0.09
	30-44	0.26	0.04	0.86	0.17
	⩾ 45	1.6	0.12	5.2	0.91
	Subtotal	2.3	0.26	6.5	1.2
Superficial x rays (HVL Al < 2 mm)	⩽ 14	0.37	0.37	0.59	0.59
	15-29	0.19	0.19	0.98	0.97
	30-44	0.03	0.03	0.34	0.23
	⩾ 45	0.019	0	0.15	0.04
	Subtotal	0.61	0.59	2.1	1.8
High-energy x rays (4-30 MV)	⩽ 14	0.74	0.36	0.72	0.19
	15-29	0.37	0.13	4.0	0.83
	30-44	1.2	0.25	8.0	1.6
	⩾ 45	7.0	0.62	35.6	5.9
	Subtotal	9.3	1.36	48.4	8.5
High-energy electrons (8-35 MeV)	⩽ 14	0.33	0.29	0.10	0.04
	15-29	0.007	0.004	0.21	0.13
	30-44	0.26	0.051	0.60	0.19
	⩾ 45	5.5	0.14	1.5	0.38
	Subtotal	6.0	0.48	2.4	0.74
	Total	45	6.6	161	30

Source: Reference 76.

TABLE 47a. POPULATION DOSE FROM BRACHYTHERAPY IN JAPAN, 1974

Number of patients by sex, age, radiation source and source position

	Male	Female	Total
Age (y)			
⩽ 14	400	1 320	1 720
15-29	180	460	640
30-44	560	3 240	3 800
⩾ 45	1 720	13 770	15 490
Radiation source			
^{226}Ra	1 120	9 780	10 900
^{222}Rn	280	210	490
^{137}Cs	160	1 400	1 560
^{60}Co	260	5 910	6 170
^{90}Sr	1 040	1 490	2 530
Source position			
Mouth	1 590	1 000	2 590
Maxilla	70	270	340
Neck	70	70	140
Breast	40	110	150
Cervix	–	13 000	13 000
Femur	40	0	40
Other	1 050	4 340	5 390
Total	2 860	18 790	21 650

Source: Reference 78.

contributions from treatments by various types of apparatus and by age group are given in table 49, and the distributions by age for neoplastic and non-neoplastic diseases are given in table 50. The GSD from brachytherapy in 1974 was estimated to be 0.012 mrad (table 47) (78).

145. The GSD from the treatment of non-neoplastic disease in the region of Munich (Federal Republic of Germany) has been estimated. One report (198) estimates that the contribution to the GSD in clinics is 0.4 mrad, and the other (197) estimates that the contribution in private practice is 0.2 mrad. These

TABLE 47b. POPULATION DOSE FROM BRACHYTHERAPY IN JAPAN, 1974

GSD, CMD and LSD by sex and age

	GSD (10^{-3} mrad)		*CMD (mrad)*		*LSD (mrad)*	
Age (y)	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*
⩽ 14	10.7	1.033	0.077	0.120	0.075	0.119
15-29	0.003	0.155	0.415	0.144	0.088	0.081
30-44	0.465	0.001	6.390	0.100	1.327	0.031
⩾ 45	0	0.001	33.280	2.724	5.469	0.493
Subtotal	11.178	1.190	40.149	3.088	6.959	0.724
Total	12.4		43.2		7.7	

Source: Reference 78.

TABLE 48. GONAD DOSE IN ADULTS IN

(mrad per rad

				X rays			
		^{60}Co gamma rays		*HVL 1.5 mm Cu*		*HVL 1.0 mm Al*	
Irradiation position[a] (V-L)	*Sex*	L	S	L	S	L	S
4-2	M	0.75	0	0.08	0	0.04	0
	F	0.55	0.01	0.04	0	0.01	0
6-2	M	1.2	0.06	0.07	0.13	0.05	0.07
	F[b]	420	1.3	125	2.4	12	0.25
7-3	M[b]	960	0.03	820	0.25	800	0.2
	F	1.0	0.11	0.03	0.25	0.05	0.14

Source: Reference 75.

Note: L = leakage radiation; S = scattered radiation.

[a] See figure XVI.

[b] The values in this line are the gonad doses due to the primary beam (of zero area).

TABLE 49. GENETICALLY SIGNIFICANT DOSE IN JAPAN, 1971

Breakdown by source, age and sex

(mrad)

Source	*Age (y)*	*Male*	*Female*	*Total*
^{60}Co gamma-ray units	⩽ 14	0.047	0.046	
	15-29	0.088	0.018	
	30-44	0.030	0.011	
	⩾ 45	0.000	0.000	
	Subtotal	0.17	0.075	0.245
Conventional x-ray units (HVL 1.5 mm Cu)	⩽ 14	0.000	0.010	
	15-29	0.013	0.000	
	30-44	0.002	0.000	
	⩾ 45	0.000	0.000	
	Subtotal	0.015	0.010	0.025
Superficial x-ray units (HVL 1.5 mm Cu)	⩽ 14	0.030	0.31	
	15-29	0.002	0.34	
	30-44	0.001	0.002	
	⩾ 45	0.000	0.000	
	Subtotal	0.033	0.65	0.683
High-energy x-ray units (4-30 MV)	⩽ 14	0.003	0.007	
	15-29	0.011	0.004	
	30-44	0.000	0.000	
	⩾ 45	0.000	0.000	
	Subtotal	0.014	0.011	0.025
High-energy electron accelerators (8-35 MeV)	⩽ 14	0.000	0.000	
	15-29	0.000	0.000	
	30-44	0.000	0.000	
	⩾ 45	0.000	0.000	
	Subtotal	0.000	0.000	
	Total	0.23	0.75	0.98

Source: Reference 75.

TABLE 50. GENETICALLY SIGNIFICANT DOSE IN JAPAN, 1971

Breakdown by type of disease, age and sex

(mrad)

	Male		*Female*	
Age (y)	*Non-neoplastic*	*Neoplastic*	*Non-neoplastic*	*Neoplastic*
⩽ 14	0.041	0.039	0.31	0.061
15-29	0.006	0.097	0.34	0.022
30-44	0.001	0.029	0.002	0.011
⩾ 45	0.000	0.000	0.000	0.000
Total	0.048	0.17	0.65	0.094

Source: Reference 75.

estimates may be compared with the 1961 estimate by Holthusen *et al.* (94), which was 2.2 mrad from both clinic and private practice.

B. THERAPEUTIC USES OF RADIOPHARMACEUTICALS

146. The therapeutic use of radiopharmaceuticals is mainly restricted to the use of ^{131}I for the treatment of hyperthyroidism, heart disease and thyroid cancer and the use of ^{32}P for the treatment of polycythemia vera. In the 1950s and early 1960s, colloidal solutions of ^{198}Au were used for serious pleural and peritoneal effusions and the patients concerned usually had limited prognosis. However, the use of this form of treatment has mainly been discontinued. The frequencies of treatments reported in West Berlin in 1970 and 1975 (93), in Sweden in 1974 and 1969 (151) and in the United States in 1966 (248) are given in table 51.

1. Iodine-131 therapy for hyperthyroidism and heart disease

147. The main use of ^{131}I therapy is for the treatment of hyperthyroidism; in the United States in 1966 (248), about three quarters of all patients treated with ^{131}I were in this category. The administered activity is usually in the range 2-10 mCi and sometimes repeated

DIFFERENT IRRADIATION CONDITIONS

at the skin)

				Electrons			
20-MV		*8-MV*		*25-MeV*		*15-MeV*	
L	S	L	S	L	S	L	S
0.3	0	0.15	0	0.05	0	0.04	0
0.2	0	0.1	0	0.03	0	0.02	0
0.4	0	0.2	0	0.1	0	0.04	0
750	0.02	650	0.04	400	0.24	0.04	0
780	0	720	0.03	1 000	0	1 000	0
0.3	0.03	0.2	0	0.1	0	0.06	0

administrations are given. A thyroid dose of about 4000 rad is often used as the treatment objective. The bone-marrow dose per unit of administered activity received has been estimated as 1.7 rad mCi^{-1} (68) and the gonad dose as 0.45-0.6 rad mCi^{-1} (19). For the treatment of heart disease, the activities are usually about 25 mCi, with similar bone-marrow and gonad doses per unit of administered activity.

148. Surveys were made by Pochin (167), Saenger (194) and Werner *et al.* (262) in populations of 59 000, 36 000 and 32 000 patients, respectively, who had received ^{131}I for the treatment of thyrotoxiosis. Typical mean bone-marrow doses of 7-15 rad had been received. The approximate total collective dose to the bone marrow in these three series would therefore be 1.4 10^6 man rad, assuming a mean dose to the bone marrow of 11 rad.

2. Iodine-131 therapy for cancer of the thyroid

149. For the treatment of cancer of the thyroid, a very high initial activity, often about 200 mCi, is administered. Subsequently, in order to suppress any further thyroid activity or to destroy any metastatic spread of the cancer, further administrations are given, often of the order of 100 mCi. Because these subsequent centres have very little uptake, most of the administered activity is excreted in the urine. The initial dose to the bone marrow per unit of administered activity is 1.7 rad mCi^{-1} (130), but subsequent administrations will give lower doses (169).

TABLE 51. RECENT SURVEYS OF THE FREQUENCY OF THERAPY WITH RADIOPHARMACEUTICALS

(Number of treatments per 1000 of population)

Radio-pharma-ceutical	*Disease treated*	*West Berlin*		*Sweden*		*United States*
		1970	*1975*	*1969*	*1974*	*1966*
^{131}I	Thyroid diseases	0.172	0.132	0.235	0.294	0.127
^{32}P	Polycythemia vera	0.011	0.015	0.031	0.038	0.017
Other		0.097	0.113	0.011	0.012	0.028
	Total	0.28	0.26	0.28	0.34	0.17

Sources: References 93, 151, 248.

150. Pochin (168) has reviewed a group of 215 patients who had been treated for inoperable thyroid carcinoma during the period 1949-1967. The group was studied in relation to the subsequent cancer risk. The collective dose to the bone marrow in the group was 27 000 man rad. It should be noted that cancer of the thyroid can be treated successfully, and patients often survive many years after the first treatment.

3. Polycythemia vera patients treated with ^{32}P

151. The treatment of polycythemia vera consists of repeated administrations of ^{32}P over a period of years at

activities of 4-8 mCi. The bone-marrow dose is 30 rad mCi^{-1} for intravenous administration. The gonad dose is in the range 2.6-7.0 rad mCi^{-1} (133). High mean bone-marrow doses of the order of 600 rad per treatment may be received (34, 214).

152. Modan and Lilienfeld (145) show that the collective dose for such patients treated by ^{32}P is sufficiently high to make epidemiological studies interesting. Of an original series of 1222 cases, 228 were treated by ^{32}P. The collective dose to the bone marrow for the group of 228 cases was 132 750 man rad.

153. Details of further studies are contained in Annex G.

IV. WASTE DISPOSAL OF MEDICALLY USED RADIOPHARMACEUTICALS

154. Much of the short-lived activity incorporated in radiopharmaceuticals used in a diagnostic investigation decays either before or during the investigation, and only a small fraction of the total activity is eventually disposed of as waste. The principal route of disposal is as liquid waste. However, therapeutically used radiopharmaceuticals do provide a substantial source of waste activity, particularly in the treatments using ^{131}I. In the case of treatments for hyperthyroidism, some 30 per cent of the activity may be released in the urine. Following the first treatment of a cancer of the thyroid, some 50-60 per cent of the administered activity (about 100 mCi) will be excreted in the urine. Further treatments, particularly of metastases, lead to the excretion of about 90 per cent or more of the administered radioactive iodine. In some countries the urine from such patients is not stored but is released as liquid waste into the sewers.

155. Few countries have complete records of the activity released to the sewers from medical establishments. The total activity administered to the patients may be used as an upper estimate. In Denmark, the total use of radionuclides has risen from 181 Ci in 1970 to 298 Ci, in 1974 (220), the total activity remaining after one year being 48 Ci and 15 Ci, respectively. The total use of ^{131}I has remained steady at about 20 Ci per year. By using the frequency data in the Danish report (53) and assuming that on the average 5 mCi of ^{131}I was used in each hyperthyroid treatment and 200 mCi in each cancer patient, one can account for about 13 Ci of ^{131}I, of which about 8 Ci would probably be excreted as urine into the sewers.

156. It is difficult to estimate the radiation doses received by the public from such releases. However, the families of the patients would be those who would be at greatest risk, and they would also receive a radiation dose directly from the activity remaining in the patient. Estimates of this dose have been made by Stieve and Kaul (227).

V. CONCLUSIONS

157. Diagnostic radiology in many technically developed countries has been growing at a rate between 5 and 15 per cent per year. Because of increasing medical requirements, the growth rate in developing countries is likely to be greater. The use of radiopharmaceuticals for diagnostic purposes has been expanding rapidly over the last decade, and many countries are reporting a doubling of the number of tests every three to five years. Radiotherapeutic practice indicates that less treatment is being carried out for non-malignant conditions using radiation, while treatment for malignant conditions is now primarily carried out using high-energy radiation from accelerators or teletherapy units.

158. Considerable information is now available on radiation doses to the skin and the gonads received in individual x-ray examinations, while the knowledge about doses to bone marrow and some other organs is currently expanding. Further information is still required, however, particularly in the case of specialized examinations. With this further knowledge it will be possible to assess the detriment that may be associated with such examinations. Consideration would then have to be given to the basis for the comparison of the benefits that are received by a patient with the estimated detriment.

159. A satisfactory amount of information is now available regarding the radiation doses to organs received during investigations involving the use of radiopharmaceuticals. In general, these doses to particular organs are of the same order or smaller than those incurred during x-ray examinations of the same region or function.

160. Published recommendations of a number of national and international bodies have made available useful information about methods of reducing radiation doses to patients, but the implementation of these recommendations is not yet universal. There is a need to encourage the estimation of the radiation doses received by organs during medical radiological procedures as a means of identifying those practices likely to give rise to high patient doses.

161. Studies of the frequency of examinations should be combined with studies of organ doses to provide collective dose estimates for each technique and investigation. Collective doses may then be used to assess relative detriments, with some limitations due to the range of individual doses, the age group and the effects under consideration. Suggestions as to possible groups of patients that may be at greater risk have been made on the basis of the known radiation doses, and further studies of this type would be of particular interest for epidemiological research.

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ANNEX G

Radiation carcinogenesis in man

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Introduction

1. In assessing the harm that might result from any form of human exposure to ionizing radiation, it is necessary to identify the types of injury that may be caused and to estimate the frequency with which each will occur following a given radiation exposure. Since the radiation may involve the whole body more or less uniformly or individual organs or tissues selectively, it is necessary to examine the sensitivity of the different tissues as well as of the body as a whole. Moreover, to be of value in estimating the effect of environmental or

occupational exposures, the estimates should be applicable over a range of doses down to very low ones delivered either at low dose rates, or in separate repeated fractions delivered at high or low dose rates.

2. There is increasing evidence that in human beings (as in animals; see Annex I, paragraph 26), the induction of malignancies represents the most important effect produced at low doses in the exposed individual, and the frequency with which such changes are induced in different tissues has been examined by the Committee in its previous reports. It is at present impossible to deduce these frequencies of radiation carcinogenesis in man from experimental work in animals (see Annex I, paragraph 5). The following review, therefore, is of estimates of the induction of malignancies by radiation that can be derived from studies of human populations in which the whole body or individual organs have been irradiated; it is intended to update information presented in the 1972 report of the Committee.[1]

I. GENERAL CONSIDERATIONS

3. The strength of the available information depends heavily upon the consistency of estimates obtained under different conditions, even though individual estimates may be subject to a variety of defects. Optimally, a valid estimate of the carcinogenic effect of radiation on a given tissue will depend upon the following factors:

(a) Study of the irradiated population over a prolonged period of several decades after exposure during which malignancies may become detectable;

(b) A criterion of diagnosis which ensures that all malignancies induced or all fatalities from such malignancies are recorded;

(c) Knowledge of the absorbed dose and dose rate, or any fractionation of the dose, and of the variation of absorbed doses in different individuals;

(d) A sufficiently uniform distribution of dose through the body or through the tissue of interest;

(e) A valid control population;

(f) A number of malignancies in the irradiated population sufficient to give statistical reliability to the excess over that expected on the basis of the control population;

(g) An adequate basis for comparing the carcinogenicity of radiations of different quality at different dose levels.

[1] In this Annex, the term "carcinogenesis" is used to include the induction not only of carcinoma but also of leukaemia or any other form of malignancy (sarcoma, lymphoma etc.). The word "malignancy" is used when the reference is to all such malignant conditions, including leukaemia as well as solid cancers, since "cancer" or "malignant tumour" should refer only to solid or focal malignancies. The term "tumour" is used without qualification when it is either clear from the context, or unimportant, whether a malignant or a benign tumour is intended.

A. LENGTH OF SURVEY AND LATENT PERIOD FOR DEVELOPMENT OF MALIGNANCIES

4. It has repeatedly been shown that after radiation exposure, malignant tumours may continue to become detectable in excess in the exposed population for long periods, often several decades. Much of the "latent period" observed in practice between the exposure and the detection of a tumour must be due to the time required for sufficient increase in size of the tumour to make it detectable. The estimated mean latency of a given type of tumour will therefore depend in part upon the methods used to detect it and upon the closeness of surveillance of the exposed population. It will depend upon the rate of cell division, cell survival and forms of local spread or metastasis of the particular type of tumour. It will also depend upon the ease of examination of the organ in which the tumour arises, detection of a small tumour obviously being much more efficient in the thyroid than, say, in the liver or pancreas. In statistics based on mortality from tumours, the interval between irradiation and death will vary also with the widely differing speed at which different clinically diagnosable tumours cause death, and this may depend on the forms of treatment available. It is uncertain whether part of the latency is also due to any form of induction period before the initially affected cell or cells start to divide and form a tumour, or before the tumour assumes "malignant" characteristics of growth and spreading. It is clear from some investigations in animals that at short intervals after irradiation the thyroid gland is found to contain tumours that are only of "benign" histological character (22), and that malignant tumours become detectable at later stages. In a recent detailed study in man (58) on the other hand, this sequence was not evident, benign tumours being detected after a longer latency, particularly in males, than malignant tumours. Some biological transition period may indeed be involved, as well as the simple growth of an initially malignant tumour to detectable size. It has, however, been shown that lung tissue from irradiated rats may show no tumours detectable by serial sectioning at short intervals of 2-3 months after exposure. Yet if sections of these lungs are transplanted into mice of a type lacking the immune mechanisms that would prevent the growth of transplanted tissues, characteristic tumours develop in the recipient mice, showing that abnormal processes are in fact acting in the irradiated lung earlier than it is practicable to detect them, even by detailed microscopic examination (79).

5. The progressive increase in size which causes human tumours to become detectable is likely to depend, as in animals (see Annex I, paragraph 74), upon the rate of tumour cell division and the balance between processes of cell production and cell destruction. The estimated "doubling time" differs widely for tumours of different types, in man as well as in animals.

6. The mean latency and the distribution of latent periods of any type of tumour may thus depend upon a number of factors characteristic both of the tumour and of the circumstances of surveillance and ascertainment in the exposed population (Annex I, para. 105). Moreover, in some instances the latency of tumour development appears to depend upon the age of the person irradiated

(for example as discussed later for thyroid and breast cancers), and the latency for development of tumours is certainly short following irradiation of the foetus *in utero* (148). It is also likely that latency may vary with the size of the absorbed dose, as appears to be the case for example for osteosarcomas following radium-226 incorporation in the skeleton (41) and for thyroid cancers following external irradiation (58), although apparently not significantly for leukaemia resulting from A-bomb irradiation at Hiroshima and Nagasaki (para. 64 and table 3). A similar variation of latency with dose is observed with chemically induced cancers in animals. In all such studies it is of course important to base conclusions upon the mean latency, or the latency for a given percentage of tumours, as studied over prolonged periods after irradiation. The "latent period" that elapses until the first tumour is detected will, on purely statistical grounds, be shorter after large doses than after smaller ones if larger doses produce larger numbers of tumours and if tumours appear after varying time intervals. The relationship between latency of tumour detection and dose size in experimental carcinogenesis is discussed in detail in Annex I (para. 109).

7. The distribution of latent periods for different tumours cannot therefore be expected to conform to any single relationship of frequency with time (7). Additional cases of cancer apparently induced by radiation may however continue to be detected for at least 30 years following exposure. Estimates of the carcinogenic effect of radiation, based on shorter periods of observation, may thus require correction, and no reliable distribution curve of latencies may be available on which to base an exact correction factor. For leukaemia, several surveys are now sufficiently prolonged from the time of exposure to demonstrate that further cases are ceasing to be detected. The distribution of latent periods under the conditions of exposure and ascertainment of those surveys can thus be defined. In particular, data published by the Japanese Life Span Study indicates that by 1972 the incidence of leukaemia in exposed survivors was close to that in the comparison group (see paragraph 63). From the data of Moriyama *et al.* (97), the mean time interval from irradiation to death has been about 14 years (see table 3).

8. For other malignancies, apart from those following irradiation *in utero*, no prospective survey appears yet to have been sufficiently prolonged to record all malignancies attributable to the exposure. The Life Span Study survey shows a small reduction in the rate at which excess deaths from malignancies other than leukaemia were occurring during 1970-1972 as compared with earlier periods (in those exposed at over 10 rad T65 in both cities, both sexes and all ages, in excess of the comparison populations (97); see paragraph 239), but this fall is not statistically significant.

9. Nor is the necessary information available from any retrospective survey (for example, of the date of radiation exposure of subjects subsequently diagnosed as developing cancers that are presumed to be radiation-induced). In such cases the distribution of latency would be unbiased only if the frequency of significant irradiation in the population within which the diagnoses were made had remained constant for long periods (e.g. 50 years) and if the likelihood of ascertainment and presentation for diagnosis were independent of time since irradiation (apart from the possibility of prior death from other causes, for which correction could ordinarily be made). These conditions fail in many cases (for example, as discussed later for the development of thyroid malignancies following thymic irradiation), since this procedure was practised only for a limited period, largely prior to 1960, and the distribution of observed latencies is probably still truncated by exclusion of the longer latent periods. Similarly, many "retrospective-prospective" surveys (for example, of the late effect of a period of radiotherapeutic practice), will underestimate latency until they have been continued for several decades after the period of the practice.

10. In many instances, particularly of the latency with which tumours are detected after irradiation of patients of different ages, no correction is in fact made for diminution of the exposed population due to death from other causes. This results in an underestimation of the number of long latencies that would otherwise be observed, particularly in studies on those irradiated at older ages.

11. Values quoted as mean latencies for tumour detection are, however, unlikely to overestimate the true value, and certain surveys indicate that this value must be large, at least for some types of malignancy and conditions for ascertainment. A number of the published estimates of mean latency of radiation-induced malignancies give values exceeding 20 years (table 1).

TABLE 1. EXAMPLES OF LONG MEAN LATENCIES RECORDED FOLLOWING THERAPEUTIC IRRADIATION

Reference	*Number of subjects*	*Site of cancer*	*Mean latency (years)*
30	20	Thyroid	20.3
89	10	Bladder	20.7
168	10	Breast	22.6
105	9	Various, on head and neck	22.8
47	37	Pharynx and larynx	23.4
77	113	Various, on head and neck	24.1
4	38	Skin	24.5
121	10	Pharynx	25.0
167	130	Pharynx and larynx	27.3
147	40	Skin (basal cell)	41.5

12. As an approximation in the absence of better information, it seems appropriate therefore to assume a median latency of about 25 years, so that the total of cancers diagnosed within this time after radiation, at least in young subjects with a long life expectancy, may represent about half of all cancers likely to have been induced. Data on otherwise undiagnosed cancers found at operation on the thyroid 24 years after neck irradiation in childhood support this estimate (see paragraph 133).

B. ASCERTAINMENT

13. Problems of complete or correct ascertainment arise in a number of surveys referred to below, on which risk estimates depend. Moriyama and his colleagues (97) emphasize that, although death certification diagnostic of carcinoma is about 90 per cent accurate, the accuracy of specification of particular sites is much less precise. Their analysis has therefore been limited to sites where the accuracy of specification is high. The reliability of death certification of primary malignant tumours of bone is also regarded as being poor in many countries, owing to death from carcinomatosis with metastases to bone often being recorded as due to primary bone tumours. This difficulty is likely to apply also to a number of other organs in which metastases from tumours of other tissues commonly occur, and death certificates may give quite unreliable information as to the primary site of cancer development.

14. In surveys based on malignant tumour incidence rather than on mortality, retrospective analyses can sometimes be reliably based on efficient tumour registries. Modan (92) however, points out that his estimates for the frequency of tumours that can commonly be removed by operation, such as those of the thyroid and skin, are likely to be underestimates, since the National Israeli Tumour Registry only came into operation 11 years after the start of the irradiations he studied and his additional check through death certificates did not detect the incidence of these operable tumours. The lack of estimates for skin tumour induction, in general, is probably due to the ease with which these tumours can be removed surgically as soon as they are diagnosed, as well as to the low incidence of such tumours when only small skin areas are irradiated.

15. In the thyroid, the ease with which small nodules can be detected implies that ascertainment is likely to be high in a population under close surveillance because of a known previous radiation exposure. Thus for example, the Marshall Islands populations exposed by fallout are examined annually and operation is suggested if palpable thyroid nodules develop. Indeed, if it is the case that in the thyroid, radiation-induced malignant tumours may develop from nodules which initially are histologically benign, this surveillance involves, as intended, a reduced risk of the development of malignant tumours.

16. On the other hand, the frequent lack of symptoms or distinctive signs from small malignant nodules of the thyroid may imply that the incidence of thyroid cancers is also underestimated in populations which are not repeatedly examined medically, since these tumours may not progress to cause death. This applies particularly to the so-called "occult sclerosing papillary" thyroid tumours. For the purposes of risk estimation, however, the omission of tumours which do not even become clinically detectable during life, is of doubtful importance.

17. In the case of most types of cancer discussed in this Annex, an average of less than 25 per cent of patients remain alive 15 years after detection of the cancer—at least as judged by the survival statistics of patients with "naturally occurring" cancers of those types. In a few forms of cancer however, prolonged survival is common, whether because of the effectiveness of surgical or other treatment, or because of slow progress of the cancer. In most cases, the accuracy of present risk estimates of cancer induction is insufficient to justify the separate estimation of fatal and non-fatal cancer induction. The following values were observed (124) for the percentage of patients registered as having developed cancer in 1954 in England and Wales and who were surviving after 15 years (values quoted are means for males and females): leukaemia, 2; lung, trachea and bronchus, 3; myeloma, 10; brain and nervous system, 13; bone, 20; large intestine, 24; rectum, 24; bladder, 25.

18. The thyroid average value, 28 per cent, results essentially from the very short survival of patients with anaplastic cancers (50-per-cent survival after 3 months (115)). The type of thyroid cancer induced by radiation, however, an adeno-carcinoma arising from follicular cells, has an unusually slow progress and a high cure rate, and here the difference between risks of cancer induction and of fatal cancer induction is very large (see paragraph 150). For the female breast and for the uterus also, the 15-year survival rates are substantial, and are estimated as 29 and 55 per cent respectively, while that for the salivary glands is 70 per cent.

C. INFORMATION ON ABSORBED DOSE

19. A number of epidemiological surveys demonstrate the occurrence of radiation carcinogenesis but cannot be used in risk estimation because the size of the original doses is not known. It is important to recognize, however, that these surveys may still have considerable value if a number of different organs can be assumed to have received about equal doses. Given an equally efficient ascertainment of tumours arising in these organs, therefore, they can be graded quantitatively for relative sensitivity to tumour induction. If, moreover, the carcinogenic risk is known for one, inferences can be drawn for the others. Thus, it may be possible to infer the sensitivity of the salivary glands from the ratio of salivary cancers to thyroid cancers following neck irradiation and from independent data on thyroid sensitivity.

20. It is equally valuable to identify the tissues in which no tumours develop when tumours do occur in equally irradiated organs, and so to establish an upper limit to the risk for relatively insensitive tissues. This inference can of course only be made if it is clear that the information examined is not selectively reporting only tumours of significantly increased incidence.

21. In some instances, dose estimates are only obtainable on a very indirect basis. Thus for example, the external irradiation estimates of the thyroid glands of the Marshall Island populations (paras. 108-111) are derived from measurements which began within a few days of the start of exposure and a theoretical basis for extrapolation to deduce earlier doses. The internal doses from concentration of radioiodine in the gland, however, are largely based on the activity that was being excreted in the urine subsequent to the ingestion of the

radionuclides and from data on the likely relationship between excretion rates and retained activity at a given interval after the period of ingestion.

22. In some instances of non-uniform internal radiation, there may be uncertainties as to dose distribution or as to the tissues over which absorbed doses should be averaged. Thus, it has become evident that osteogenic sarcomas arise mainly from the endosteal cells of bone and that the dose as averaged over tissues lying within 10 μm of the bone surface is the relevant one, while the mean dose throughout the bone is not. Thus, it is necessary to use different models for dosimetric calculations for short-lived radionuclides like radium-224, from which most of the energy of disintegration is given up while the isotope is still present at its initial site of deposition on bone surfaces, and for long-lived nuclides like radium-226, which become distributed throughout bone during the course of their disintegration. Materials with long effective half-lives in tissue present further problems in determination of the dose relevant to risk estimation, since it cannot be known how much of the dose delivered during the long latent period of any tumours that occur is relevant to tumour induction and how much is "wasted radiation" occurring during the subsequent development of an established tumour.

23. The occurrence of osteosarcomas following incorporation of radium-226 is associated with the development of about one third as many carcinomas arising from the comparatively small mass of mucous membrane which covers bone surfaces in the mastoid and other intracranial cavities (41). It is not possible at present, however, to deduce the sensitivity of such membranes to carcinogenesis, since radon is formed from the radium and retained in these cavities in concentrations that are at present still undetermined, and the relevant dose is therefore unknown.

24. Rather similar problems arise in connection with the carcinogenicity of "thorotrast" where the incidence of tumours in the liver (mainly cholangio-endotheliomas) can be related to the level of concentration of the thorium dioxide in the liver. The sensitivity of the liver to radiation carcinogenesis cannot be established with certainty, however, for several reasons. Particles of the thorium dioxide tend to aggregate and produce necrosis of the immediately surrounding tissue, so that much of the alpha radiation is absorbed either in dead cells or in the particles themselves. Moreover, it remains possible, although not likely, that the chemical properties of the thorium dioxide, as well as the radiation emitted by the thorium and its daughter products, contribute to its carcinogenicity (see paragraph 283).

25. The problems in deriving a risk per unit absorbed dose for lung tissue from statistics of lung cancer development in uranium miners are similar, since the doses to the bronchi and alveoli of the lung depend critically upon the deposition and location of products of radon decay. Although a relationship is established between the radon concentration in air samples in mines and the mortality amongst miners who have worked in them, any radiation risk estimates derived for lung tissues as a whole are necessarily indirect.

26. Problems of a different type arise in attempting to derive the risk per unit absorbed dose of tissue exposure to radiations of low linear energy transfer (LET) from observations, for example, on the populations exposed at Hiroshima to mixed neutron and gamma radiation. The greater carcinogenicity of neutrons than of gamma radiation per unit absorbed dose, as shown in various experimental studies in animals, prevents any simple inference of the frequency of tumour induction per unit of energy absorbed (but see paragraphs 48 to 61). It has indeed been suggested (94) that certain types of malignancy may be preferentially induced by radiation of high LET.

27. Even in the analysis of effects of medical exposure to low-LET radiation there may be difficulties in estimating the likely absorbed dose, for example in the lung, resulting from known skin exposure with specified field size and position. The absorbed dose in bone from radiation of low energy may also be particularly difficult to estimate with confidence.

D. SUITABILITY OF DOSE LEVEL AND DOSE DISTRIBUTION

28. Valuable information has been derived from epidemiological studies of patients previously treated for ankylosing spondylitis by local irradiation of affected parts of the spine. These studies show an increase in cancer in certain organs that are likely to have been heavily irradiated as a result of their frequent inclusion in the direct beam. These increases, or at least those following single courses of therapy, can potentially be used to evaluate the sensitivity of these organs, once estimates are made of the dose they will have received and if due allowance can be made for the likely normal incidence of different forms of cancer in this condition.

29. Estimates have also been made of the frequency with which leukaemia is induced by this treatment. These estimates have then been related to the mean absorbed dose to the bone marrow by averaging, throughout the total mass of the marrow, the dose delivered to the fractions of marrow irradiated in the various treatments (see paragraphs 78-80 and 83-84). Such estimates of leukaemia induction per unit dose as averaged over the whole marrow are not unduly discrepant with those derived from conditions of more or less uniform marrow irradiation. It must be recognized, however, that these conditions involve an entirely non-uniform exposure of the tissue at risk and that, on biological grounds, there is ample evidence that the protection of a small volume of marrow from irradiation may allow "recolonization" of irradiated marrow by unirradiated marrow cells, and that this is of importance to continued marrow function, at least following high local exposures.

30. These difficulties may, however, be more apparent than real if carcinogenesis is related to events induced by radiation in single cells or small groups of cells without significant reaction between affected and unaffected cells. To the extent that this is true, we are concerned with the number of cells involved and with the estimated dose to each. In this way it may be valid to use

observations in which, for example, part of the gut or part of the total skin area has been irradiated to derive estimates for the carcinogenic effect of irradiating the whole gut or the whole skin.

31. It may be noted that a gross non-uniformity of the irradiation of cells of an organ will always occur with alpha radiation, since even a uniform concentration of an alpha emitting nuclide is likely to involve a high deposition of energy in a few cells and no deposition in the many cells through which no alpha track passes, unless the nuclide is present at very high activities.

32. If data are being analysed on the basis of an assumed linearity between dose and frequency of effect, the arithmetic mean dose throughout the population of cells at risk will in any case form the appropriate index with which the tumour incidence should be compared. If, however, the range of doses to which cells are exposed exceeds that over which a linearity of the dose-effect relationship can be assumed to apply, then the mean dose over the tissue as a whole can at best be only an approximation to the relevant parameter (see Annex I, chapter III, section B).

33. For many forms of tumour induction in animals, there is evidence (Annex I, paras. 140-154) that, for uniform irradiation of various tissues, the number of tumours induced increases to a maximum (often at absorbed doses of the order of a few hundred rad or more) and then decreases, presumably as the cell-killing effect of the radiation predominates over the tumour-inducing effect. (The maximum yield per unit absorbed dose occurs at a somewhat lower dose.) It follows from this, firstly, that for highly non-uniform radiation, estimates based on mean tissue dose may overestimate the risk of non-uniform irradiation and, secondly, that estimates based on uniform high doses may underestimate the risk per rad of uniform low doses. The paucity or absence of thyroid cancers following the radioiodine therapy of hyperthyroidism, for example, is thus not necessarily in conflict with the relatively frequent induction of thyroid cancers by moderate or low doses. The absence of any consistent increase in leukaemia following the radium treatment of cancer of the cervix uteri has similarly been attributed to the effect of cell killing in the parts of the bone marrow which are most heavily irradiated (see paragraph 82).

34. It follows also that, at very high doses (e.g., several thousand rad) the number of tumours induced per unit dose may be lower than that at lower doses (e.g. a few hundred rad). Moreover, there is now abundant evidence in animals, and some evidence in man, that the dose-effect relationship at these lower doses is non-linear, at least for certain tumours (Annex I, paras. 30 and 112). Indeed, it has been suggested on theoretical and microdosimetric grounds, that the tumour-inducing effect of radiation is likely to be represented substantially by the sum of a linear term in dose corresponding to the consequences of single events due to ionization tracks passing through sensitive cell structures, and of a quadratic term in $(\text{dose})^2$ corresponding to damage due to two events (125, 157). It must be emphasized therefore that the frequency of tumours induced per unit absorbed dose at a given dose level applies strictly only at that dose level, and that the likely frequency per rad at low dose levels of a few rad or less, which are of most concern in radiation protection, cannot be assumed to be equal to the frequency observed per unit absorbed dose at higher levels. Similarly, the frequency observed in populations exposed at different doses cannot be taken as that applicable at the mean dose, unless the dose range within the group is small. These considerations apply particularly to radiation of low LET.

35. If the carcinogenic effects of radiation are in fact attributable only to the sum of one- and two-event processes, with a decrease of effectiveness at very high doses due to cell death and dependent on similar contributions, the relationship of frequency of effect E to absorbed dose D has been described by

$$E = (aD + bD^2)\, e^{-(cD + dD^2)}$$

At very low doses, the effect per unit dose E/D tends towards a. For moderate doses, this ratio would be given approximately by

$$E/D = a\,[1 + (b/a)\,D]\,[1 - (c + dD)\,D]$$

The value of $(c + dD)D$ is likely to be small for all values of D which are substantially below that at which the maximum induction of tumours occurs. On this basis the yield per unit absorbed dose at low doses is likely to be overestimated by that at rather higher doses by the factor $1 + (b/a)D$).

36. Data on the genetic effects of low-LET radiation in the mouse and on the induction of chromosome aberrations in several mammalian species including man which have been analysed in this way suggest values of b/a in the range 0.01-0.03 (20), and it has been suggested that similar values may apply for carcinogenesis. If this is so, it would indicate that estimates of carcinogenic effects per rad derived at doses of 100 rad of low-LET radiation could only overestimate the frequency of effects per rad at low dose by a factor of between 2 and 4.

E. SUITABILITY OF COMPARISON POPULATIONS

37. The excess incidence of malignant disease in an irradiated population can be reliably estimated only by comparison with a control population which is similar in all respects except that it has not been equally irradiated, and this condition is seldom fully achievable.

38. In the important studies on late effects of radiation in patients after radiotherapy the problem is particularly difficult, since it is usually hard to establish and follow up a control group of patients, with the same disease and of the same severity, but untreated by radiotherapy, since the selection of patients for such treatment usually correlates with the stage or severity of the disease. Yet, it is difficult to be sure that some form of malignant disease may not be slightly increased in incidence in patients with the disease being treated. The radiation exposure itself may be unlikely to produce more than a small increase of this sort, so that spurious results may be caused if comparisons are made with the

incidence of malignant disease in a sample of the general population, matched only for age and sex. If the excess incidence in the irradiated, compared with the general, population correlates with the radiation dose received, and if this dose does not correlate with the severity (or type) of disease treated, the comparison may be valid. It may also be valid when the disease treated is one such as ringworm of the scalp, which appears very unlikely to be associated with increased malignancy, at least of tissues other than the skin, but here controls by unirradiated patients with ringworm have in fact been possible.

39. In the treated ankylosing spondylitics, it has been pointed out that the excess incidence of cancer of the colon cannot be regarded as evidence of radiation induction of this form of malignancy, since ankylosing spondylitis is known to be associated with ulcerative colitis and the incidence of cancer of the colon is increased in patients with ulcerative colitis. In addition, little was originally known of any association between either the disease itself, or the drugs used in control of its symptoms, and the incidence of other malignancies, except that in an initial survey (37) one case of leukaemia occurred in a thousand patients with ankylosing spondylitis who were not treated by radiotherapy. Further data have, however, now been obtained (120) showing no increased mortality from leukaemia, cancer of the colon or other malignancies as compared with that in the general population, in 1021 patients with ankylosing spondylitis followed during a mean period of 8.5 years, and who had not been given x-ray therapy. Similarly, the raised incidence of cancer of the breast in patients irradiated for acute post partum mastitis could only be attributed reliably to the radiation if it was known that there is no increase in such cancers in untreated patients with this form of mastitis. It is particularly valuable therefore that a survey has now been made (138) on the breast cancer incidence in such untreated patients (see paragraph 176). The increased incidence of thyroid cancer in children following neck irradiation for enlargement of the thymus was similarly regarded as possibly being due to some effect of thymic malfunction, associated both with the enlargement that was being treated, and with a failure of the immune reactions to a developing cancer, so that cancer incidence might be increased in such patients. It was only when it was found that the increased thyroid cancer incidence was associated with neck irradiation for a variety of other conditions in infancy that it could be asserted that the radiation was likely to be responsible for the excess. In the same way, leukaemia is known to occur in patients with polycythaemia vera whether treated with ^{32}P or not. Control series of untreated polycythaemic patients are only valid if the duration of the disease when untreated with ^{32}P is as long as when it is so treated. In general, the ^{32}P treatment is effective in prolonging life and may, therefore, be apparently associated with a higher incidence of leukaemia purely because the patients so treated live long enough to allow the development of what may be a natural sequel of prolonged polycythaemia.

40. A further example of the hazards of using the general population as a comparison group for patients with a particular disease treated by radiation is given by follow-up studies of hyperthyroid patients (128) treated with radioactive iodine. The incidence of leukaemia was found to be slightly higher in the group of patients so treated than in members of the general population of the same age and sex. Fortunately, however, a control series had been studied of patients with the same condition treated by surgery in which a similar slight excess of leukaemia was found. It would have been hard to predict, and perhaps even to suppose, that leukaemia would be increased in frequency in hyperthyroid patients, and particularly in hyperthyroid patients who had been cured of their disease by adequate treatment, and the excess might have been used as a basis for radiation risk estimation if the appropriate control series had not been studied.

41. In the very important epidemiological studies of the incidence of cancer in A-bomb survivors in Hiroshima and Nagasaki, the establishment of an appropriate control group has always presented difficulties. In mortality studies, the general mortality rates at appropriate age and sex in the Japanese population as a whole have been used, but are subject to criticism in several respects. Firstly, living conditions in the two cities were very obviously difficult for a long period after the explosions, and may have involved factors which might influence mortality rates even for malignant disease. Secondly, the populations exposed were depleted of men of military age, and particularly those of this age and in good health; and, while the difference in sex distribution could be adjusted, the adjustment would not necessarily be accurate if based on statistics for the whole of Japan, even if these were confined to the years at issue, since the distribution may well have been different in urban and rural areas. Thirdly, and particularly in regard to carcinoma of the bronchus, it is known that the incidence of this condition differs in urban and rural communities so that comparisons between the survivors in the two cities and those for Japan as a whole are not necessarily valid. Moreover, it is known that the mortality from tumours of the lung in Japan rose considerably between 1967 and 1972 (from $12.9\ 10^{-5}$ to $17.0\ 10^{-5}$ per year). The use of the 1967 values (97) as controls for estimating more recent radiation induction of lung tumours in Hiroshima and Nagasaki may therefore overestimate this induction. The use of the mortality in those exposed at 0-9 rad may therefore be preferable. In various estimates made in this report, both bases of comparison are shown, even though the small numbers of death occurring in the 0-9 rad group may considerably reduce the accuracy of estimates based upon comparison with this group (see paragraph 45).

42. In addition, the immediate mortality at the time of the explosions must necessarily have been selective to some extent, involving those in different states of health to different degrees, and this in itself may have influenced the mortality rates for different conditions amongst the survivors. Moreover, those surviving in the high exposure groups are likely not only to have been subjected to a more powerful selection of this type at the time of the explosions, but in addition may well have had other injuries, ailments or difficulties in living conditions which may have correlated strongly with the magnitude of the exposure that they received, or with the position in the city at which these exposures were received.

F. FURTHER FACTORS AFFECTING THE PRECISION OF RISK ESTIMATES

43. Even when populations irradiated at known dose are followed over sufficiently long periods of time, with full ascertainment of resulting malignancies and with an adequate control group for comparison, several other factors will affect the precision of the resulting estimate. The size of the exposed population is of great importance for detecting an excess of most types of tumour following irradiation. Since the incidence of many types of tumours following radiation appears to be in the range of 5-20 per million per rad, radiation-induced tumours will usually not occur in more than, say 1 per cent of those exposed. Such an excess may be readily detectable in an exposed population of a few hundreds if the type of tumour induced occurs rarely in the absence of radiation. If, however, a small frequency of induced tumours has to be distinguished statistically from a large number of similar tumours occurring naturally, populations of many thousands may need to be studied.

44. The statistical uncertainties involved in estimates based on small numbers of tumours are increased if the incidence in the comparison population itself involves small numbers of tumours also.

45. For example, it has been emphasized (para. 41) that the incidence of malignant disease in the irradiated survivors at Hiroshima and Nagasaki cannot necessarily be estimated accurately by comparison with the general mortality rates for Japan as a whole. The same applies with equal emphasis for morbidity rates, particularly since the populations of Hiroshima and Nagasaki are likely to have been under much closer medical surveillance for the particular purposes of the health study than other populations. For these reasons therefore, the incidence of malignant disease in the exposed groups has often been compared with the incidence, either in residents of the two cities who were not in the cities at the time of the explosion, or in groups exposed only to radiation at doses of 0-9 rad. When such comparisons are made however, the incidence of diseases in the control groups may be subject to substantial statistical uncertainty in view of the small numbers of tumours occurring in these groups. The estimate of risk based on these comparison groups may, therefore, be more valid than when the comparison is with the Japanese health statistics as a whole, but may be so imprecise that this advantage is lost.

46. Throughout the following sections, attempts have been made to indicate the statistical reliability of the estimates and rates quoted, usually by stating the 90% confidence limits involved, as determined by the Poisson distributions depending upon the number of cases observed. Thus, whenever an estimate is followed by a statement of two alternative values within parentheses, for example "51 (26-88) 10^{-6}" it is implied that the expectation 51 10^{-6} has 90% confidence limits of 26 10^{-6} and 88 10^{-6}. These values give only a minimum estimate of the confidence zones if other sources of error affect the estimate. Where several such sources of random error can be evaluated and where standard errors of a mean value are quoted in consequence, it must be remembered that probabilities cannot necessarily be derived from values of the standard error on the assumption of a symmetrical distribution.

47. In quoting the amount by which an observed number of cases (e.g. of deaths from a disease) exceeds the expected number, the size of the excess may be negative, or one of the confidence limits with which it is estimated may be so. In such cases the excess is noted with its negative value, or is quoted simply as being negative (with the abbreviation "neg."). Thus for example, for an observed number of 3 that has 90% Poisson confidence limits of 0.8 and 7.8 and an expected number of 2.2, the excess would be expressed as 0.8 (−1.4-5.6) or 0.8 (neg.-5.6), and rates derived from such an excess are quoted similarly. Since so many estimates in this Annex are necessarily based on small excesses of numbers observed over those expected, it is important to indicate in this way the accuracy of the stated excess or excess rate on statistical grounds and the confidence with which it can be asserted even to be positive.

G. WEIGHTING FACTORS FOR NEUTRONS

48. For neutrons and for alpha radiation, estimates of risk per unit absorbed dose cannot be used in any direct way for estimating risk per unit absorbed dose from radiations of low LET for two reasons. Firstly, radiations of high LET are known to be more harmful than those of low LET per unit absorbed dose, and the RBE, or ratio of absorbed doses causing a given frequency of effect, may vary for different types of effect. Moreover, even for a given type of effect and quality of radiation, the RBE is likely to vary with the dose levels at which the comparison is made or with the frequency of effects (76, 125).

49. There are considerable difficulties therefore in expressing the carcinogenic risks observed in A-bomb survivors in any form which is applicable to radiation in general. In Hiroshima in particular, a substantial proportion (23-35 per cent in the different dosage groups) of the estimated kerma (tissue kerma in free air, T65 estimates) is attributable to neutrons.

50. In Nagasaki this percentage is much lower, less than 2 per cent in all dose groups. In principle, it would be possible to obtain approximate risk estimates for low-LET radiation for various forms of malignancy from the mortality data in Nagasaki. In fact, however, many of the estimates from this city are of low statistical reliability, those from Hiroshima being determined with considerably greater accuracy.

51. For leukaemia, however, relatively accurate risk estimates can be made for several dose groups in each city. In this case, therefore, it is possible to compare the relative effectiveness of neutrons and gamma radiation in these dose groups in inducing leukaemia, if it is assumed that a given absorbed dose of high-LET radiation was equally effective in each city, and that the same applies to equal absorbed doses of low-LET radiation. For this comparison two steps are required. Firstly, an estimate

must be made of the mean absorbed doses of high- and low-LET radiation in bone marrow resulting from the neutron and gamma radiation in each city and for each group examined. For bone marrow, values for the ratio mean absorbed dose/mean kerma are under investigation (71). Preliminary estimates however (70) indicate that the ratio for gamma radiation is likely to be about 0.55. For neutrons, the corresponding ratio is estimated as 0.26 for the absorbed dose of high-LET radiation (from protons induced by neutron capture or by recoil) with an additional 0.07 by induced gamma radiation.[2]

52. As the second step, a biological weighting factor W for the effectiveness of high- relative to low-LET radiation in inducing leukaemia can be derived by equating the induction rates—in excess cases per person-year per unit absorbed dose—in the two cities, giving the component of absorbed dose due to high-LET radiation in each city the same weighting factor.

53. Thus, if the mean absorbed doses in marrow from gamma radiation and from neutron-induced protons in a given dose (kerma) group are $D(\mathrm{H}.\gamma)$ and $D(\mathrm{H.p})$ for Hiroshima, and $D(\mathrm{N}.\gamma)$ and $D(\mathrm{N.p})$ for Nagasaki, the value of W for this dose group may be derived from the equation

$$\frac{M(\mathrm{H.obs}) - M(\mathrm{H.exp})}{P(\mathrm{H})\,[D(\mathrm{H}\cdot\gamma) + W\,D(\mathrm{H}\cdot\mathrm{p})]} = \frac{M(\mathrm{N.obs}) - M(\mathrm{N.exp})}{P(\mathrm{N})\,[D(\mathrm{N}\cdot\gamma) + W\,D(\mathrm{N}\cdot\mathrm{p})]}$$

where $M(\ldots)$ represents the number of deaths from leukaemia observed (obs) or expected (exp) in Hiroshima (H) or Nagasaki (N), and $P(\mathrm{H})$ and $P(\mathrm{N})$ are the populations exposed in the relevant dose groups in Hiroshima and Nagasaki.

54. For example, in those exposed at over 200 rad (kerma) the mean absorbed doses in marrow of low- and high-LET radiation can be estimated as 155 and 24.4 rad, respectively, in Hiroshima and 181 and 1.4 rad in Nagasaki. The number of deaths from leukaemia in this dose group in Hiroshima was 28 as compared with 1.3 expected on the basis of the 0-9 rad group, the corresponding values being 15 and 1.2 in Nagasaki. The number of persons was 1301 in Hiroshima (the average number of survivors during the period of survey) and 1191 in Nagasaki. For this kerma group therefore

$$\frac{28 - 1.3}{1301\,(155 + 24.4\,W)} = \frac{15 - 1.2}{1191\,(181 + 1.4\,W)}$$

whence $W = 7.6$.

55. Estimates of W can be derived in the same way for lower dose groups considered separately, but are very imprecise, with the standard error (SE) of sampling approaching or exceeding the expected value itself. The values of such a weighting factor can, however, be estimated with reasonable confidence for the (overlapping) groups of *all* those exposed at over 100 rad, over 50 rad, or over 10 rad. On this basis, the values are as follows:

Kerma group (rad)	>200	>100	>50	>10
Weighting factor W, by comparison with:				
0-9 rad group	7.6	11.4	14.4	19.3
SE	±4.2	±5.2	±6.6	±9.4
Japanese National Statistics	7.3	10.6	13.0	15.8
SE	±4.1	±4.7	±5.5	±6.6

56. These values clearly suggest an increase in effectiveness of high- relative to low-LET radiation in leukaemia induction as progressively lower dose levels are included (also see Annex I, paragraph 176). As stated, however, no adequate estimate can be made of the value of W at lower doses, owing to the uncertainty in risk estimates in these dose groups that results from the small excess of observed over expected cases. Thus, for example, the estimate of W for those exposed at 100-199 rad kerma (using comparison with the 0-9 rad group) is 47, with the standard error about 67.

57. These estimates are based on the mortality from leukaemia in the two cities in members of the Life Span Study, for whom the kerma has been estimated. Substantially larger numbers of deaths from this disease have been recorded in the Leukaemia Registry, but values of the kerma are not known for many of these individuals. If approximate kerma estimates are made for this larger population, however, on the basis of the distribution of the whole A-bomb-exposed population in 1950, the excess mortality from leukaemia in this group is more nearly proportional to estimated kerma in both cities (13). On this basis the variation of W with kerma might therefore be considerably reduced.

58. The values quoted in paragraph 55 can however be used to obtain tentative risk estimates for the induction of leukaemia by low-LET radiation over the stated dose ranges in the two cities.[3] Thus, in table 4, in addition to estimates of excess mortality rate per rad kerma, rates are quoted also per unit of weighted absorbed dose, in which the high-LET component of the tissue dose is weighted by the value appropriate to the dose group considered.

59. For malignancies other than leukaemia, the risk estimates, in particular for Nagasaki, are too uncertain to allow any adequate values to be derived for separate weighting factors appropriate to each malignancy. In previous reports, risk rates have been quoted per rad kerma without an estimated allowance for the neutron component of the exposure. The reports of the joint

[2] A recent study by Hashizume *et al.* (53a) estimates that for bone marrow the ratio of mean absorbed dose to mean kerma would be about 0.65. For neutrons, the ratios would be 0.25 for proton induction, and 0.10 for gamma radiation induction by neutrons. The use of these ratios would lower the values of the weighting factors given in paragraph 55 by about 10 per cent.

[3] This comparison should correctly be made at equal weighted absorbed dose, rather than at equal kerma. When such comparisons are made, estimates of W are somewhat lower in the high dose range with values of 5.4, 7.8 and 14.2 at weighted absorbed doses of 190, 150 and 90 rad respectively. The necessity for averaging doses and leukaemia rates over wide dose intervals in this analysis also introduces errors, to the extent that the low-LET dose-effect relationship departs from a simple linear proportionality between dose and effect. These errors prove not to be large, however, when calculated on the basis of likely estimates for the factors, discussed in paragraph 35, which may determine linear and quadratic components in such relationships.

Atomic Bomb Casualty Commission (ABCC)–Japanese National Institute of Health (JNIH) surveys also give dose ranges in rad (kerma) but refer in some instances to "RBE dose estimates in rem" (e.g., reference 67, table 5), using the RBE of 5 which Ishimaru *et al.* (63) note as being applicable for neutrons in leukaemogenesis.

60. In the absence of other estimates for the effectiveness of neutrons in inducing malignancies in man, and since the estimates of leukaemia mortality now yield weighting factors for different dose groups as shown in paragraph 55, these weighting factors have been used in later chapters to derive risk estimates for other malignancies, in addition to those quoted per rad (kerma). The use of this procedure is not intended to imply that the RBE for neutrons in inducing malignant change is necessarily the same at a given dose for all types of malignancy. It is of interest however that the induction rates in the two cities for a range of malignancies for which approximate risk estimates can be made, do appear to be statistically consistent with the use of the same weighting factors for all types. The intention in using these factors for other malignancies is thus solely in order to derive from the important observations in Hiroshima, risk estimates that may be more applicable to low-LET radiation than those derived directly from kerma, or absorbed dose, having large components of high-LET radiation. For this purpose it appears preferable to use factors which reflect a dose dependent RBE and which are based on other human carcinogenic data observed within the same dose groups, than to apply a constant value for RBE derived from quite different sources.

61. In the case of the breast and the thyroid, estimates have been published (9, 53) for the ratios of absorbed dose D to kerma K, both for gamma radiation (γ) and for neutrons (n) as inducing proton (p) or gamma (γ) radiation in tissues. Mean values for various modes of irradiation are as follows:

	D_γ/K_γ	D_p/K_n	D_γ/K_n
Breast	0.80	0.55	0.045
Thyroid	0.76	0.33	0.10

These ratios have been used in deriving risk rates for the weighted absorbed doses.

62. For evaluating the risks of alpha radiation, either in bone sarcoma induction by radium or lung carcinoma by daughter products of radon, no comparable biological basis is available for estimating any RBE, or weighting factor, that should be applied to the high-LET radiation of tissues in these cases. Risk rates are quoted, therefore, per rad of alpha radiation and require to be interpreted in the light of other evidence as to the likely RBE for alphas at the dose levels concerned.

II. LEUKAEMIA

A. LEUKAEMIA IN A-BOMB SURVIVORS

63. The seventh report on mortality data in the JNIH-ABCC Life Span Study (97) included information on deaths in exposed populations to the end of 1972, and indicated that the annual frequency of deaths from leukaemia had returned to about the level observed in the unexposed or only lightly exposed comparison populations (table 2 and fig. III). During the three-year period 1970-1972, only 3 deaths occurred in the groups exposed at known doses greater than 10 rad, as compared with 2.7 expected by comparison with the 0.9 rad group, and with 2.1 expected on the basis of

TABLE 2. EXCESS MORTALITY FROM LEUKAEMIA IN HIROSHIMA AND NAGASAKI BY PERIOD

Dose groups 10->200 rad T65
Males and females, all ages

Period	*Observed*	*Expected*	*Excess*	*Man rad year (10^6)*	*Excess rate ($10^{-6}\,y^{-1}\,rad^{-1}$)*
HIROSHIMA					
Compared with 0-9 rad group					
1950-1954	16	2.9	13.1 (6.9-21.6)	5.0	2.6 (1.4-4.4)
1955-1959	22	5.5	16.5 (9.0-26.3)	5.6	3.0 (1.6-4.7)
1960-1964	12	1.5	10.5 (5.3-18.0)	5.2	2.0 (1.0-3.4)
1965-1969	11	2.7	8.3 (3.2-15.8)	4.9	1.7 (0.7-3.2)
1970-1972	3	1.5	1.5 (neg.-6.8)	2.7	0.5 (neg.-2.5)
1950-1972	64	14.2	49.8 (36.7-65.1)	23.4	2.1 (1.7-2.7)
Compared with Japanese National Statistics					
1950-1954		1.1	14.9 (8.9-23.2)		3.0 (1.8-4.7)
1955-1959		2.0	20.0 (12.7-29.2)		3.6 (2.3-5.3)
1960-1964	as above	2.3	9.7 (4.6-17.1)	as above	1.9 (0.9-3.3)
1965-1969		2.6	8.4 (3.6-15.6)		1.7 (0.7-3.2)
1970-1972		1.5	1.5 (neg.-6.3)		0.5 (neg.-2.3)
1950-1972		9.6	54.4 (41.8-69.2)		2.0 (1.5-2.5)
NAGASAKI					
Compared with 0-9 rad group					
1950-1954	8	1.5	6.5 (2.2-13.2)	3.7	2.0 (0.7-4.0)
1955-1959	5	1.1	3.9 (0.7-9.6)	3.7	1.1 (0.2-2.6)
1960-1964	4	0.7	3.3 (0.5-8.7)	3.5	0.9 (0.1-2.5)
1965-1969	3	2.6	0.4 (neg.-6.0)	3.4	0.1 (neg.-1.8)
1970-1972	0	1.2	−1.2 (neg.-3.2)	1.9	−0.6 (neg.-1.7)
1950-1972	20	7.1	12.9 (5.4-22.7)	16.2	1.3 (0.7-2.1)
Compared with Japanese National Statistics					
1950-1954		0.6	7.4 (3.4-13.8)		2.3 (1.0-4.2)
1955-1959		0.7	4.3 (1.3-9.8)		1.2 (0.4-2.6)
1960-1964	as above	1.1	2.9 (0.3-8.1)	as above	0.8 (0.4-2.3)
1965-1969		1.1	1.9 (neg.-6.7)		0.6 (neg.-2.0)
1970-1972		0.6	−0.6 (neg.-2.4)		−0.3 (neg.-1.2)
1950-1972		4.1	15.9 (9.1-25.0)		1.0 (0.3-1.9)

Source: Reference 97.
Note: The 90% confidence limits are indicated in parentheses.

Japanese National Statistics. While these differences are not significant, it is noted that a small significant excess was still present in the two subgroups that had previously shown the highest frequencies. Thus, in Hiroshima in the groups exposed at 100-200 rad and at over 200 rad, 2 and 1 deaths occurred during this latest period as compared with 0.2 and 0.1 expected on the basis of the 0.9 rad group or of Japanese National Statistics. With this expectation, 3 or more deaths would occur by chance with a probability of only 0.0035, although the testing of these two subgroups selectively because they showed higher incidences must somewhat increase the probability of this difference being fortuitous. While, therefore, some mortality may have been persisting, the contribution to deaths during the last 3 years of the 22.25 years of the survey appears to have been only about 1.5 per cent of the total excess leukaemia mortality.

64. As shown in table 2, the annual death rate per man rad rose somewhat from the first (1950-1954) to the second (1955-1959) five-year period of survey, then fell progressively. Ignoring any cases that may have arisen prior to October 1950, the mean interval from radiation exposure until death from leukaemia has been 13.7 years (with median 12.5 years), as judged from the annual incidence rates. If this mean interval is determined for excess deaths of those exposed in each dose group (table 3), no relationship between interval to death and size of dose is evident.

TABLE 3. MEAN INTERVAL FROM EXPOSURE TO DEATH FROM LEUKAEMIA 1950-1972 IN HIROSHIMA AND NAGASAKI

Males and females, all ages

(Years)

Population	*Dose group (T65 kerma)*					
	0-9	*10-49*	*50-99*	*100-199*	*>200*	*All*
Hiroshima						
Excess deaths	12.0	10.8	5.5	11.0	27.2	66.5
Mean interval	10.1	15.8	12.5	15.0	14.1	13.7
SE[a]	±0.9	±1.2	±3.6	±2.0	±1.1	±0.6
Nagasaki						
Excess deaths	4.7	0.0	(neg.)	2.3	14.3	20.6
Mean interval	19.1	–	–	10.2	13.8	13.8
SE[a]	±4.5	–	–	±1.8	±1.6	±2.1
Hiroshima and Nagasaki						
Mean interval	12.6	15.8	(12.5)	14.1	14.0	13.7
SE[a]	±1.4	±1.2	(±3.6)	±1.8	±0.9	±0.6

Source: Reference 97.

[a]SE = standard error. The values of standard error are based on the number of deaths from leukaemia in the different groups.

65. Ichimaru *et al.* (61) show the number of cases of acute and chronic leukaemia with onset in each year from 1947 to 1971 including all confirmed cases in the ABCC Leukaemia Registry. For those who had received a kerma of 100 rad or over, the mean interval between exposure and onset (mean latency) of leukaemia was as follows (in years):

Type of leukaemia	*All cases*	*Excess cases[a]*	*SD[b]*	*SE*	*Approximate median latency*
Acute	11.8	11.5	5.9	0.9	11
Chronic	11.1	11.0	6.4	1.7	9
All	11.6	11.4	6.0	0.8	10

[a]As compared with onsets in unexposed groups.

[b]SD = standard deviation.

Since these values are based on the onset of individual cases, and since the numbers of persons in the fixed sample was decreasing slowly with time, the mean intervals based upon incidence *rates* would be slightly longer. Excess numbers of cases in the group exposed at 1-99 rad are too small for analysis of latency.

66. As judged by recorded month of onset, there appear to be no significant differences in latency between different types of acute leukaemia, although that for acute moncytic is slightly shorter than the average for other acute types, as seen from these data (years):

Type of acute leukaemia	*Number of cases*	*Mean latency*	*SD*	*SE*
Granulocytic	19	12.4	4.9	1.1
Stem cell	5	13.2	6.1	2.7
Lymphatic	15	10.8	6.9	1.8
Monocytic	7	9.2	3.8	1.4
All		11.5	5.9	0.9

67. Clear evidence is now obtained, however, of a variation in latency with age at exposure, at least for acute leukaemias and possibly also for the chronic (granulocytic) type induced. From the recorded month and year of onset of leukaemia between October 1950 and December 1971 in those who had received a kerma of 100 rad or more in either city, the following mean latencies are determined:

Age at exposure (years)	*Acute leukaemias*				*Chronic leukaemia*			
	Number of cases	*Mean latency (years)*	*SD*	*SE*	*Number of cases*	*Mean latency (years)*	*SD*	*SE*
<15	11	9.4	3.3	1.0	5	9.3	0.8	0.4
15-29	15	11.0	5.3	1.4	4	11.3	9.1	4.6
30-44	10	14.7	6.4	2.0	4	12.4	9.1	4.6
⩾45	7	15.2	4.2	1.6	1	12.6		

TABLE 4. EXCESS MORTALITY FROM LEUKAEMIA IN HIROSHIMA AND NAGASAKI, 1950-1972

Males and females, all ages

Dose group (rad kerma)	*Observed*	*Expected*	*Excess*	*Excess rate per unit kerma (10^{-6} rad^{-1})*	*Excess rate per unit weighted absorbed dose (10^{-6} rad^{-1})*
HIROSHIMA					
Compared with 0-9 rad group					
10-49	17	9.2	7.8 (1.6-16.8)	37 (5-80)	–
50-99	7	2.2	4.8 (1.1-11.0)	29 (7-67)	–
100-199	12	1.5	10.5 (5.4-17.9)	51 (26-88)	–
>200	28	1.3	26.7 (18.6-37.1)	57 (39-79)	61 (41-84)
>100	40	2.8	37.2 (27.2-49.5)	55 (40-73)	47 (34-63)
> 50	47	5.0	42.0 (31.3-54.9)	50 (37-65)	38 (28-50)
> 10	64	14.2	49.8 (36.7-65.1)	47 (35-61)	31 (22-39)
Compared with Japanese National Statistics					
10-49	17	6.2	10.8 (4.6-19.3)	52 (22-92)	–
50-99	7	1.5	5.5 (1.8-11.7)	33 (11-71)	–
100-199	12	1.0	11.0 (5.9-18.4)	54 (29-90)	–
>200	28	0.9	27.1 (19.0-37.5)	57 (40-79)	62 (43-86)
>100	40	1.9	38.1 (28.3-50.2)	56 (52-74)	50 (35-67)
> 50	47	3.4	43.6 (32.9-56.5)	52 (39-67)	42 (32-54)
> 10	64	9.6	54.4 (41.8-69.2)	52 (40-66)	38 (29-48)

Dose group (rad kerma)	*Observed*	*Expected*	*Excess*	*Excess rate per unit kerma (10^{-6} rad^{-1})*	*Excess rate per unit weighted absorbed dose (10^{-6} rad^{-1})*
NAGASAKI					
Compared with 0-9 rad group					
10-49	2	3.5	−1.5 (neg.-3.3)	−22 (neg.-47)	–
50-99	0	1.2	−1.2 (neg.-1.9)	−15 (neg.-24)	–
100-199	3	1.2	1.8 (neg.-6.7)	11 (neg.-41)	–
>200	15	1.2	13.8 (8.0-24.4)	35 (20-52)	61 (35-91)
>100	18	2.4	15.6 (9.2-23.5)	28 (16-44)	48 (28-76)
> 50	18	3.6	14.4 (8.0-23.1)	22 (12-36)	38 (20-61)
> 10	20	7.1	12.9 (6.1-22.0)	18 (6-33)	30 (10-55)
Compared with Japanese National Statistics					
10-49	2	2.0	0.0 (neg.-4.3)	0 (neg.-62)	–
50-99	0	0.7	−0.7 (neg.-2.3)	−9 (neg.-29)	–
100-199	3	0.7	2.3 (0.1-7.1)	14 (1-43)	–
>200	15	0.7	14.3 (8.5-22.4)	36 (21-56)	63 (37-98)
>100	18	1.4	16.6 (10.2-25.3)	29 (18-45)	50 (31-78)
> 50	18	2.1	15.9 (9.5-24.6)	25 (15-38)	42 (25-64)
> 10	20	4.1	15.9 (9.1-25.0)	22 (13-35)	37 (22-59)

Source: Reference 97.
Note: The 90% confidence limits are indicated in parentheses.

68. The effect of age at exposure on the frequency with which leukaemia has been induced in Hiroshima and Nagasaki is now clearly shown (14) by a study of the number of excess deaths per million person-year-rad in different age groups. As estimated by the number of deaths from leukaemia from October 1950 to September 1974 in the Adult Health Study Populations exposed at Hiroshima and Nagasaki, the induction rate is highest in the groups aged 0-10 years and over 50 years at exposure, with excess mortality rates of 3.2 (2.8-3.6) 10^{-6} and 3.4 (2.8-4.1) 10^{-6} y^{-1} rad^{-1} respectively. The rate is lowest in those who were aged 10 to 20, with a value of 1.0 (0.7-1.2) 10^{-6} y^{-1} rad^{-1} and intermediate for age groups 20-35 and 35-50 years at exposure, with values of about 1.9 (1.5-2.2) 10^{-6} y^{-1} rad^{-1} in each group. These differences in mortality rate, as estimated in the period up to 29 years from exposure, are not clearly attributable to differences in latency with age, since excess deaths have been occurring in all age groups in a comparable way since the beginning of the period surveyed (i.e., from 5 years from exposure).

69. The mortality from leukaemia in Hiroshima and Nagasaki is not reported separately for the two sexes in current JNIH-ABCC Life Span Studies but the appendix of the latest review of the ABCC Leukaemia Registry data (61) records the sex of patients developing any form of this disease. Of 57 cases with onset from 1950 to 1971 in people estimated to have received a kerma of 100 rad or more, 32 occurred in males and 25 in females. From Report 7 of the Life Span Study (97) the number of person years at risk during this period appears to have been about 47 370 in males and 61 390 in females (the Registry study uses total person-years which are about 7 per cent higher but does not quote values separately for the two sexes). On this basis, the leukaemia incidence is somewhat higher in males than in females. It is of some interest, however, that the incidence of acute leukaemias in this dose group appears to be equal in the two sexes, while that of chronic (granulocytic) leukaemia is considerably higher in the male:

	Males		*Females*	
Type of leukaemia	*Incidence (10^{-4} y^{-1})*	*Cases*	*Incidence (10^{-4} y^{-1})*	*Cases*
Acute	4.2 (2.8-6.1)	20	3.7 (2.6-5.3)	23
Chronic	2.5 (1.5-4.1)	12	0.3 (0.1-1.0)	2
All	6.8 (4.9-9.1)	32	4.1 (2.8-5.7)	25

However, the numbers involved are small and the age structure of the male and female populations differed appreciably, with a relative deficiency of males aged 20-35 and a slight relative preponderance of males at ages over 35.

70. The natural annual incidence rate of leukaemia in Japan, as judged by cancer registry data (35) is somewhat lower in females than in males, with values of 2.7 and 3.7 10^{-5} y^{-1} in females for age standardized populations in two Japanese registries, as compared with 4.4 and 4.3 10^{-5} y^{-1} in males. It is rather lower than in registries in many other countries (which have mean rates for 58 other registries of 4.4 and 6.8 10^{-5} y^{-1} in females and males). The incidence rates in members of the Master Sample exposed at less than 5 rad at Hiroshima and Nagasaki were 3.1 and 5.7 10^{-5} y^{-1}, respectively. The incidence rate of chronic lymphatic leukaemia in this group was only 0.1 10^{-5} y^{-1} (2.7 per cent of all cases) as compared with a mean of 1.2 10^{-5} y^{-1} (22 per cent of all cases) in 22 registries in other countries reporting leukaemia by type (35).

71. During the total period 1950-1972, the number of deaths from leukaemia in the Life Span Study Group in Hiroshima (97), at known kerma of over 10 rad exceeded the number expected on the basis of the 0-9 rad group by about 50 (with 90% confidence limits 37 and 65). The corresponding excess for Nagasaki was 13 (6-22). Expressed as rates per million exposed and per unit kerma, these excesses correspond to 47 (37-65) 10^{-6} rad^{-1} and 18 (6-33) 10^{-6} rad^{-1}; and table 4 gives rates for the different (kerma) dose groups compared with both the 0-9 rad group and the Japanese National Statistics.

72. The rates are given also for *all* those exposed at over 10, 50, 100 and 200 rad. For these groups, table 4 gives estimates also of the induction rate per rad (weighted) absorbed dose, using the weighting factors for neutrons derived above in paragraph 55. These estimates assume the ratios of absorbed dose to kerma for bone marrow of 0.55 and 0.26 for gamma and neutron radiation, respectively, as discussed in paragraph 51. The distribution of mean numbers exposed, and neutron component of kerma, for each dose group is given in table 5.

TABLE 5. ESTIMATED KERMA AND NUMBERS EXPOSED IN LIFE SPAN STUDY DOSE GROUPS

Males and females, all ages, 1950-1972

	Hiroshima			*Nagasaki*		
Dose group (rad)	*Mean kerma (rad)*	*Per cent from neutrons*	*Mean number of persons*	*Mean kerma (rad)*	*Per cent from neutrons*	*Mean number of persons*
10-49	21.9	20	9 533	21.0	0.0	3 302
50-99	70.2	19	2 350	70.5	0.3	1 120
100-199	138.6	22	1 473	145.7	1.0	1 127
>200	363.2	26	1 301	334.7	1.7	1 191

Source: Reference 97.

73. In the eighth report on mortality data in the Life Span Study (14), the excess mortality rate per unit kerma from leukaemia in the 24-year period 1950-1974 has been

$56\ (51\text{-}61)10^{-6}$ rad^{-1} in Hiroshima,
$35\ (29\text{-}41)10^{-6}$ rad^{-1} in Nagasaki, and
$46\ (42\text{-}50)10^{-6}$ rad^{-1} in both cities combined,

these rates being estimated from the slopes of (variance-weighted) regression lines of mortality rate upon kerma. They correspond closely with the excess rates for the period 1950-1972 as based on comparison between the >200 rad group and rates in the 0-9 rad group, as would be expected if

(a) no substantial excess mortality has occurred in 1972-74;

(b) the regression line is influenced substantially by the large numbers in the 0-9 rad group and the large excess in the >200 rad group. The additional deaths from leukaemia in 1972-74 have in fact been 6 in those exposed at 10 rad or over in both cities, as compared with about 3.7 expected on the basis of the 0-9 rad group (see paragraph 240). The previous excess for 1950-72 was 63 deaths.

74. The types of leukaemia that had developed in members of the ABCC Master Sample exposed at 5 rad or over at Hiroshima and Nagasaki differed significantly from the types occurring in the groups who were relatively unexposed (at less than 5 rad), according to the report of Ishimaru *et al.* (63), analysing the incidence of leukaemia from October 1950 to September 1966. The types of leukaemia occurring between October 1950 and December 1971 are now reported by Ichimaru *et al.* (61). Their data show differences in relative frequency of the different types in those exposed to radiation in the two cities, but corresponding differences are also seen between the "control" groups for these cities. Thus, no differences are seen, either in Hiroshima or in Nagasaki between the relative frequencies in those exposed at less than 1 rad, and in those who were not in the city at the time of the bomb.

A comparison of relative frequencies in <1 rad group and the National Institute of Cancer (NIC) group shows the following:

(a) For all specified types of leukaemia:

Hiroshima, $\chi^2 = 3.4$, 5 degrees of freedom (d.f.), not significant;
Nagasaki, $\chi^2 = 8.2$, 5 d.f., not significant;

(b) For specified types and groups of acute and chronic unspecified types:

Hiroshima, $\chi^2 = 3.8$, 7 d.f., not significant;
Nagasaki, $\chi^2 = 9.8$, 7 d.f., not significant.

Comparing the combined control series for Hiroshima with that for Nagasaki, however, there appears to be a clear difference in relative frequencies:

(a) For all specified types, $\chi^2 = 24.8$, 5 d.f., $P < 0.001$:

(b) For specified and unspecified groups, $\chi^2 = 29.5$, 7 d.f., $P < 0.001$.

The difference is due mainly to a relative excess of acute lymphatic and chronic granulocytic types in Hiroshima and of acute granulocytic and chronic lymphatic types in Nagasaki.

75. When the groups which were heavily exposed (at or over 100 rad kerma) in the two cities are compared, there is some indication of a significant difference in relative frequency of types of leukaemia (with $\chi^2 = 8.0$, 4 d.f., $P = 0.09$ comparing specified types and $\chi^2 = 8.3$, 5 d.f., $P = 0.15$ including unspecified groups), the main contribution to the difference being again a relative excess of chronic granulocytic leukaemia in Hiroshima and of acute granulocytic leukaemia in Nagasaki. The difference is much clearer when the incidence in all those exposed at over 1 rad is compared in the two cities ($\chi^2 = 17.4$, 4 d.f., $P < 0.005$ and $\chi^2 = 17.1$, 5 d.f., $P = 0.005$), the main difference again being due to a relative excess in Hiroshima of the chronic, and in Nagasaki of the acute granulocytic types.

76. Since, however, this difference is also evident between the control series for the two cities, a difference in the types of leukaemia *induced* by radiation in these cities can only be established by estimating the frequencies of *excess* cases of different types in each city. In each city, the leukaemia rate in those who were unexposed was about 12 per cent of that in those who were exposed at or over 1 rad. Part of the difference between the types of leukaemia observed in those exposed at Hiroshima and at Nagasaki may therefore merely reflect the similar differences observed between the control series in the two cities.

B. LEUKAEMIA IN POPULATIONS IN THE MARSHALL ISLANDS IRRADIATED FROM FALLOUT

77. Leukaemia has developed and has proved fatal in one inhabitant of the Marshall Islands who was exposed to radiation from fallout in 1954. The leukaemia was of the acute myelogenous (promyelocytic) type (26). Quite clearly the occurrence of one case might be due to chance rather than to radiation. In a population estimated to have received about 11 870 man rad of exposure, however, if the expectation of leukaemia was, for example, 20 cases per million per rad, the chance of 0, 1 and over 1 cases occurring would be 0.82, 0.16 and 0.02. No excess incidence of other forms of malignancy, apart from that of the thyroid (see paragraphs 108-111) has been observed.

C. LEUKAEMIA FOLLOWING PELVIC IRRADIATION

78. Following x-radiation of the pelvis in the treatment of metropathia haemorrhagica, Smith and Doll (142) observed an excess death rate from leukaemia of 16.3 per 10^5 woman-years at risk, during the period of 5 or more years after treatment. Since the mean marrow dose was 134 rad, this rate corresponds to $1.22\ (0.25\text{-}2.8)10^{-6}$ rad^{-1} y^{-1}. Since the mean period of follow-up from the time of treatment was 19.0 years, and since no excess was observed in the first 5 years, the estimated leukaemia risk to 19 years in women becomes $17\ (3\text{-}36)10^{-6}$ rad^{-1} at this dose level.

79. The 7 cases of leukaemia (2.33 expected) were diagnosed at 11.0 ($\pm$ 2.1 SE) years after exposure and death occurred at 11.6 ($\pm$ 2.0 SE) years after exposure.

Correcting for the decreasing number of patient years at risk gives mean intervals of 12.4 and 12.9 years to diagnosis and to death, values which clearly are not discrepant with those observed in the leukaemia registry and in the mortality data from Hiroshima and Nagasaki.

80. Brinkley and Haybittle (18) made a follow-up of 277 women for a mean period of 16.1 years after an x-ray induced menopause involving a mean pelvic dose of about 735 rad. No deaths from leukaemia were observed, but only 0.24 were expected on the basis of normal incidence at the ages concerned, and only a further 0.83 cases would have been expected if the induction rate per woman-year and per rad found by Smith and Doll had applied.

81. Alderson and Jackson (2) followed up 2049 patients of whom 15 per cent were treated with radium and 85 per cent with x rays in the therapy of menorrhagia. No deaths from leukaemia were observed during the first 5 years but 4 occurred subsequently as compared with 1.09 expected. Risk estimates are difficult to obtain owing to the non-uniform pelvic irradiation from radium. Dickson (32) observed no significant increase in leukaemia in 4010 women treated with radium for benign uterine haemorrhage, but less than 50 per cent of the patients were adequately traced and this negative finding is therefore of doubtful significance.

82. A number of studies, which are reviewed by Smith and Doll (142) show no significant increase in leukaemia following pelvic irradiation for carcinoma of the cervix, in many cases by radium. It was, however, suggested by Hutchinson (60) that the negative findings in these studies are due to the much higher doses given in treatment of cervical cancer than those used for metropathia, so that considerable cell killing is likely to take place in the areas of pelvic marrow which are irradiated.

D. LEUKAEMIA FOLLOWING TREATMENT OF ANKYLOSING SPONDYLITIS BY X-IRRADIATION

83. In a survey of patients who had received one or more courses of radiotherapy for ankylosing spondylitis, Court Brown and Doll (29) observed an excess mortality rate from leukaemia and aplastic anaemia of $4.2\ 10^{-3}$ during an average period of 9.7 years in patients fully followed up, and $4.7\ 10^{-3}$ in a rather longer but less complete follow-up for an average of 11.4 years. Since 10 years appears to be about the median interval between irradiation and death from radiation induced leukaemia, a total induction in the region of $9\ 10^{-3}$ cases might be expected. It was likely that an average dose of about 880 rad was delivered to 40 per cent of the bone marrow. If this can be regarded as equivalent to an average dose of 350 rad, the total induction rate per unit absorbed dose is estimated as $25\ 10^{-6}$ rad^{-1}, the number of excess cases observed determining 90% confidence limits of $(20\text{-}31)\ 10^{-6}$ rad^{-1}. The mean interval in years from irradiation to death had been as follows:

Follow-up	*By deaths*	*By death rates*
Complete to 1960	6.2 ±0.5 (SE)	8.6
Incomplete to 1963	6.6 ±0.5 (SE)	7.9

84. In a further survey of the patients who had received only one course of radiotherapy (36), an excess of 31-6.5 = 24.5 (15.9-35.3) deaths from leukaemia were observed in 14 109 patients followed for a mean period of 9.5 years. This survey covered about 134 000 person-years at risk, 11 900 of them being within the period starting 17.5 years after treatment during which no further excess deaths from leukaemia occurred (1 observed, 0.96 expected). With an estimated mean marrow dose of 321 rad, this excess corresponds to an annual risk of $0.57\ 10^{-6}$ y^{-1} rad^{-1} over the period of survey, this rate having been $0.78\ 10^{-6}$ y^{-1} rad^{-1} during the first 6 years and $0.49\ 10^{-6}$ y^{-1} rad^{-1} during the subsequent period, until the time at which excess deaths ceased to occur. The total risk is $5.4\ 10^{-6}$ rad^{-1} as estimated from the whole group, which was studied for a mean period of 9.5 years. This value, however, is an underestimate of the true expectation because decreasing numbers were at risk during the periods when leukaemia incidence may have been maximal, since many patients were withdrawn from survey when they received a second course of treatment. A more valid risk estimate may be derived, however, by summing the excess mortality rates, rather than the number of deaths, at successive time intervals after exposure, as if a cohort of patients were being followed without withdrawals from survey except as a result of death. When this is done the total risk until 20 years, when excess leukaemia deaths had ceased to occur, is $11.4\ (7.5\text{-}16.4)\ 10^{-6}$ rad^{-1}.[4] The mean interval from irradiation to death from leukaemia was 6.6 ± 0.9 (SE) years, or 7.4 years as based on excess leukaemia rate per person-year at the different time intervals after exposure. These intervals, and those noted in paragraph 83, are thus clearly shorter than those observed in Hiroshima and Nagasaki.

E. LEUKAEMIA FOLLOWING OTHER RADIOLOGICAL PROCEDURES

85. An increased incidence of leukaemia has been observed in the various series of patients followed up after the use of Thorotrast as a diagnostic contrast medium (see paragraphs 283 ff.). As shown in table 6, a total excess of 53.7 cases has occurred in series including 4594 subjects followed for a mean period of 27 years after receiving a mean dose of 26 ml of Thorotrast. Risk estimation from these data is subject to considerable uncertainties in respect to irradiation of already dead cells, or to any possible chemical carcinogenic action of thorium oxide, as discussed in paragraph 283. Subject to these reservations, the induction rate from the absorbed dose delivered to the end of the period of follow-up would be $33\ (24\text{-}39)\ 10^{-6}$ rad^{-1} of alpha radiation. Since the thorium remains in the tissues and continues to irradiate the bone marrow, however, much of this

[4] An additional 5 patients died with leukaemia recorded on the death certificate, although not as the primary cause of death; and for 2 patients, death was recorded as due to aplastic anaemia but, on review, it was considered that a more appropriate diagnosis would have been of leukaemia. If these 7 patients are included with those recorded as dying of leukaemia, and if 3 further patients are excluded in whom leukaemia is known to have been present at the time of treatment, the total excess leukaemia mortality rate per unit absorbed dose within 20 years from treatment becomes 13.5 (9-20) 10^{-6} rad^{-1}.

TABLE 6. LEUKAEMIA FOLLOWING THOROTRAST INJECTION

Reference	Country	Follow-up period (years)	Dose (ml)	Dose to bone marrow (rad)		Number of subjects	Cases of leukaemia and anaplastic anaemia	
				At end of follow-up	10 years from end of follow-up		Observed	Expected
141	Portugal	30	26	387	258	1 231	20	0
42	Denmark	28	23	322	207	756	11	(3.7)
69	United States	10	24	120	0	724	3	0
72	Germany, Fed. Rep. of	30	30	444	296	1 750	25	2.4
96	Japan	30	16	271	189	133	1	0.2
	Mean	27	26	353	221			
	Total					4 594	60	6.3

radiation is likely to be "wasted" in the sense that it is delivered after leukaemia may have been induced. If a mean latency of 10 years is assumed for leukaemia, and the dose estimated for the period of 10 years less than the mean duration of survey, the rate would be 53 (41-67) 10^{-6} rad^{-1} of alpha radiation.

86. A small excess incidence of leukaemia occurred in a series of 2872 children who had had scalp irradiation for tinea capitis, but only a very tentative risk estimate can be made from these data. The cranial marrow dose was estimated (131) as 385 rad, but the proportion of the active marrow which is in the cranium of a child is uncertain. Atkinson (8a) has estimated that 7 per cent of the active bone marrow of children is in the skull, and on this basis the mean marrow dose may have been in the region of 30 rad. The excess leukaemia incidence was of 4.7 (1.0-10.9) cases, the confidence limits ignoring variability in estimation of the control rates. These values give a risk estimate of 50 (10-130) 10^{-6} rad^{-1}, but there are obviously considerable uncertainties, apart from the statistical imprecision in this estimate.

87. No additional information has become available since the Committee's 1972 report on the possible induction of leukaemia by ^{32}P as used in the treatment of polycythemia vera. As noted in that report (Annex H, para. 85) it remains difficult to derive valid radiation risk estimates from study of the sequels of this treatment. The position is further complicated by the evidence that the frequency of subsequent acute leukaemia is not directly related to the amount of ^{32}P administered, and varies according to the size of the spleen at the time of treatment (21).

88. No further data have been published on the follow-up of hyperthyroid patients treated with ^{131}I or by surgery (1972 report, Annex H, para. 78). Since the initial survey of hyperthyroid patients continued for a mean period of only about 10 years, terminating in mid-1967, a further study might be informative, but the estimated mean marrow dose, of only about 10 rad, makes it doubtful whether useful results would be obtained. In the series of patients treated for thyroid cancer at high dose levels with ^{131}I (1972 report, Annex H, para. 73), no further cases of leukaemia have developed despite a further 9 years of follow-up of this series (118).

89. Additional studies have been made of the exposures likely to have been received by radiologists in the course of their occupation (49) but no further evidence has been obtained from which corresponding risk rates are derived.

F. SUMMARY

90. Leukaemia is thus induced by radiation with a mean latency to diagnosis of about 10 years. Estimates of the mean or median interval from exposure to death, under widely different conditions of irradiation, vary from about 8 to 13 years. These mean intervals are probably about half those which apply for other cancers. They do not appear to differ considerably for different types of leukaemia. They do, however, vary with age at exposure, estimates from Hiroshima and Nagasaki increasing from 9 to 15 years with increasing age at the time of exposure; and the latency is short after pre-natal exposure. The mean latency does not appear to vary with dose in a consistent manner, and the increased incidence after exposure appears to have almost ceased after about 30 years.

91. All acute forms, and the chronic granulocytic type of leukaemia are induced, the former types predominating. No evidence has yet appeared indicating that chronic lymphatic leukaemia is induced by radiation.

92. The frequency of induction per unit dose increases with age from early adult life, but is also relatively high following exposure in childhood, and perhaps also *in utero* (see chapter VIII). There is no clear evidence of a difference in induction rate in the two sexes.

93. There are no reliable bases for determining directly the frequency with which leukaemia is induced in the adult at absorbed doses of low-LET radiation of less than about 100 rad. The total deaths from leukaemia in the Life Span Study 1950-1972 in those estimated to have been exposed at 0-9 rad were recorded (97) as higher than those in people who were not in the cities ($P = 0.065$) and were also higher than expected on the basis of Japanese National Statistics ($P = 0.004$), but neither comparison allows estimates of any precision.

94. The mortality rates for leukaemia in Hiroshima in kerma ranges of 10 to 50 rad and higher allow induction rates to be estimated, but here the neutron component of the dose complicates the interpretation of the estimates. For Nagasaki, the estimates for several dose groups are too imprecise to be useful. Here however, estimates derived from the inclusive groups of all over 200 rad, over 100 rad etc. are based on adequate numbers. These estimates (table 4) suggest clearly that the frequency of leukaemia induction per unit kerma decreases with decreasing kerma, and hence with decreasing absorbed dose. As the inclusive dose groups are widened to include a progressively greater contribution from those exposed at lower dose, the rate per unit kerma falls from 35 10^{-6} rad^{-1} at mean kerma 330 rad, to 18 10^{-6} rad^{-1} at mean kerma 100 rad, the rate per unit *absorbed* dose in this group being 33 10^{-6} rad^{-1} at mean dose about 55 rad. This decrease of effect per rad with decreasing dose is perhaps to be expected for the predominantly low-LET radiation and suggests a value of about 30 10^{-6} rad^{-1} as an upper limit for the likely effectiveness of low absorbed doses of low-LET radiation.

95. This inference would be consistent with estimates derived above for the rates, per million per rad, of 25 and of 11 following x ray treatment of ankylosing spondylitis, and of 17 after pelvic x-irradiation. The tentative estimates of 50-55 rad^{-1} of alpha radiation from thorotrast deposits and of 50 (10-130) following treatment of tinea in children are not inconsistent.

96. An estimate in the range (15-25) 10^{-6} rad^{-1} might thus be taken for the induction rate for low-LET radiation in a population of all ages, probably with a somewhat higher rate in the young and in the elderly, and lower in early adult life. It must be emphasized, however, that this estimate is derived predominantly from rates observed following absorbed doses of over 100 rad. While the rate per unit dose from doses of a few rads is unlikely to be higher than this value, it might be substantially lower.

III. THYROID CANCER

97. The Committee's previous reports have shown the thyroid gland to be an organ of high sensitivity for radiation carcinogenesis. Indeed, considering that the mass of the gland is typically about 20 g, much of which is cell-free colloid, the sensitivity per cell is likely to be considerably higher than for most other types of tissue.

98. At the same time, the malignant tumours induced have consistently been of a histologically well-differentiated type which usually develops only slowly and which can often be completely removed by operation or successfully treated with radioiodine even if metastasized. For this reason the Committee has previously quoted risks in terms of morbidity rather than of mortality. It will, however, be necessary to assess the likely contribution to fatal cancers as well as to cancer induction, from thyroid irradiation (paras. 148 and 149).

99. In its previous reports, the Committee has reviewed information indicating the induction of thyroid cancer by radiation in Japanese A-bomb survivors, in residents of Marshall Islands exposed to radioactive fallout, in patients therapeutically irradiated from external sources, and in children treated for hyperthyroidism with radioiodine.

A. THYROID CANCER IN A-BOMB SURVIVORS

100. From the report of Wood *et al.* (163) it was evident that thyroid cancer had been induced by radiation in members of the Adult Health Study Sample of Hiroshima and Nagasaki. It was clear that the rate of induction was greater in females than in males, and the sex ratio of affected females to males was 2.2 in the group exposed at distances to 1400 m. The rates of induction were much higher in those who were exposed proximally than in those distally exposed as examined in females, the number of male cases being too small for statistical tests. For females of all ages combined, the group exposed within 1400 m had a rate of 2.5 times as high as that for those exposed at distances greater than 3000 m.

101. The rates were also expressed in terms of estimates of kerma at different ranges, but it was difficult to derive values for the annual incidences per unit kerma since available records were only of the total number of cases diagnosed at examination about 20 years after exposure. With assumptions as to the mean dose corresponding to the stated dose ranges, however, the Committee made tentative estimates of induction rates corresponding to between 10-20 cases per million per rad for males, and 20-40 for females, for kermas in the range 25-200 rad. The variation of induction rate with age at the time of exposure was not clear from the data then available.

102. Since the last report of the Committee, a further detailed study has been published (109) of thyroid cancers diagnosed between 13 and 26 years after exposure in members of the Adult Health Study population. This examination clarifies further the greater induction rate in females, the histological type of tumour induced, the rate of induction per unit absorbed dose and, to some extent, the variation of induction rate with age at the time of exposure. Of the 74 thyroid cancers recorded in the population studied only 40 were diagnosed during life (see paragraph 104). The other 34 were found first at autopsy and were neither detected during life, nor judged to have been detectable by normal clinical examination. They were usually small and of the papillary sclerosing type, although sometimes showing metastases to local lymph nodes. The study by Sampson *et al.* (130) of tumours of this type was discussed in the Committee's 1972 report, where it was noted that the frequency of these tumours was increased by about 23 per cent in autopsies in females receiving kermas of over 50 rad. The high prevalence in unirradiated subjects, however, in about 16 per cent of autopsies, was regarded as casting doubt on the clinical importance of these tumours. Indeed, Woolner (164) has reported a study of 140 cases of occult papillary

carcinoma of the thyroid observed during a 30-year period and regards the presence of these tumours as having no effect on mortality.

103. The autopsy findings of Parker *et al.* (109) rely on routine autopsy methods, rather than on serial sections of the thyroid, and the authors consequently report a lower incidence of such "clinically silent" tumours in the unirradiated group (receiving kermas of less than 1 rad). The observed frequencies at autopsy were 1.3 and 1.1 per ten thousand person-years of observation in males and females respectively, tumours of this type having been detected in about 0.15 per cent of autopsies. Two thirds of these tumours were of the papillary sclerosing type, the remainder being either papillary or follicular. As in the study by Sampson *et al.* (130), there was a significant increase in the frequency of these "clinically silent" tumours in females who had received 50 rad or more, but no such increase was detectible in males. The numbers of tumours detected only at autopsy in the low-dose (less than 1 rad and not-in-city) and high-dose (greater than 50 rad) groups appear to have been as follows:

	Low-dose group		*High-dose group*	
	Male	*Female*	*Male*	*Female*
Tumours:				
Papillary	0	0	1	3
Follicular	0	4	0	0
Sclerosing papillary	5	3	1	8
Person years (10^3)	38	63	20	23

indicating an increase in incidence rate for papillary and for sclerosing papillary tumours in females.

104. The remaining 40 thyroid cancers had been diagnosed clinically during the course of the Adult Health Study. Of these, 9 occurred in persons who had received less than 1 rad. Six cases, with 3.9 expected, occurred in those exposed to between 1 and 49 rad. A further 25 cases (4.5 expected) occurred in those exposed to 50 rad or more and the analysis in the report is based essentially upon this more heavily exposed group. Comparing this group with those receiving less than 1 rad or not in the city at the time of the bomb, the excess of cases diagnosed clinically corresponds to a rate of 2.2 (0.7-5.0) per 10 000 person-years in the male, and 5.0 (2.9-7.9) in the female. The mean dose for the exposed group is not stated, but appears, from the distribution of person-years at risk in the three exposure groups quoted, to have been about 200 rad kerma. If so, and since observations covered thirteen years, the total excess incidence for the period 13-26 years from exposure corresponds to rates of 14 (5-31) 10^{-6} and 33 (19-52) 10^{-6} per rad kerma in males and females, respectively. The rates per rad absorbed dose would be 20 (6-44) 10^{-6} and 47 (27-73) 10^{-6}, assuming ratios of absorbed dose to kerma as in paragraph 59 for gamma radiation and neutrons: or of 11 (3-24) 10^{-6} and 24 (14-38) 10^{-6} per rad of absorbed dose weighted according to the weighting factors for neutrons given in paragraph 55. The rates for both cities combined would be 37 10^{-6} and 19 10^{-6} per rad weighted absorbed dose.

105. The relationship between excess incidence and age at the time of exposure could not be examined in males, since too few cases were observed. In females, the ratio of the incidence in those exposed at over 50 rad to that in the group with minimal exposure was noted as being greater in those younger than 20 at the time of exposure than in older age groups. The relative risk is difficult to interpret, however, in view of the few cases occurring in the unexposed group, in three of the four age groups only one case having been observed. The absolute increase, therefore, appears to be a more reliable index of tumour induction, and was probably, although not necessarily, higher in those aged less than 10 years at the time of exposure than in the other three age groups. Thus, the excess numbers of cases per 10 000 person-years in the four age groups, as compared with the incidences observed in the unexposed group, were 14.2 (5.0-32.7), 4.9 (1.9-10.3), 3.6 (1.4-6.9), and 5.4 (0-16.2) in those aged less than 10 years, 10-19 years, 20-49 years, and 50 years and over, respectively. The observed occurrence of 4 cases in females aged 10 years or less at the time of exposure would only have been equalled with a chance of $P = 0.04$ if the rate of induction at this age were equal to the average of rates at all other stages. A fall of induction rate D, with age A is also of probable significance ($r = -0.85$, $P = 0.08$, the data being fitted by the equation $D = 11.6 - 0.22A$). The suggestion that the gland in childhood may have several times the sensitivity of the adult gland thus continues to support the earlier indication from study of the same subjects (130) in which the percentage incidence of thyroid cancers in those exposed at less than 1400 m was 1.1 ± 0.62 in those aged less than 10 at the time of exposure, as compared with 0.22 ± 0.13 in those aged 20 or over. The excess incidence in those aged between 10 and 20 had an intermediate value of 0.83 ± 0.29.

106. Of the 40 tumours diagnosed clinically, histological examination of 34 tumours in high and low dose ranges showed that papillary and follicular cancers both had higher incidences per person-year in the high-dose group, of 50 rad or over, than in the group who were not in the cities or who received less than 1 rad, clearly significant increases occurring in females. The number of clinical cancers were as follows:

	Low-dose group		*High-dose group*	
	Male	*Female*	*Male*	*Female*
Tumours:				
Papillary	1	6	4	12
Follicular	0	2	1	7
Sclerosing papillary	0	0	0	1
Person years (10^3)	38	63	20	32

As in previous series of radiation-induced thyroid cancers, no anaplastic or medullary tumours were observed (see paragraph 138). The absence of anaplastic cancers is of importance, since these are rapidly growing and commonly inoperable tumours. The absence of medullary carcinomas may suggest that the parafollicular cells of the thyroid are less sensitive to tumour induction than are follicular cells, but this difference may arise merely because fewer parafollicular cells are present in the thyroid and at risk. Only one of the 40 clinically diagnosed cancers had caused death at the time of the report.

107. Tumour registry data for the period 1959-1970 (14) show incidence rates of thyroid cancer per unit kerma of about 10 (5-15) 10^{-6} rad^{-1} for Hiroshima and 11 (5-17) 10^{-6} rad^{-1} for Nagasaki. These would correspond to rates per unit absorbed dose of about 14 (7-20) 10^{-6} rad^{-1}, and 14 (6-23) 10^{-6} rad^{-1}, with equal rates in the two cities. The rates per unit weighted absorbed dose would however differ substantially in Hiroshima and Nagasaki, with values of about 4 (2-6) and 13 (6-20) 10^{-6} rad^{-1}, respectively.

B. THYROID CANCER IN POPULATIONS IN THE MARSHALL ISLANDS EXPOSED TO THYROID IRRADIATION FROM FALLOUT

108. The Committee's 1972 report described the development of 4 thyroid cancers in residents of certain of the Marshall Islands who had been exposed in 1954 to fallout (25), both by external radiation and by ingestion of radioiodine.

109. By September 1976, 3 further thyroid cancers had developed and the total incidence at that time corresponded to 7 such tumours in 243 subjects exposed to both external and internal radiation (27). To within 22 years from exposure, therefore, the diagnosed incidence rate per unit absorbed dose was 145 (70-270) 10^{-6} rad^{-1} (table 7).

TABLE 7. INCIDENCE OF THYROID CANCER IN MARSHALL ISLANDS POPULATIONS

Age at exposure (years)	*Number of subjects*	*Estimated collective dose to thyroid (man rad)*	*Number of cancers*	*Rate per unit absorbed dose (10^{-6} rad^{-1})*
in utero	4	595	0	0 (0-5000)
<10	83	25 315	2	80 (15-250)
10-18	34	7 980	2	250 (45-790)
>18	122	14 645	3	205 (55-535)
Total exposed	243	48 535	7	145 (70-270)
Unexposed	504	–	0	

Source: Reference 27.

110. These data neither support nor exclude a greater sensitivity in childhood, the induction rates per unit absorbed dose in those aged less than 10 years and in those aged more than 18 years at exposure being 80 and 205 10^{-6} rad^{-1}. Both estimates, however, have wide confidence limits and are consistent with the average rate for all ages (table 7).

111. All the cancers have occurred in females (27), indicating a significantly higher induction rate than in males:

> 7 cancers in 130 females exposed, rate 5.4 (2.5-10.2) per cent
>
> 0 cancers in 113 males exposed, rate 0.0 (0.0-2.7) per cent

No cancers were observed in 504 subjects who were unexposed, and no data are available on the relative frequency of naturally occurring thyroid cancers in the two sexes in this population.

C. THYROID CANCER IN PATIENTS THERAPEUTICALLY IRRADIATED FROM EXTERNAL SOURCES

112. Since the Committee's last review of this subject in its 1972 report, further information has become available on the carcinogenic effect of radiation of the thyroid in infancy and in childhood. The earliest reports had been of radiotherapy given for supposed enlargement of the thymus, and the possibility could not be excluded that some abnormality of the thymus, for example in relation to immune mechanisms, was in itself determining an increased incidence of subsequent thyroid carcinoma, since control series did not include children with a corresponding thymic enlargement (see Annex I, paragraph 59).

113. Subsequent evidence, extensively reviewed by Lindsay and Chaikoff (80) however, made it clear that thyroid cancers were developing after irradiation for a wide variety of clinical conditions in infancy or childhood, so that the development of the cancers could not be attributed simply to pre-existing thymic abnormality. Indeed, it seems likely in retrospect that most of the thymus glands irradiated for a supposed enlargement may in fact have been normal.

114. The prospective study of Pifer *et al.* (112) was described in the Committee's 1964 report, which also noted that the analysis by Toyooka *et al.* (153) indicated that 29 of 34 thyroid tumours (malignant and benign) had developed in 472 children treated by combined anterior and posterior radiation fields, whereas only 5 tumours developed in 2111 children treated by anterior fields only.

115. A further report of this study was published in 1967 (56), when 2876 children had been followed for the mean period of 16.5 years, during which 19 thyroid carcinomas had been diagnosed as compared with only 0.14 expected. Since the mean absorbed dose to the thyroid was about 160 rad with the field size ordinarily used, this incidence corresponded to a mean rate of about 40 10^{-6} rad^{-1}.

116. In reviewing these and other series of irradiations involving the thyroid in infancy or childhood, Dolphin (38) in 1968 suggested that the frequency of tumours observed by various authors after different periods of follow-up could be corrected to allow for tumours which might develop subsequently. This correction was made on the basis of information on an observed distribution of latent periods between irradiation and the diagnosis of thyroid cancers. On this basis he inferred that the ultimate incidence would be of about 100 10^{-6} rad^{-1} following mean doses of a few hundred rads delivered in infancy.

117. In 1968, Hempelmann (57) reported further on the series previously described by Pifer *et al.* (112), extending the mean period of follow-up to about 25 years and reporting the diagnosis of further thyroid cancers in the "high-risk subgroup C" involving irradiation by both anterior and posterior fields with an estimated mean thyroid dose of 335 rad. In this group the excess incidence rate of thyroid cancers per unit absorbed dose corresponded to about 130 10^{-6} rad^{-1} as

diagnosed within an average of 25 years following irradiation. Several surveys, however, indicate much lower incidences. For example, Janower and Miettinen (68) found evidence (by postal questionnaires) of only 2 thyroid cancers, as compared with 0.4 expected on the basis of control populations, in 466 subjects irradiated in infacy or childhood at a mean thyroid exposure of about 400 R, surveyed at 30 years after exposure. These values correspond to a risk of only 10 (0-30) 10^{-6} rad^{-1}.

118. A further report by Hempelmann *et al.* (58) has modified the general applicability of the risk estimates derived from the high-risk subgroup C. It is now suggested that much of the increased risk in this group, as compared with the other groups studied, is likely to have been due to a higher induction rate per unit absorbed dose in Jewish than in non-Jewish children, and to the fact that a large proportion of children in subgroup C were Jewish.

119. Table 8 gives separate estimates of these risks. The somewhat higher rates observed for each racial category in subgroup C as compared with other groups is thought likely to be due to the closer surveillance of children from subgroup C and probably also to the longer mean follow-up of this group (31 years) than for others (23.5 years). The dose-effect relationship for thyroid cancers was consistent with, but not necessarily diagnostic of, a linear function (although that for benign tumours appeared not to be). For the dose range and follow-up times involved, these data indicate mean risk estimates of about 160 10^{-6} rad^{-1} and 50 10^{-6} rad^{-1} for Jews and non-Jews in the United States of America irradiated in childhood. This difference may, of course, be due to cultural or environmental circumstances, for example, influencing diet or surveillance, rather than to any genetically determined racial factor. Hempelmann refers to reports (103, 133) indicating a somewhat higher mortality from spontaneous thyroid cancer in Jews than in non-Jews in New York City. Israeli Cancer Registry data (35) show no increased incidence for Jews born in Israel but moderate increases for Jews born elsewhere, as compared with registries from other countries, and particularly if the unusually high values from the 5 Hawaiian registries are excluded (table 9).

TABLE 8. THYROID CANCER FOLLOWING X-RAY EXPOSURE IN CHILDHOOD

Exposure group	*Racial origin*	*Number of cancers*	*Number of subjects*	*Mean dose (rad)*	*Rate (10^{-6} (man rad)$^{-1}$)*
"Subgroup C"	Non-Jewish	4	136	388	76 (26-174)
	Jewish	9	125	410	176 (92-306)
Other groups	Non-Jewish	9	2 506	87	41 (22-72)
	Jewish	2	105	153	124 (22-392)
All groups	Non-Jewish	13	2 642	102	48 (28-76)
	Jewish	11	230	293	163 (92-270)

Source: Reference 58.

TABLE 9. THYROID CANCER REGISTRATION

Persons of all ages

(Annual rate per 100 000)

	Actual		*Age-standardized*	
Registry	*Males*	*Females*	*Males*	*Females*
Israeli				
All Jews	1.6	4.1	1.8	4.2
Jews born in:				
Israel	0.2	1.0	0.3	2.0
Africa or Asia	1.8	5.2	1.6	4.6
Europe or United States	3.2	6.6	2.0	4.0
Non-Jews	0.9	1.2	1.2	2.0
55 other registries				
Mean	1.1	3.2	1.2	3.4
± SD	±1.0	±3.1	±1.1	±3.2
50 other registries[a]				
Mean	0.8	2.5	0.8	2.6
± SD	±0.5	±1.3	±0.6	±1.4

Source: Reference 35.

[a]The 55 registries just above less the 5 Hawaiian registries.

120. The frequency with which thyroid cancer was diagnosed in irradiated females was 2.3 times that in males. This difference was significant and arose mainly owing to a 5-fold difference in frequency in subjects aged 15-29 at the time of diagnosis, the frequencies being equal in the two sexes for those younger or older than these ages. The ratio of 2.3 was considerably lower than that for "naturally occurring" cancer of the thyroid in the two sexes in the same district. No relationship was found between latency and size of dose.

121. A significant excess was observed of 4.7 (1.0-10.9) cases of leukaemia but no estimate of mean marrow dose is available. With regard to other tissues within the radiation field, it may be noted that no malignant tumours of the salivary glands are now regarded as having occurred, the four salivary tumours noted previously now being regarded as benign mixed tumours of these glands. Only one cancer of breast, diagnosed since completion of the main survey, has occurred.

122. Observations published by Modan *et al.* (92) in 1974 suggest that thyroid cancer may be induced by irradiation in childhood (at ages less than 15) at very

much lower absorbed doses. They report a follow-up for 12 to 23 years of 10 902 children irradiated for ringworm of the scalp and subsequently reported as showing an incidence of thyroid cancer in excess of that observed in control populations. One such population was of an equal number of controls matched for age, sex, country of origin and date of immigration into Israel. The second control group consisted of siblings who had not been irradiated and who were within 5 years of age of the irradiated child.

123. The development of thyroid cancers was ascertained in part by reference to a central tumour registry, which was regarded as having 95-per-cent completeness of ascertainment, but which had only been in operation since 1960. Since the irradiations were carried out between 1949 and 1960, this check was supplemented by examination of death certificates, and review of hospital records in the event of deaths involving malignancies or suspicions of malignancies. In both methods of ascertainment, the investigator was unaware of whether the name sought was that of an irradiated or a control subject. By these means, twelve thyroid cancers were shown to have developed, as against 2.0 expected on the basis of the rates observed in the two control series. It was emphasized that this frequency of induction represents an underestimate since ascertainment may not have been complete during the initial period of 0-11 years after irradiation. The minimum induction rate is thus 0.09 (0.04-0.16) per cent.

124. Careful estimates were made (159) of the absorbed dose expected in the thyroid. A "phantom" was irradiated in conditions similar to those used originally, with 5 scalp fields at 350 R per field. The absorbed dose was estimated to vary somewhat in different parts of the thyroid gland from 6.2 to 7.4 rad with an average value taken as 6.5 rad. It is of very considerable interest that on this basis the incidence rate is in close agreement with that observed by Hempelmann following much higher mean doses, Modan's (minimum) estimate for a period of 13-24 years from irradiation being 140 (70-240) 10^{-6} rad^{-1}, but for an estimated mean dose of a few rads only. It is to be noted that this high risk derives (as in paragraph 118) from data on the irradiation of Jewish children.

125. During irradiation, the neck, face and parts of the head were shielded with lead-rubber sheeting. It is clear however, and is emphasized by the authors, that the estimate of dose depends critically on the assumption that the children maintained a constant position during irradiation and did not move so that the thyroid came into the primary field. Since these fields involved an air exposure (focus/skin distance of 25-30 cm) of 350-400 R per field, such errors in alignment would only require to have occurred during radiation of, for example, 5 per cent of fields (and each child was irradiated with 5 fields) for the mean thyroid dose to have been 3 times as high as estimated. Modan has in fact repeated the thyroid dose estimation (160) using a variety of different head positions simulated on the phantom, and with different filtrations (0-1 mm of aluminium). With air doses of 350-400 R to the scalp, the maximum range of estimates for either thyroid lobe was 4-17 rad; but the average value (8.8 rad) differed little from the original best estimate of 6.5 rad. It remains apparent therefore, that malignant thyroid tumours may be induced by quite low doses from external irradiation in children, and that the rate of induction per unit absorbed dose may be comparable with that following mean doses higher by a factor of 50 or so. It may be noted however that in a smaller series of 2215 children irradiated at comparable doses for the same condition (139), six thyroid tumours developed, of which all were classed as benign and none malignant, after a mean follow-up period of 20.5 years.

126. The induction of tumours of brain, salivary gland and possibly skin in this series is dealt with in appropriate sections (see paragraphs 254, 257 and 294).

127. It should be noted that, despite the evidence for the carcinogenic effect of radiation on the thyroid in infancy and in childhood, no excess of thyroid cancers has been observed by Stewart (152) or by McMahon (83) to result from irradiation *in utero*. Both these studies, however, were of mortality, in contrast to those of Hempelmann (58) and Modan (92) which recorded morbidity. The slow progress and low mortality of radiation induced thyroid cancers could therefore account for this difference in findings.

128. Reference has already been made to the long latency between irradiation and clinical diagnosis of many malignant tumours, including those of the thyroid. The occurrence of the small occult sclerosing papillary thyroid cancers, found in high frequency at autopsies on subjects without evidence of thyroid disease during life, in itself shows that tumours with histological characters of malignancy and with metastases to lymph nodes may not develop to a clinically diagnosable state during the lifetime of the subject.

129. Even for clinically significant thyroid cancers, the mean latency appears to be long. Prospective determinations of this mean latency are liable to be truncated by inadequate periods of observation. Retrospective determinations may be affected by the fact that thymus irradiation in infancy was practised only over a limited period of time so that estimates, which have been based largely on resulting tumours developing during childhood, tend to be dependent upon the date of the survey. De Groot and Paloyan (30) however, record a mean age of 20.3 years in 20 patients presenting with thyroid cancer whose glands had received absorbed doses, probably in the region of 500-900 rad, when these patients had a mean age of 7.4 years.

130. Moreover, the available evidence suggests that the latency increases with age at the time of irradiation. Raventos and Winship (122) indicate a rise in mean latency from 10 to about 17 years following irradiation in infancy or during adolescence respectively. Greene (48) obtained similar results in 59 subjects developing thyroid carcinoma, with mean latencies of 9.8 ± 0.7 (S.E.), 12.4 ± 2.3, and 19.0 ± 3.2 years following irradiation at ages of less than 1 year, 1-17 years and over 17 years respectively. Analysis (118) of a number of separate publications also suggests a latency *(L)* rising with age at irradiation *(A)* until adult life, according to the equation $L = 9.4 + 0.27A$.

131. Parker *et al.* (109) point out that new cases continue to be detected in the Adult Health Study population and that 25 new cases have been ascertained in the 5-year period since June 1966 (i.e. at 21-26 years after exposure) as compared with 49 in the previous 8-year period. It is of some significance however, that this ascertainment largely involves cases only detected at autopsy. For clinically ascertained cases, only 6 have been detected in this 5-year period as compared with 34 in the previous 8 years. If the ascertainment truly reflects the rate of new clinical presentations during the corresponding periods, this may suggest some reduction in the incidence of new cases with time.

132. This point is of great importance for estimating the total expected development of tumours during the whole lifetime of irradiated subjects. A report of considerable interest in this connection is that of Refetoff *et al.* (123). These authors describe the findings on examination and at operation on patients who had been irradiated for a variety of reasons (commonly for tonsillar and thymic enlargement) in childhood and who had come for examination only because they were aware of the possible consequences of thyroid irradiation, and not because of any abnormality detected clinically or by themselves. Of 100 patients so examined, operation was recommended in 18 patients who had either discrete thyroid nodules, diffuse enlargement of the gland or abnormal consistency in the absence of raised thyroid autoantibodies. Operation was performed in 15 of these patients, a total extracapsular thyroidectomy being carried out. In 7 cases thyroid carcinomas were found, 5 being shown to be invasive, while 5 were multifocal in character. Four of the glands removed were multinodular, 1 was diffusely enlarged and 1 showed a single nodule on palpation, so that none of these tumours appear to have been of the occult sclerosing papillary type. All were either papillary, follicular of mixed in character.

133. The mean age at irradiation was 4.7 ± 5.2 (SD) years and the mean interval since irradiation was 24.4 ± 5.2 years. The estimated dose to the thyroid varied with the reasons for irradiation, but had an average throughout the whole group of about 750 rad. It is of considerable interest that this incidence of thyroid cancer, undetected clinically at 24 years after irradiation, in 7 per cent of subjects corresponds to a rate of 95 (45-175) 10^{-6} rad^{-1}, which is close to estimates of the frequency with which such tumours are diagnosed clinically at intervals of up to about 20 years following irradiation in childhood or infancy, as in the series reported by Pifer, Hempelmann and others. If all the tumours detected by Refetoff and his colleagues would have become diagnosable clinically during the lives of these subjects, these observations would appear to confirm that a median latency for clinical detection of thyroid cancer following irradiation in infancy may be of the order of 25 years.

134. Similar observations are reported by Arnold *et al.* (8) on 1452 persons with a history of x-ray therapy to the neck for benign disease 18-35 years previously. In 21 per cent, clinical or imaging studies indicated the possibility of abnormality and 193 were explored surgically. Thyroid malignancy was found in 56 of these, the tumours being of the occult papillary type, of diameter less than 1.5 cm, in 40 (11 with metastases to nodes), larger papillary tumours being present in 11 (4 with nodal metastases) and follicular cancers in the remaining 5 (2 with nodal metastases). These observations do not allow risk estimation, since the original radiation exposures are not known and since the persons examined may have been subject to some selection. The detection of such tumours in 4 per cent of irradiated subjects, with 1.1 per cent of other than the sclerosing papillary type, at 2 or 3 decades after irradiation, however, supports both the high incidence and the slow progress of such induced tumours. Becker *et al.* (12) report similar findings in adults who had been irradiated in infancy or childhood, and who were operated upon because of scintigraphic abnormalities at a mean time of 25 years after irradiation. Of 15 operated, 8 were found to have thyroid cancers.

135. Favus *et al.* (45) also examined during 1974, 1056 subjects who had had radiation therapy during the 1940s and 1950s and who were examined in order to detect any resulting abnormality, and not because of any symptoms or known evidence of thyroid disease. If palpable or scintigraphic abnormalities were found, operation was suggested and the findings at operation were known in 182 of the 270 subjects in whom this advice was given, a total of 60 thyroid cancers being found. Of these, 15 were microscopic in size, 6 were less than 5 mm in diameter and 39 were larger. Capsular invasion was noted in 12, blood vessel invasion in 5, and lymph node involvement in 17. Of the tumours larger than 5 mm in diameter, 10 were papillary and 27 were of mixed papillary and follicular structure, only 2 being follicular.

136. The thyroid dose could be most reliably estimated in a group of 859 subjects who had had x-irradiation of the tonsil or nasopharynx only. Their mean age at exposure was 5.4 years, and at examination 32.8 years. The mean dose to the thyroid was estimated at 725 rad, and 57 thyroid cancers were found in this group, corresponding to a risk of 85 (65-105) 10^{-6} rad^{-1} at this dose level, the rate for cancers greater than 5 mm diameter being about two thirds this value and the rate in an unirradiated population being small. Three cancers occurred in the remaining subjects with an estimated 42 600 man rad to the thyroid giving a similar total risk, of 70 (20-185) 10^{-6} rad^{-1} after a slightly shorter period, of 26 years since irradiation at a mean age of 6.7 years. Taking account of the fact that histological findings were known in only two thirds of those subjects for whom surgery was recommended, the authors estimate an annual risk of 4.5 10^{-6} y^{-1} rad^{-1} for the group receiving tonsillar and nasopharyngeal irradiation only, and emphasize that this may be an underestimate of the final risk. If no bias was introduced in the actual selection for surgery of those for whom it was recommended on clinical or scintigraphic evidence, the risk by 27.4 years would be 125 (100-155) 10^{-6} rad^{-1}, with microscopic tumours forming about 25 per cent, and tumours larger than 5 mm forming about 65 per cent of this total.

137. Paloyan *et al.* (108) report the histological findings in 38 thyroid cancers found at operation upon 70

subjects who had nodular thyroids and had had irradiation to the neck in childhood:

13 were papillary (7 in males, 6 in females), 6 having nodal metastases but none with remote metastases

8 were follicular (4 in males, 4 in females), 3 with nodal, and 2 with remote metastases

17 were of mixed papillary and follicular structure (9 in males and 8 in females), 11 with nodal and 2 with remote metastases.

138. These histological findings are characteristic of most reports of radiation induced thyroid cancer, and no excess of anaplastic or medullary cancers has been identified. Only two anaplastic tumours appear to have been reported as following radiation exposure, one being diagnosed 6 years after external irradiation in infancy (140), and the other following radioiodine treatment (10). In both cases the previous irradiation may perhaps have been fortuitous, but it still cannot be excluded that the types of tumour that develop are those characteristic at the age at which they are diagnosed, since the majority of irradiations studied have been in childhood, and tumours arising in early adult life are rarely anaplastic. One case of a probable fibrosarcoma of the thyroid after irradiation has been noted by Hempelmann (see paragraph 148).

D. THYROID CANCER IN PATIENTS TREATED WITH ^{131}I

139. The Committee reported in 1964 (154) that a thyroid carcinoma of low grade malignancy had developed in a child treated for hyperthyroidism with ^{131}I but noted that, apart from this instance, no association had been reported between this treatment and the development of thyroid cancer.

140. In a recent study, Safa *et al.* (129) have followed 87 patients treated in 1949 with ^{131}I for hyperthyroidism at ages of between 3 and 18 years. During the period of follow-up, 5-25 years (with mean 12.3 years), no deaths and no cancers were observed in these patients. The authors refer to a total of seven reports, including their own, in which such patients have been followed clinically for average periods of about 10 years, and in which 2 cases of cancer had developed among the total of 273 patients reported. They emphasize the need for continued and longer periods of follow-up and indeed, if the mean latent period for the development of thyroid cancer following irradiation in childhood is in fact 20-25 years, this estimate must be treated with reserve. It does, however, tend to exclude a high rate of induction following high doses in children. It remains uncertain whether this is attributable to the over-active state of the irradiated gland in hyperthyroidism or to the high absorbed doses used in this treatment, probably of the order of several thousands of rad, with which substantial cell killing must be associated. It is in fact noted that hypothyroidism developed in 40 per cent of the children treated in this series, and in 48 per cent in the six other series noted. Since clinical hypothyroidism ordinarily develops only when the thyroid function, as measured by its radioiodine uptake, has fallen to below about 5 per cent of normal, it is to be presumed that considerable cell killing or inhibition must have taken place in these patients.

141. In adults no excess of thyroid cancer has been observed following the radioiodine treatment of hyperthyroidism in a large series of patients followed for an average time of about 10 years (33). Isolated instances are reported in which such a cancer has followed radioiodine treatment in an adult (87), 11 such cases are noted in one review (90). In view of the very large numbers of patients who have been treated in this way, however, with a predominance of females in the higher age groups at which thyroid cancer incidence is normally greatest, the numbers at present reported do not suggest any excess above a chance expectation. On the basis of the age and sex distribution of patients being treated for hyperthyroidism with radioiodine, an incidence of 44, and a mortality of 16, cases per million patient-years were estimated to be likely to occur by chance among these patients (114) if the normal incidence of thyroid cancer is the same in hyperthyroid patients as in the general population. Since the total experience from this treatment is likely considerably to exceed 1 million patient-years, the present evidence appears to exclude any substantial cancer induction by irradiation at these high doses in adults also. It is, however, important to note that the period of follow-up of many patients is still relatively short, since these treatments were only started 35 years ago and only became common within the last 25 years. Moreover, the activity ordinarily administered has been reduced within the last 10-15 years and it will remain important to confirm that no increased cancer incidence occurs following this use of the rather lower absorbed doses, now commonly in the region of about 4000 rad.

E. SUMMARY

142. In summary, therefore, it is evident that thyroid cancers are induced by radiation at absorbed doses of over 100 rad and probably even at less than 10 rad. The induction rate per unit absorbed dose appears to be somewhat higher in females than in males, and is probably also rather higher in infants and children than in adults. The mortality from radiation-induced thyroid cancers is, however, low, at least during the first 20 years after irradiation, so that although the thyroid shows a high rate for radiation induction of malignancies, it has a relatively low rate for induction of fatal malignancies.

143. The cancers induced are ordinarily of papillary or follicular type; anaplastic or medullary thyroid cancers have not been reported. The frequency of small occult sclerosing papillary tumours is increased by radiation, but these appear to have little or no effect clinically or on mortality.

144. The induction rate per unit absorbed dose in females has been found to be between 2 and 2.5 times that in males in surveys in which this point has been examined. Thus, a ratio of 2.3 is derived from the data

of Parker *et al.* (para. 104) for clinically diagnosable tumours, and also from those of Hempelmann *et al.* (para. 120). In the Marshall Island populations, Conard *et al.* (para. 111) observe rates of 5.4 (2.5-10.2) per cent in females, and 0.0 (0.0-2.7) per cent in males.

145. None of the studies of therapeutic irradiation involving the thyroid give evidence on an effect of age at exposure on cancer induction rate, since adequate groups of people irradiated at different ages have not been equally followed up. However, the findings of Parker *et al.* in Hiroshima and Nagasaki described in paragraph 103 indicate an apparent dependence upon age at exposure, for tumours diagnosed clinically 13-26 years subsequently. The mean rate of detection per ten thousand person-years of survey of those aged less than 10 at exposure was 4.1 ± 2.1 times that for those aged 20 or over at exposure, considering males and females together. The ratio in males could not be determined with adequate accuracy, but that in females was 3.7 ± 2.2. The rate for the males and females who were exposed at age 10-20 is perhaps slightly higher (1.6 ± 0.8 times) than in those who were aged 20 or over. It must be recognized, however, that these inferences as to a variation of induction rate with age at exposure, depend critically upon the assumption that the latent period between irradiation and detection of a tumour does not in itself depend upon age at irradiation. The observations recorded in paragraph 130 suggest that in fact the mean latency may increase with increasing age at exposure, and this effect might explain the present apparent difference in induction rates at different ages.

146. On the other hand, the induction rates observed in the irradiated Marshall Islands population (para. 110) do not support this indication of an age effect, those aged less than 10 at exposure having only 0.4 times the induction rate per unit absorbed dose of those aged over 18. The confidence limits of these estimates are, however, too wide to exclude the possibility of some age effect in the direction observed in Hiroshima and Nagasaki. In the Marshall Islands populations the thyroid doses tended to be considerably higher in children than in adults owing to the greater concentrations of ingested radioiodine in the smaller glands of children. A lower induction rate might perhaps therefore be associated with doses causing substantial cell killing, and cases of impairment of thyroid function were in fact observed in several of these children.

147. In the populations studied, estimated induction rates until about 25 years have mainly been in the range 50-150 10^{-6} rad^{-1} (table 10). The rates in Hiroshima and Nagasaki are, however, conspicuously lower, with values of 37 10^{-6} rad^{-1} absorbed dose on the data of Parker *et al.* (109) or 14 10^{-6} rad^{-1} on those of the Tumor Registry (14). The lower rates in these cities involve some ascertainments by autopsy but depend also on repeated clinical examinations in the Adult Health Survey, so should truly reflect morbidity and not only mortality. It is to be noted that the incidence rates of clinically diagnosed thyroid cancer in the reference populations (those not in the cities, or exposed at less than 1 rad) appear to be substantially higher, at least in females, than in other Japanese, or other national, tumour registries (table 11). These relatively high rates for unirradiated populations in Hiroshima and Nagasaki may well reflect the close surveillance in the Adult Health Survey; if so, they should apply equally in the exposed and the unexposed groups. Moreover, the estimated induction rates would only be increased by about 20 per cent even if the control rates were taken as zero. There appears, therefore, to be no obvious

TABLE 10. THYROID CANCER-INCIDENCE RISK ESTIMATES

Text reference (para.)	*Population studied*	*Period of study (years since irradiation)*	*Type of radiation*	*Dose (rad)*		*Risk in period of study (per unit of absorbed dose) (10^{-6} rad^{-1})*
				Mean	*Range*	
102-106	Hiroshima and Nagasaki (38% male)	13-26	Gamma and neutron	about 200 (kerma)	50->200	37 (23-54); 19 (12-28), weighted dose
107	Hiroshima Nagasaki	14-25	Gamma and neutron		by regression, 0->200	14 (7-20) 14 (6-23)
108-111	Marshall Islands (47% male)	To 22	Internal and external (low-LET)	200	27-1150	145 (70-270)
114-120	Infants and children	To 24 (mean)	Radiotherapy to neck	119	63%<100 29%>200	48 (28-76), non-Jewish; 163 (92-270), Jewish
135-136	Mainly children	To 27 (mean)	Radiotherapy to neck	725	±185	85 (65-105), operated cases; 125 (100-155), inferred, all cases
132-133	Children	Operations at 24 (mean)	Radiotherapy to neck	725	180-1 500	95 (45-175)
122-125	Children	To about 18 (mean)	Radiotherapy to scalp	6.5 (estimated)	4-17	140 (70-240)

TABLE 11. THYROID CANCER INCIDENCE
Persons of all ages
(Annual rate per 100 000)

	Males		*Females*	
Hiroshima and Nagasaki, Unirradiated (clinical diagnoses)	2.7 (0.1-12.5)		12.6 (6.3-22.8)	
Japanese registries	*Uncorrected*	*Corrected*[a]	*Uncorrected*	*Corrected*[a]
Miyagi prefecture	0.7	0.8	2.0	2.0
Okayama prefecture	1.3	1.1	3.8	3.3
58 other registries Mean ± SD	1.1 ± 1.0	1.2 ± 1.2	3.0 ± 3.1	3.4 ± 3.3
53 other registries[b] Mean ± SD	0.9 ± 0.6	0.9 ± 0.6	2.4 ± 1.3	2.6 ± 1.4

Source: Reference 35.
[a]Corrected to population of standard age.
[b]Excluding 5 Hawaiian registries (see paragraph 119).

explanation for the apparent difference between induction rates estimated for these cities and from other sources. The tumour registry data, and the rates observed in unirradiated populations in Hiroshima and Nagasaki, tend to exclude a low rate of spontaneous thyroid cancer as a possible explanation for the low induction rate (table 11), although Parker *et al.* quote one report (132) as indicating a low *mortality* rate for this malignancy in Japan.

148. Few radiation-induced thyroid cancers are reported to have caused death. De Groot and Paloyan (30) record that one patient, out of 20 with thyroid cancers following childhood irradiation, had died during a (mean) period of about 22 years from irradiation, although 4 had post-operative recurrences of the disease. Parker *et al.* (109) note 6 deaths within 26 years of exposure at Hiroshima and Nagasaki in their 40 patients whose thyroid cancer was diagnosed clinically, but only one of these deaths was attributable to the cancer. Wilson *et al.* (162) record 2 deaths from the cancer amongst 58 patients with thyroid malignancies following neck irradiation, occurring within 23 years of exposure. Six of their patients, however, had lung metastases and one had bone metastases. Hempelmann (58) observed no deaths during a mean follow-up of 24 years on 24 patients with apparently radiation-induced thyroid cancer. One other irradiated patient was said to have died subsequently from a fibrosarcoma of the thyroid, but histological confirmation was not obtained.

149. These four reports, therefore, enumerate 4 deaths (or 5, including the fibrosarcoma) occurring in 142 subjects with apparently radiation-induced thyroid cancer, indicating a fatality rate of about 3 per cent within a mean period of 24 years from irradiation.

150. If, ignoring the lower values from Japan, the risk of induction is taken as 50-150 10^{-6} rad^{-1} within about 25 years of irradiation (table 10), with equal numbers to be detected subsequently (para. 132), the lifetime risk of a fatal induced thyroid cancer should be of the order of 5-15 10^{-6} rad^{-1}, assuming a 3-per-cent fatality risk per 25 years, both for the earlier and for the later developing tumours. Such estimates are necessarily tentative but reflect the apparently high frequency and low mortality of radiation-induced thyroid cancer.

IV. BREAST CANCER

A. BREAST CANCER IN A-BOMB SURVIVORS

151. The study of Wanebo *et al.* (158) of the occurrence of breast cancer in A-bomb survivors in Hiroshima and Nagasaki was described in the Committee's 1972 report. In view of the low mortality of most forms of breast cancer during the early years after diagnosis, Wanebo *et al.* examined the incidence of this disease in members of the morbidity sample of the JNIH-ABCC Adult Health Study, and based their evidence on findings at the 6-month health examinations made on this group. This clinical evidence was supplemented by records of local tumour registries, surgical pathology diagnoses, autopsy diagnoses and death certificates. As compared with incidence rates observed in groups exposed to 0-9 rad or not in the city at the time of the bomb explosion, a significant excess of cases was found in the exposed groups, the relative risk increasing with the estimated kerma. The total excess was 11.6 (15 observed compared with 3.4 expected) in females exposed at known doses in excess of 10 rad. If, as suggested by the numbers in each dosage group, the mean dose was in the region of 130 rad, an induction rate of 24 (12-40) 10^{-6} rad^{-1} can be inferred (table 12).

152. While this excess was noted as being statistically significant, it was emphasized that part of the excess might possibly be due to factors other than the radiation, since parity, duration of lactations and frequency of married status were not equal in the exposed and comparison groups and these factors are known to affect breast cancer incidence (85). However, Wanebo *et al.* (158) found no differences in marital status, parity or length of lactation among the 16 women with, and 7819 women without, breast cancer who answered a questionnaire on these points. The average period of lactation in 10 fertile patients with breast cancer who had lactated was shorter than in women without breast cancer (36 months compared with 50 months), but most of this difference was explainable by the fact that there were fewer children in the breast-cancer group. No relationship was found between the frequency of any of these epidemiological factors and radiation dose.

TABLE 12. INCIDENCE AND MORTALITY FROM BREAST CANCER IN HIROSHIMA AND NAGASAKI COMBINED

Females, all ages

Dose group (rad)	*Observed*	*Expected*	*Excess*	*Man rad (10^4)*	*Excess rate (10^{-6} rad^{-1})*	*Induction rate (cases or deaths per thousand persons exposed)*
			INCIDENCE *1958-1966*			
10-39	4	1.14	2.9 (0.2-8.1)	0.023	128 (44-358)	2.3 (0.2-6.4)
40-89	2	0.77	1.2 (neg.-5.5)	0.051	24 (neg.-108)	1.5 (neg.-6.9)
90-199	4	0.72	3.3 (0.6-8.5)	0.110	30 (5-77)	4.1 (0.7-10.6)
>200	5	0.76	4.2 (1.2-9.7)	0.294	14 (4-78)	4.9 (1.4-10.3)
Total	15	3.39	11.6 (5.9-19.7)	0.478	24 (12-41)	3.1 (1.6-5.3)
			INCIDENCE *1950-1972*			
Compared with 0-9 rad group						
10-49	19	15.2	3.8 (neg.-13.4)	0.172	22 (neg.-78)	0.5 (neg.-1.8)
50-99	6	4.0	2.0 (neg.-7.9)	0.150	13 (neg.-51)	0.9 (neg.-3.9)
100-199	8	2.5	5.5 (1.5-11.9)	0.205	27 (7-59)	3.8 (1.0-8.2)
>200	4	2.3	1.7 (neg.-6.9)	0.480	4 (neg.-14)	1.2 (neg.-4.9)
Total	37	24.0	13.0 (3.1-25.1)	1.011	13 (3-25)	1.0 (0.2-1.9)
Compared with Japanese National Statistics						
10-49		12.0	7.0 (0.4-15.9)		41 (2-93)	0.9 (0.1-2.0)
50-99	as	3.2	2.8 (neg.-8.6)	as	19 (neg.-58)	1.3 (neg.-4.0)
100-199	above	2.0	6.0 (2.0-12.4)	above	29 (10-60)	4.1 (1.4-8.5)
>200		1.8	2.2 (neg.-7.4)		5 (neg.-15)	1.6 (neg.-5.4)
Total	37	19.0	18.0 (8.6-29.6)	1.011	18 (9-30)	1.4 (0.7-2.3)

Sources: References 97, 158.
Note: The 90% confidence limits are indicated in parentheses.

153. No further data have been published on the status of the exposed populations in respect of these factors. Examination of the mortality experience in the Life Span Study (97), however, now indicates a significant excess also of deaths from breast cancer occurring in these survivors.

154. For females of all ages and from both cities, the deaths from breast cancer observed from 1950 to 1972 in groups at known doses greater than 10 rad totalled 37. The number expected, on the basis of the 0-9 rad group, was 24; as compared with Japanese National Statistics, 19. From evidence as to the mean doses within these groups, the excess mortality corresponds to rates per unit kerma of 19 (6-35) 10^{-6} rad^{-1} in Hiroshima compared with Japanese National Statistics, and 16 (4-34) 10^{-6} rad^{-1} in Nagasaki. Table 13 gives the mean rates for the different dose groups. The corresponding rates per unit absorbed dose (see paragraph 61) for those exposed at 10 rad or over would be 26 (8-48) 10^{-6} rad^{-1} for Hiroshima and 20 (5-42) 10^{-6} rad^{-1} for Nagasaki, with close agreement between the two cities. The rates would, however, differ substantially if expressed per unit weighted absorbed dose (using weighting factors as in paragraph 55), with values of 6 (2-11) and 17 (4-37) 10^{-6} rad^{-1} in Hiroshima and Nagasaki, respectively. Similar rates apply for higher dose groups in Hiroshima but somewhat lower ones in Nagasaki. While mortality rates per unit kerma of 10-20 deaths per million per rad are consistent with a morbidity rate of 24 (12-41) cases per million per rad, the consistency must be due in part to overlap in the information on which each estimate depends. Thus the morbidity study made use of data from death certificates and autopsy data, and the mortality study included deaths occurring up to 1972, and so will have incorporated records of patients alive in 1966 when the morbidity study terminated.

155. Both in the study of excess morbidity (158) and in that of excess mortality (97) from breast cancer (fig. I), the excess rate per unit kerma in the lowest dose groups considered (10-39 or 10-49) is higher than the average, whereas that in the highest dose group (> 200 rad) is lower than the average rate per unit kerma (table 12). It is difficult to interpret this observation (see Annex I, paragraphs 140-151), which is of uncertain significance statistically, and the agreement of the two reports on this point may be due in large part to their study of the same population. When the rate of induction in various dose groups (cases or deaths occurring per 1000 exposed) is considered in relation to the mean received in each group, there is no clear indication of a kerma giving a maximum yield of tumours (fig. I), since the fall at kerma above 200 rad is statistically not significant. In the mortality studies the total yield falls as the mean kerma rises from 140 to 350 rad in the two highest dose groups, but the estimate in the highest group depends upon only 4 deaths as compared with 2.3 or 1.8 expected, and the significance of this fall is very doubtful.

156. The mortality data suggest that the frequency with which breast cancer has been induced by radiation at Hiroshima and Nagasaki depends considerably upon age at the time of exposure. No deaths from breast cancer had occurred by the end of 1972 in those who were less than 10 years of age at the time of the bomb, of whom 2757 (as at October 1, 1950) had been exposed at known doses of 10 rad or more. Few deaths in excess of

TABLE 13. EXCESS MORTALITY FROM BREAST CANCER IN HIROSHIMA AND NAGASAKI, 1950-1972

Females, all ages

(Compared with Japanese National Statistics)

Dose group (rad kerma)	*Observed*	*Expected*	*Excess*	*Excess rate per unit kerma (10^{-6} rad^{-1})*	*Excess rate per unit absorbed dose (10^{-6} rad^{-1})*
			HIROSHIMA		
10-49	13	9.5	3.5 (neg.-10.2)	27 (neg.-78)	
50-99	4	2.4	1.6 (neg.-6.8)	15 (neg.-65)	
100-199	6	1.3	4.7 (1.3-10.5)	39 (11-87)	
>200	3	1.1	1.9 (neg.-6.7)	7 (neg.-25)	9 (neg.-34)
>100	9	2.4	6.6 (2.3-13.3)	17 (6-34)	22 (8-45)
> 50	13	4.8	8.2 (2.9-15.9)	17 (6-32)	23 (8-43)
> 10	26	14.3	11.7 (3.9-21.8)	19 (6-35)	25 (8-47)
			NAGASAKI		
10-49	6	2.5	3.5 (0.1-9.3)	86 (2-228)	
50-99	2	0.8	1.2 (neg.-5.5)	26 (neg.-121)	
100-199	2	0.7	1.3 (neg.-5.6)	14 (neg.62)	
>200	1	0.7	0.3 (neg.-4.0)	1 (neg.-19)	1 (neg.-23)
>100	3	1.4	1.6 (neg.-6.4)	5 (neg.-21)	6 (neg.-26)
> 50	5	2.2	2.8 (neg.-8.3)	8 (neg.-24)	10 (neg.-30)
> 10	11	4.7	6.3 (1.5-13.5)	16 (4-34)	20 (5-42)

Source: Reference 97.

Note: The 90% confidence limits are indicated in parentheses.

expectation had occurred in those aged 20 or over, most of the excess occurring in those who were 10-19 years old at the time of the bomb explosion. The following data refers to exposures at or greater than 10 rad kerma:

Age group	*Person-years 1950-1972*	*Death from breast cancer*		*Total excess per unit kerma (10^{-6} rad^{-1})*
		Observed	*Expected*	
0-9 years	49 740	0	–	0 (neg.-19)
10-19 years	64 253	10	0.4	34 (18-59)
>20 years	174 319	27	23.7	6 (neg.-23)
All	288 312	37	24.1	13 (3-34)

157. In view of the small number of deaths that have resulted from breast cancer, it is difficult to make any reliable estimate of induction rates, except for age 10-19. Table 14 shows that, for most dose groups, the estimates are non-significant or negative and, even where significant, have wide confidence limits. For those who were aged 20-34, only 2 out of 7 dose groups indicate apparently significant induction, at rates likely to lie between 1 and 40 10^{-6} rad^{-1}; for ages at or over 50, the 100-199 rad group gives a value of 155 (17-457) 10^{-6} rad^{-1}, all others being negative or non-significant; and no group gives a significant result for those aged 35-49. It can only be stated, therefore, that exposures have

TABLE 14. EXCESS MORTALITY FROM BREAST CANCER IN HIROSHIMA AND NAGASAKI, 1950-1972

Females, all ages, dose ⩾ 10 rad

(Compared with mortality in 0-9 rad group)

(Deaths per million per rad kerma)

Dose group (rad kerma) \ *Age at exposure (years)*	*10-19*	*20-34*	*35-49*	*⩾50*	*⩾20*	*⩾10*	*Total cases*		
							Observed	*Expected*	*Excess*
10-49	141 (51-305)	neg	neg	9 (ns)	neg	26 (ns)	19	15.4	ns
50-99	94 (24-250)	27 (ns)	neg	neg	neg	16 (ns)	6	4.0	ns
100-199	neg	26 (ns)	37 (ns)	155 (17-457)	48 (13-103)	31 (8-66)	8	2.5	
>200	13 (2-40)	10 (ns)	neg	neg	neg	4 (ns)	4	2.2	ns
>100	9 (1-28)	15 (1-28)	4 (ns)	47 (ns)	14 (2-33)	12 (4-25)	12	4.7	
> 50	19 (7-41)	17 (2-42)	neg	18 (ng)	9 (ns)	13 (4-25)	18	8.7	
> 10	34 (18-59)	10 (ns)	neg	16 (ns)	6 (ns)	15 (4-87)	37	24.1	
Total cases:									
Observed	10	8	12	7	27	37			
Expected	0.4	5.3	12.6	5.8	23.7	24.1			
Excess		ns	neg	ns	ns				
Mean kerma (rad)									
>10-rad groups	98	81	72	61	74	81			

Source: Reference 97.

Note: neg = estimated excess negative.

ns = excess not significant (at $P = 0.05$).

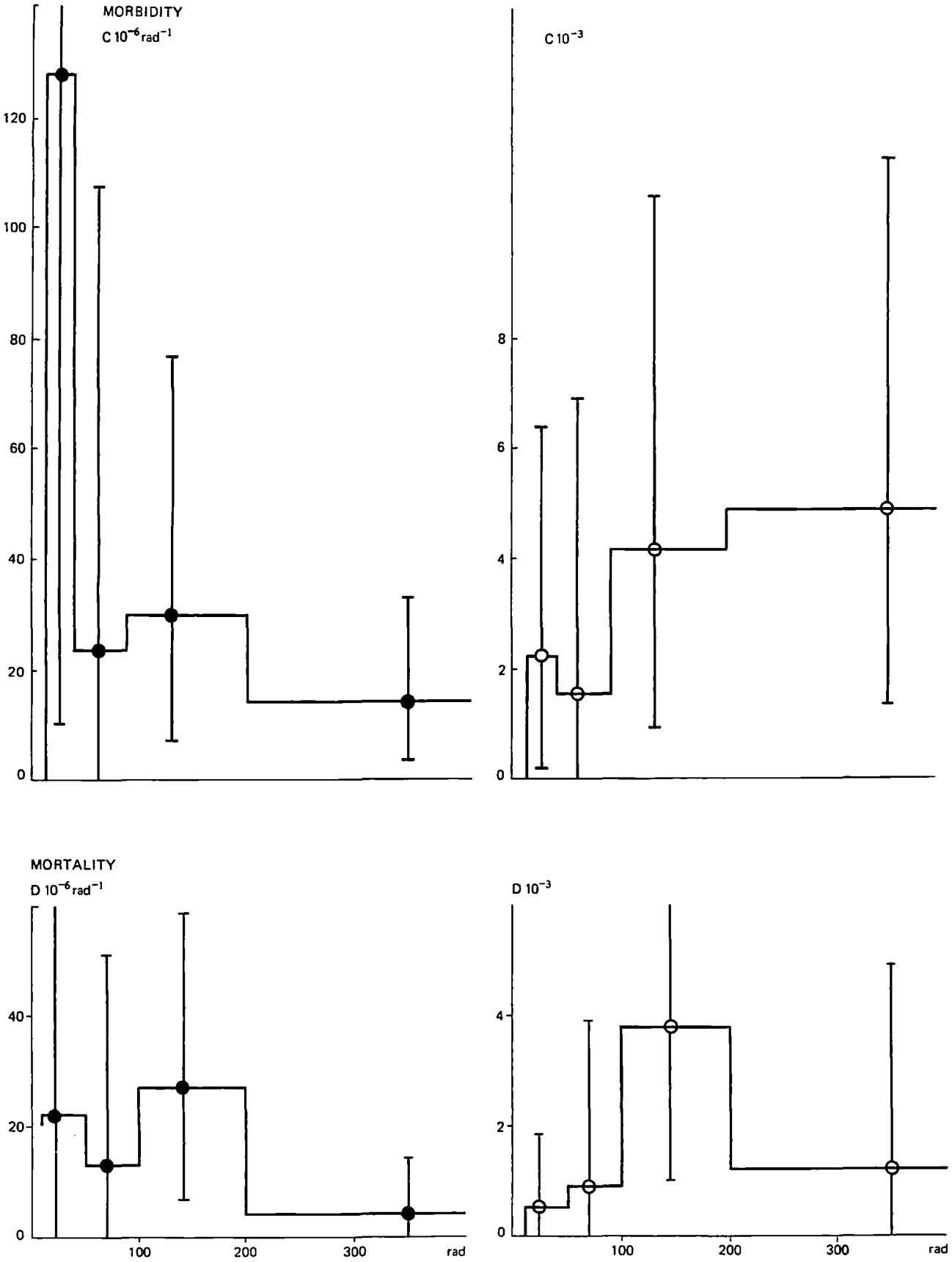

Figure I. Variation of breast cancer induction rate with T65 kerma (Hiroshima and Nagasaki, females, all ages, periods as in Table 12)

Excess rates as compared with 0-9 rad group

Upper diagrams—morbidity (158), excess cases (C) induced
Lower diagrams—mortality (97), excess fatal cases (D) induced
Left diagrams—excess cases or deaths per million man rad
Right diagrams—excess cases per thousand persons
(Ranges indicate 90% confidence limits)

induced breast cancer, fatal within 29 years in those who were aged 10-19, probably also at a low rate in those who were older, but not, or not yet, in those who were younger.

158. It has, however, been emphasized (13) that mortality is far inferior to incidence as an indication of radiation induction of breast cancer and that, whereas the annual excess mortality rates in Hiroshima and Nagasaki in 1950-1974 were 0.43 and 0.26 10^{-6} y^{-1} rad^{-1}, the excess incidence rate during the period 1950-1969 was about 1.5 10^{-6} y^{-1} rad^{-1} in both cities. The incidence of breast cancer in A-bomb survivors has now been reviewed (88) in considerable depth and detail using numerous sources to ascertain the frequency with which breast cancer has occurred in members of the Life Span Study during this period.

159. This report makes a full analysis of

(a) The frequency with which breast cancer is induced in females of each of five age groups (0-9, 10-19, 20-34, 35-49, ⩾ 50);

(b) the distribution in time since exposure (and therefore also in age) with which induced cancers are detectable in each age group;

(c) the way in which the frequency of induced breast cancers increases with estimated kerma or absorbed dose in breast tissue.

160. In the exposed group as a whole, the breast cancer incidence started to increase above expectation within 10, but probably not within 5, years of exposure. In women of different ages at exposure, however, the subsequent time course of the detection of breast cancers differed. In those who had been less than 10 years old, no breast cancers had been detected (by 1969). In those who had been 10-19, few were diagnosed prior to 1960, but in 1965-1969 an ecesss was detectable at an annual rate which exceeded that observed in those who had been older at the time of the bombs. These differences in time course prevent any simple comparison of the way in which ultimate total risk may vary with age. For example, it is not yet known whether those exposed at age 0-9 will show a large excess when they reach the age at which hormonal or other influences determine a full expression of "latent" cancers, or will show only a minimal excess because only few breast cells had developed, and were exposed to radiation, at the time of the bomb explosion.

161. For breast cancers detected in the period surveyed, however, of 5-24 years after exposure, the annual risk per unit kerma of inducing breast cancer varied with age as follows:

Age at exposure (years)	*Cases*	*Person years* 10^6	*Annual incidence per unit kerma, estimate ± SD* (10^{-6} y^{-1} rad^{-1})
0-9	1	0.198	0
10-19	38	0.250	2.4 ± 0.8
20-34	76	0.292	2.1 ± 0.8
35-49	76	0.252	0.6 ± 0.8
⩾50	40	0.115	1.4 ± 1.7
⩾10	230	0.909	1.9 ± 0.45

the incidence rates being determined by estimated slopes of maximum likelihood regression of annual incidence on kerma.

162. The variation of incidence with dose, for all those aged 10 years or more, was consistent with a linear relationship. It is of considerable interest that the slope of this regression was closely similar in the two cities, despite the difference in neutron component of the radiation. Thus, the risk estimates per unit kerma for all aged 10 or over were 1.8 ± 0.6 and 2.0 ± 0.7 10^{-6} y^{-1} rad^{-1} in Hiroshima and Nagasaki; or, when the populations were standardized with regard to age distribution, were 1.90 10^{-6} y^{-1} rad^{-1} in Hiroshima and 1.88 10^{-6} y^{-1} rad^{-1} in Nagasaki. The corresponding rates per unit absorbed dose would be 2.6 10^{-6} y^{-1} rad^{-1} in Hiroshima and 2.4 10^{-6} y^{-1} rad^{-1} in Nagasaki.

163. The mean latency after which induced cancers were detected did not vary with dose, 50 per cent of all tumours diagnosed between 1950 and 1969 being detected by about 18 years from exposure in each age group (0 to 9, 10 to 99 and ⩾ 100 rad, for women less than 30 years old at the time of exposure).

164. Wanebo *et al.* (158) report that the histological types of tumours occurring in subjects who had been exposed in Hiroshima and Nagasaki at over 60 rad (T65 kerma estimate) were similar to those occurring in those who were exposed at lower dose. Of 12 cancers from the former group, 11 were duct carcinomas, one was a comedo carcinoma, and all were of infiltrating character. In the latter group also, all were infiltrating, 8 being ductal, one a comedo type and one an infiltrating colloid carcinoma. A more recent survey (74) confirms this indication that types of breast cancers are induced in about the proportions in which they occur "spontaneously" in the same population, the great majority being infiltrating ductal carcinomas. This type represented 85, 85 and 76 per cent of cancers examined in unirradiated persons (at 0 rad, or not in the cities), in those exposed at 1-99 rad, and in those exposed at 100 rad or over respectively. The tumour had remained intraductal, and therefore presumably of good prognosis, in 13, 9 and 21 per cent in these groups. Other types of cancer represented only a small proportion of each series. (The total series was of 225 cancers classified histologically, with 118, 74 and 33 from the three groups). Yoshizawa and Kusama (168) have surveyed a number of published series of radiation-induced breast cancers and note that most such cases are reported as of ductal origin.

B. BREAST CANCER FOLLOWING EXPOSURE IN DIAGNOSTIC RADIOLOGY

165. The occurrence of breast cancer in patients treated for pulmonary tuberculosis by artificial pneumothorax was reported by Mackenzie in 1965 (82) to be in excess of expectation, and this excess was regarded as probably attributable to the large number of fluoroscopic examinations required to control the lung collapse. Breast irradiation will have been substantial, since Mackenzie's patients commonly faced towards the x-ray tube rather than towards the screen during the

fluoroscopies. Myrden and Hiltz (99) extended this survey, and reported 22 cases of breast cancer in 300 patients treated with pneumothorax (7.3 per cent) and four cases in 483 patients not so treated (0.8 per cent). The annual incidence in the pneumothorax treated patients was about 6.5 times that in the general female population of Nova Scotia, but that in the tuberculous patients untreated by pneumothorax did not differ significantly from this general rate. There was commonly an agreement between the side on which the carcinoma developed and that on which the pneumothorax, when unilateral, was established.

166. In its 1972 report the Committee discussed estimates of the dose likely to have been delivered to breast tissue and concluded that it may have been in the range 4-20 rad per examination. On the basis of this estimate, and of the number of examinations involved, which commonly exceeded 100, it was concluded that the observed excess of 20 cases in 300 treated patients would correspond to a rate of (20-120) 10^{-6} cases per rad as diagnosed in the 20 years following initial exposure with 90% confidence limits of (15-160) 10^{-6} rad^{-1}. Myrden and Quinlan (100) state that a further follow-up which now extends for 22-32 years, of 326 patients with pneumothorax shows 32 breast cancers to have developed (as compared with 22 in the group in 1967). A control group of 535 patients with pulmonary tuberculosis but without pneumothorax or multiple fluoroscopies have shown seven breast cancers compared with four in 1967. Without correcting for the patient-year total of surviving patients, the excess cancer incidence rate appears now to be of (30-140) 10^{-6} rad^{-1} on the dosimetric basis assumed in the last report of the Committee, with confidence limits (20-200) 10^{-6} rad^{-1}. This estimate may be low since it is uncorrected for the death of 104 of the original 326 patients, and the failure to trace 18 others. Brown (19) has used the frequency with which the tumour and the pneumothorax were on the same or on different sides of the body, to estimate the dose that is likely to have been delivered to the breast on the side opposite to the pneumothorax. By this method he obtains a factor of 1.5 by which he considers that the estimate of risk per unit absorbed dose to the breast (on the side of the pneumothorax) should be increased, to determine the risk for equal irradiation of both breasts.

167. The additional 10 cancers have developed in patients who were aged 20 to 39 at fluoroscopy and crude incidences suggest a rather lower induction rate in those over 30 at the time of exposure:

Age (years)	*Patients (initial number)*	*Breast cancers*	*Incidence (%)*
0-19	59	6	10 (4-20)
20-29	181	23	13 (9-18)
⩾30	86	3	4 (1-9)

The cancers have proved fatal in 14 of the 32 fluoroscoped patients, and in 3 of the 7 others.

168. Boice and Monson (17) have reported a significant excess of breast cancer (41 observed and 23.3 expected) in 1047 women who had had an average of 102 fluoroscopies during pneumothorax or pneumoperitoneum treatment and who were followed up for a mean period of 26.8 years. Just over half of the total person-years at risk were in the period of 15-45 years after exposure. No excess occurred (15 observed, 14.1 expected) in 717 women from the same sanatoriums who had not had such treatment for their tuberculosis.

169. The excess breast cancer incidence started to appear 15 years after the exposures and was continuing at 40 years from exposure. The risk increased with estimated dose in a way consistent with a linear dose-effect relationship. For the whole group, the mean dose to breast was estimated as 150 rad assuming a 15-s exposure yielding a 1.5-rad dose to breast per fluoroscopy. This implied a total risk during the 26.8 year period of follow-up of (41-23.3)/(1047× 150) = 113 (50-190) 10^{-6} rad^{-1}. The authors estimate an annual risk rate of 6.2 (2.8-10.7) 10^{-6} y^{-1} rad^{-1} by comparison with New York State health statistics (or 5.6 relative to the comparison group of patients). A rate of 2.9 10^{-6} y^{-1} rad^{-1} is obtained by fitting a linear regression to all data, or 8.2 if this analysis is confined to doses of less than 300 rad. For doses less than 100 rad an increased risk was observed but was not statistically significant. However, the relationship between excess rate and estimated absorbed dose in the breast was consistent with linearity over the whole range of doses used, although some reduction of risk is suggested by the data at high doses (corresponding to over 150 fluoroscopies).

170. Most of the observed excess, 10.7 (4.9-18.8) cases, occurred in 341 women who were younger than 20 (although older than 13) at the time of the exposure. The remainder, 7.0 (−0.8-17.1) cases, was observed in 706 women of 20 or older at exposure, who were followed up for a mean time (26.9 years) comparable with that for those aged under 20 (26.4 years). The total excess rate during these periods of time taking account of the estimated mean breast dose at each age (17a) is 162 (74-285) 10^{-6} rad^{-1} for those who were under 20 and 78 (−8-189) 10^{-6} rad^{-1} for those who were 20 or over. The wide 90% confidence zones clearly prevent any determination of risk rates at higher ages than 20 (although the excess rate is just significant for ages 20-29, at 108 (11-297) 10^{-6} rad^{1}). They do, however, appear to indicate that the rates are highest in those exposed in adolescence. For all cases, the mean interval between exposure and diagnosis of a breast cancer was 24.4 years. Allowing for the expected incidence at different periods, the mean latency for induced cases is estimated as about 27 years.

171. The authors emphasize the substantial uncertainties in estimating retrospectively the doses to the breast. From questions to patients and physicians it was concluded that the patient faced the tube in about one quarter of all the examinations. Interviews with physicians led to the acceptance of a mean exposure time of 15 s, and to the conclusion that 69 per cent of physicians had worked with the fluoroscope shutters open so that both breasts were exposed to radiation: 81 per cent always also scanned the opposite lung.

Estimates of dose, and thus of risk, are therefore more nearly applicable per patient than per single breast: and it was in fact found that the cancer was on the same side as the pneumothorax in 17 cases, and on the opposite side in 12.

172. As noted in the 1972 report of the Committee (Annex H, para. 120), the high incidence of breast cancer in the series reviewed by Myrden and Hiltz (99) may have resulted from the procedure adopted, with the patient facing the x-ray tube so that breast tissue received high doses. Similar frequencies have not been observed in several other series, in which the same position was not used, or if mortality rather than morbidity was studied, as in the report of Kitabatake *et al.* (78). Here 568 patients, who had received an average of 75 pneumothorax refills between 1941 and 1961, were reviewed in 1975. No deaths had resulted either from breast cancer (0.4 expected) or from lung cancer (1.6 expected).

173. Similarly Delarue *et al.* (31) found no increased incidence of breast cancer in patients followed for a minimum of 20 years, and who had had multiple fluoroscopies in the supine position (i.e. with back towards the x-ray tube and receiving 17 rad per examination, whereas the prone position would have involved 308 rad per examination). Six breast cancers had developed in 269 fluoroscoped patients as compared with 8 in 260 patients who had not been fluoroscoped.

174. It is of interest that Janower and Miettinen (68) report the occurrence of 3 breast cancers in 466 individuals who were irradiated for thymic enlargement during childhood or infancy. No estimate is given for the dose to breast tissue but that to the thymus was about 400 R and the anterior radiation field used in 92 per cent of cases was planned to extend down from the level of the suprasternal notch, with a maximum cone diameter of 12.7 cm. Two breast cancers were recorded in 2604 unirradiated controls, the period of follow-up (from irradiation to the date of the postal questionnaire) being 30 years. On the basis of the control series, the probability of 3 or more breast cancers occurring in the exposed group would be 0.006—but this estimate is not strictly valid since the incidence of breast cancers is tested for statistical significance *because* it is raised. If breast tissue received the same exposure as the thymus, a risk estimate of (3-0.4)/(466 X 400), or 14 (2-40) 10^{-6} R^{-1}, is obtained. The risk per rad cannot be derived with confidence, but is unlikely to be higher by a factor of more than 1.25.

C. BREAST CANCER FOLLOWING RADIOTHERAPY TO THE BREAST

175. Mettler *et al.* (91) reported 13 confirmed cases of breast cancer occurring among 606 patients treated for acute post-partum mastitis by radiation to the breast area. The mean exposure of the irradiated breast was 346 R. Only one breast was irradiated in many cases, and the mean exposure of breast tissues as a whole was estimated at about 210 R. This incidence, which was observed during follow-up periods of 10-25 years, was clearly in excess of that (5.9 cases) expected in a general female population at the same ages. No data were available however of the incidence of breast cancer following post-partum mastitis untreated by radiation. If radiation were, however, the sole factor responsible, the excess would correspond to an induction rate of 55 (15-115) 10^{-6} rad^{-1} to all breast tissue.

176. An important further study (138) on this group of patients has now been reported, in which it was possible to examine the incidence of breast cancer in two groups of patients who had had post-partum mastitis—which had been treated by x-ray therapy in one group but not in the other. The incidence was examined also in further control groups consisting of sisters of members of each of these groups. This procedure is of value in controlling, not only against possible differences in breast cancer incidence for genetic reasons in different families, but also against any such differences in different localities since the irradiated patients were mainly from one town and the unirradiated patients from another. All diagnoses were confirmed histologically.

177. The dose to the irradiated breast was commonly in a range corresponding to an exposure of 100-400 R in air, and the mean absorbed dose was estimated as 377 rad to this breast. The average dose to both breasts was estimated as 247 rad per treatment.

178. The breast cancer incidence in irradiated women started to exceed that expected on the basis of the control groups at 12-15 years after irradiation. Thereafter, new cases appeared annually in excess of the expectation in 0.27 per cent of exposed subjects. There was some suggestion of a decrease in latency with increasing exposure, but this was of uncertain significance. The time intervals until detection of 25 per cent of excess cases (percentage of all cases diagnosed by 30 years, determined by life-table methods), with 80% confidence zones were:

Dose group (R)	*Interval to 25% of cases (years)*
50-199	20.5 (17.7-22.0)
200-400	19.4 (13.0-21.6)
400-1 100	13.9 (8.5-16.7)

179. The relationship between relative risk and mean exposure to both breasts remained closely consistent with linearity until a mean exposure of 234 R (group 200-229 R). The relative risk at the highest exposure, at 401 R (group 300-550 R), however, was lower than that at 234 R, with a value about 0.57 (0.31-1.03, 80% confidence zone) of that expected if the linear regression had continued. This indication of a maximum yield of cancer at a mean absorbed dose in the region of 300 rad is not as clearly established in other human epidemiological findings (but see figures I and II) but is commonly demonstrable for cancers in animals (see Annex I). The dose-effect relationship for estimated dose to single breasts (rather than mean dose to both

breasts) does not show as clear an initial linearity, but the relative risk again reaches maximal values of 3.53 (at 264 R) and 3.55 (at 452 R) and then falls to 2.29 (at 733 R).

180. No excess of cancers was detected within 10 years of irradiation, and life-table methods were used to derive the subsequent annual risk of cancer induction until 34 years from irradiation, the population (571 women) having been followed up over a mean period of 25.2 years. The estimated annual rate in the whole exposed group during this 24-year period was $8.3\ 10^{-6}\ y^{-1}R^{-1}$ where the value for the exposure is taken as the mean value for both breasts. In a separate analysis, the annual risk from irradiating one breast was estimated to be $5.0\ 10^{-6}\ y^{-1}R^{-1}$. Over 80 per cent of the total number of cancers induced would be diagnosed only after 20 years following exposure.

181. The risk of cancer induction was somewhat greater in those exposed at an age of over 30 than in those who were younger:

Age at exposure (years)	*Number of subjects*	*Induction rate ($10^{-6}\ y^{-1}\ R^{-1}$)*
15-29	397	7.3
⩾30	173	12.0

182. In the period of survey, 7 of the 37 breast cancers occurring in the exposed group had proved fatal, as had 8 of 34 cancers in the comparison groups. The time intervals between irradiation and death, and between detection of the cancer and death, were not reported, but the figures indicate a mortality risk from breast cancer within a mean period of 25 years from exposure which is about one fifth the incidence risk during the same period. This unusually low fraction of breast cancers proving to be fatal (see paragraph 18) is likely to be due to the short average period of follow-up since many of the cancers were only recently diagnosed, and to the fact that most of the women treated were in the younger age groups at the time of exposure.

183. It is of interest that the risk per unit exposure proved to be about equal following treatments given in 1 or 2 fractions (mean total exposure 143 R, risk $8.3\ 10^{-6}\ y^{-1}R^{-1}$) or in 3 or more fractions (mean total exposure 235 R, risk $9.6\ 10^{-6}\ y^{-1}\ R^{-1}$), suggesting that increasing the number of fractions does not reduce the carcinogenic effect of the total dose given, although here the exposure per fraction does not appear to have differed greatly in the two groups. The risks per unit dose are unlikely to be higher than those quoted per roentgen by factors of more than 1.1.

184. This study is of particular value in presenting adequate controls for any increased incidence of breast cancer following acute post-partum mastitis *per se*, as well as tending to exclude genetic or geographical bias, since the two groups of patients with mastitis and their sibling controls were drawn from different parts of New York State. It appears to determine the observed carcinogenic effect as being due to radiation, although, as the authors note, the effect of radiation on inflamed and lactating breast might differ quantitatively from that on normal breast tissue.

185. Another prolonged follow-up study (11) has been made of patients who had had x-ray treatment of breast conditions, and in whom an increased incidence of breast cancer was detected subsequently. Radiotherapy was given to 1115 women in the period 1927-1957 at the Radiumhemmet in Stockholm for benign diseases of the breast, mainly for fibroadenomatosis, but for acute mastitis in 120 cases and for chronic mastitis in 49. In most instances only one breast was irradiated, the mean dose to this breast being relatively high, about 845 rad. In 1023 of these patients, who were followed up for a mean period of 31.5 years, 115 cancers occurred in the irradiated breasts, and 20 in unirradiated breasts, at periods of over 5 years after irradiation. From Swedish breast-cancer incidence data (available since 1970), the expected number in each breast having regard to the ages of patients at risk would have been 19.9; or, since 14 per cent of patients had irradiation to both breasts, 28.7 per irradiated breast.

186. The excess in unirradiated breasts is not significant. That in irradiated breasts corresponds to a risk rate of $(115\text{-}28.7)/(1168 \times 845) = 87\ 10^{-6}\ rad^{-1}$ per breast to 31.5 years or about $175\ 10^{-6}\ rad^{-1}$ per patient if both breasts had been irradiated.

187. Excluding 9 cancers which were detected within 6 years of treatment, the mean latency from irradiation to diagnosis was 23.6 years. The distribution of latencies (uncorrected for a presumably diminishing number of person-years at risk during later periods) was shown by the observation that 13 per cent of cancers developed at 6-14 years from irradiation, 38 per cent at 15-23 years, 34 per cent at 24-32 years and 15 per cent at over 32 years. The mean latent period decreased somewhat with increasing dose:

Dose group (rad)	*Latency mean ± SE (years)*
1-499	25.8 ± 1.4
500-999	25.5 ± 1.2
1 000-1 499	21.6 ± 1.9
1 500-3 999	19.3 ± 1.4

However, the mean administered dose increased markedly with age at the time of treatment (from 420 rad at age 10-29, to 770 rad at age 30-49 and 960 rad at age 50 or over), and it is uncertain whether the mean period of follow-up varied with age at exposure, or whether latency varies with this age *per se*. Either factor, or the increased death rate of older patients from other causes, might possibly be responsible for the apparent relationship between latency and dose. A small apparent reduction in mean latency with age at exposure (from 26 years following irradiation at ages less than 30, to 22 years for greater ages) may well be due to the confounding of dose size with age.

188. The authors show that the numbers of cancers induced per rad and per breast vary markedly with age at

exposure in a manner similar to that seen in other studies, with apparently higher incidence rates following exposure at ages less than 30:

Age at irradiation (years)	*Number of breasts*	*Breast cancers*		*Excess rate per breast (10^{-6} rad^{-1})*
		Observed	*Expected*	
10-19	28	2	0.25	219 (18-757)
20-29	205	31	3.4	308 (212-429)
30-39	333	28	8.3	89 (52-136)
40-49	311	20	8.9	40 (16-73)
⩾50	119	7	3.1	34 (1-88)
All	996	88	24.0	90 (69-114)

These values relate to the total excess numbers of cancers detected, and indicate an increased sensitivity of the breast to cancer induction at younger ages, unless the periods of follow-up varied so markedly with age that the reduction at greater ages merely reflects a lower ascertainment of induced tumours. This appears most improbable in view of the magnitude of the reduction in rate.

D. SUMMARY

189. In summary, therefore, it is clear that breast cancers may be induced with relatively high frequency by radiation, particularly in adolescence and early adult life. The cancer is of the type arising initially from duct cells, but is commonly found to be infiltrating breast tissue. Cases start to appear in excess of normal expectation within 10 years of irradiation, and new cases continue to appear for over 30 years more, the mean latency probably being in the region of 25 years.

190. Three bases can be used for estimating the carcinogenic risk of breast irradiation in women: namely, from the Japanese Life Span Study, from sequels of repeated fluoroscopy, and following radiotherapy to the breast. From Hiroshima and Nagasaki mortality records, the risk rate per rad kerma for 1950-1972 was about $0.6\ 10^{-6}$ per year, or $13\ 10^{-6}$ during the whole period by comparison with the 0-9 rad group, or $19\ 10^{-6}$ as compared with Japanese National Statistics. The rates per rad for 1950-1974 as determined by regression analysis over all dose groups were 0.43 and $0.26\ 10^{-6}\ y^{-1}\ rad^{-1}$ for Hiroshima and Nagasaki, respectively, or 0.36 for the two cities combined.

191. On incidence data, however, the mean annual rate per unit kerma for 1950-1969 was $1.9\ 10^{-6}\ y^{-1}\ rad^{-1}$ for those aged 10 or over at exposure, of $1.5\ 10^{-6}\ y^{-1}\ rad^{-1}$ for the whole exposed population, giving an average incidence rate over the period of about $30\ 10^{-6}\ rad^{-1}$ for all ages. This incidence rate, of 3 or 4 times the mortality rate in the same period, appears consistent with a rather slow course and high cure rate for breast cancer of the types induced (see paragraph 18 and reference 40).

192. The risk rates inferred from studies following radiological procedures, however, are considerably higher. After multiple fluoroscopic examinations, one study (para. 168 ff.) gives an annual rate of $6.2\ 10^{-6}\ y^{-1}\ rad^{-1}$ for those patients surviving 10 years after the examination, and about $4\ (2\text{-}7)\ 10^{-6}\ y^{-1}\ rad^{-1}$ for the whole series (with an incidence rate per unit absorbed dose of about $110\ (50\text{-}190)\ 10^{-6}\ rad^{-1}$ during the mean follow-up of 27 years). It is likely that much of the estimated breast dose applied bilaterally, but rates for uniform irradiation of both breasts might be somewhat higher. The dose estimates must however be regarded as highly uncertain owing to lack of direct evidence as to the duration of the fluoroscopies.

193. In another study (para. 165), dose estimates are also quite uncertain, but an annual rate in the region of $(1\text{-}7)\ 10^{-6}\ y^{-1}\ rad^{-1}$ is suggested (with an integral effect of $(20\text{-}50)\ 10^{-6}\ rad^{-1}$ over the 22-32 year period of present follow-up). The rates in this study should probably be increased by about 50 per cent to apply for bilateral breast irradiation.

194. Following radiotherapy, a survey (para. 176 ff.) with detailed control studies yielded an estimated annual incidence rate of $8.3\ 10^{-6}\ y^{-1}\ R^{-1}$ for bilateral breast irradiation (implying a total incidence rate of $210\ 10^{-6}\ R^{-1}$ in the 25-year mean period of follow-up). Analysis based on single-breast exposure gave the somewhat higher annual rate of $10\ 10^{-6}\ y^{-1}\ R^{-1}$. The further study following irradiation for various benign breast conditions (para. 185) yielded a rate of about $2.8\ 10^{-6}\ y^{-1}\ rad^{-1}$ for single-breast exposure (corresponding to a total risk for bilateral exposure of $175\ 10^{-6}\ rad^{-1}$ during the mean period of 31.5 years follow-up).

195. There is thus a substantial discrepancy between the induction rates estimated for the Japanese populations and those for patients exposed to either diagnostic or therapeutic radiological procedures. Although surveyed over comparable periods of time, 25-30 years after exposure, the Japanese incidence rates per unit kerma for those older than 10 at exposure, have been $1.9\ 10^{-6}\ y^{-1}\ rad^{-1}$ or about $2.5\ 10^{-6}\ y^{-1}\ rad^{-1}$ (absorbed dose). The rates estimated following radiological procedures range from 2 to 10, with a figure of $(6\text{-}8)\ 10^{-6}\ y^{-1}\ rad^{-1}$ being consistent with all of these series.

196. Mortality risk rates are estimated at about 0.25 times the incidence rates in the Japanese Life Span Study. In one of the surveys after fluoroscopy the mortality rate was 0.45 times the corresponding incidence rate, whereas following one radiotherapy series it was 0.2 times the incidence rate. To a period of 25-30 years after exposure therefore, approximate values for the total risk rates per unit absorbed dose (bilateral absorbed dose) to adults would be of an incidence of about $50\ 10^{-6}$ on Japanese data, or $200\ 10^{-6}$ on surveys following radiological procedures. The corresponding mortality risk rates within this period would be about $10\ 10^{-6}$ from the Japanese studies, or about $60\ 10^{-6}\ rad^{-1}$ from radiological surveys.

197. Several factors may contribute to the discrepancy between these sources of risk estimates. Firstly, the natural incidence of breast cancer in Japan is somewhat lower than in most other countries, with an average annual incidence rate in females in 2 Japanese cancer registries of 11 and $14\ 10^{-5}\ y^{-1}$, as compared with a mean value in 41 registries in other countries of 46 (SD 23) $10^{-5}\ y^{-1}$. This difference in incidence is due mainly to a lower incidence at older ages in Japan than elsewhere. This is strikingly demonstrated by estimating the ratio between the mean incidence rate for age 60-75 to that for age 40-55. In the 2 Japanese registries, this

ratio is less than 1 (0.59 and 0.69, and 0.64 for Japanese populations in Hawaii). In the 41 other registries for which the ratio can be derived, the lowest value is 0.97 and the mean is 1.48 (SD 0.24). It is not obvious, however, how this striking difference would affect the induction of tumours by radiation or their expression.

198. It must also be recognized that the whole basis of the dose–and therefore the risk–estimation for the surveys following fluoroscopy, depends upon the opinion of physicians that the average time that they spent on pneumothorax fluoroscopies, which in most cases ceased to be performed many years previously, was 15 s. It is hard to feel sure that this estimate would be accurate, and easy to imagine that it could be systematically biased in one direction or the other. In addition, in the studies following radiotherapy, the abnormality of the breast tissue clearly also represents another source of possible bias since, although it has now been clearly shown that acute post-partum mastitis is not followed by any increased breast cancer incidence, the irradiation of an infected and lactating gland could possibly be more carcinogenic than that of the normal gland.

199. It remains clear, however, that the breast is of relatively high susceptibility to radiation carcinogenesis, particularly when exposed during adolescence.

V. LUNG CANCER

200. In the 1972 report the Committee discussed estimates for lung cancer incidence in survivors of the A-bomb explosions at Hiroshima and Nagasaki, in uranium miners, in patients irradiated for ankylosing spondylitis and in certain groups of tuberculous patients who were likely to have received repeated diagnostic chest x rays.

A. LUNG CANCER IN A-BOMB SURVIVORS

201. Further information has been published on mortality from lung cancer in the JNIH-ABCC Life Span Study (97). During the period 1950-1972, 100 deaths occurred from malignant neoplasms of trachea, bronchus and lung (referred to in this section as "lung cancer") in the groups exposed to known doses in excess of 10 rad (table 15). The numbers expected on the basis of the mortality experience in the 0-9 rad group are 78.4, so that the excess is 21.6 (6-40). However, it must be noted, firstly, that the induction of any cancers in the group exposed at 0-9 rad will reduce the estimate of risk for the higher dose groups, and secondly, that the small number of deaths occurring in this 0-9 rad group will, in itself, increase the statistical uncertainty of the control rate and therefore of the estimate of excess in other groups.

TABLE 15. EXCESS MORTALITY FROM CANCERS OF THE TRACHEA, BRONCHUS AND LUNG IN HIROSHIMA AND NAGASAKI BY DOSE GROUP, 1950-1972

Males and females, all ages

(Compared with 0-9 rad group)

Dose group (rad)	*Observed*	*Expected*	*Excess*	*Excess rate per unit kerma (10^{-6} rad^{-1})*	*Excess rate per thousand persons (10^{-3})*
			HIROSHIMA		
10-49	49	34.4	14.6 (2.8-28.6)	70 (13-137)	1.5 (0.3-2.9)
50-99	13	9.0	4.0 (neg.-12.3)	24 (neg.-75)	1.7 (neg.-5.3)
100-199	10	5.8	4.2 (neg.-11.3)	21 (neg.-56)	2.9 (neg.-7.7)
>200	8	4.4	3.6 (neg.-10.0)	8 (neg.-21)	2.8 (neg.-7.7)
>100	18	10.2	7.8 (1.2-16.7)	12 (2-26)	
> 50	31	19.2	11.8 (3.2-22.6)	14 (4-27)	
> 10	80	53.6	26.4 (10.4-44.6)	25 (10-42)	
			NAGASAKI		
10-49	7	12.4	−5.4 (neg.-1.9)	−78 (neg.-27)	neg. (neg.-0.5)
50-99	1	4.2	−3.2 (neg.-0.8)	−41 (neg.-10)	neg. (neg.-0.6)
100-199	7	4.0	3.2 (neg.-9.4)	19 (neg.-57)	2.8 (neg.-8.4)
>200	5	4.2	0.8 (neg.-6.5)	2 (neg.-17)	0.7 (neg.-5.5)
>100	12	8.2	3.8 (neg.-11.6)	7 (neg.-21)	
> 50	13	12.4	0.8 (neg.-8.3)	1 (neg.-13)	
> 10	20	24.8	−4.8 (neg.-6.6)	−7 (neg.-9)	

Source: Reference 97.

Note: The 90% confidence limits are indicated in parentheses.

202. In Hiroshima, 80 deaths occurred in those exposed at known doses of 10 rad or more, as compared with 53.6 expected on the basis of the 0-9 rad group, indicating an excess of 26.4 (10.4-44.6). This excess corresponds to an induction rate of 25 (10-42) 10^{-6} rad^{-1} (kerma). No estimates have been published for the ratio of absorbed dose in lung to kerma for gamma and neutron radiation. Table 16, however, shows that the rates per rad kerma do not differ considerably from those per rad weighted absorbed dose, using weighting factors as in paragraph 55, and absorbed-dose/kerma ratios based either on the Committee's assumption in its 1972 report of the lung as being at a depth of 4 cm, or on the values quoted for a deep-sited organ such as the stomach (53).

TABLE 16. EXCESS MORTALITY FROM LUNG CANCER PER UNIT OF WEIGHTED ABSORBED DOSE,[a] HIROSHIMA, 1950-1972

Males and females, all ages
(Compared with rates in 0-9 rad group)

Kerma group (rad)	*Excess rate per unit kerma (10^{-6} rad^{-1})*	*Excess rate per unit weighted absorbed dose (10^{-6} rad^{-1}) using absorbed dose/kerma ratio*	
		As for 4-cm depth	*As for stomach*
>200	8 (neg.-21)	7 (neg.-18)	11 (neg.-28)
>100	12 (2-26)	8 (1-16)	14 (2-31)
> 50	14 (4-27)	8 (2-15)	15 (4-29)
> 10	25 (10-42)	11 (4-19)	24 (10-40)

[a] See paragraph 202.

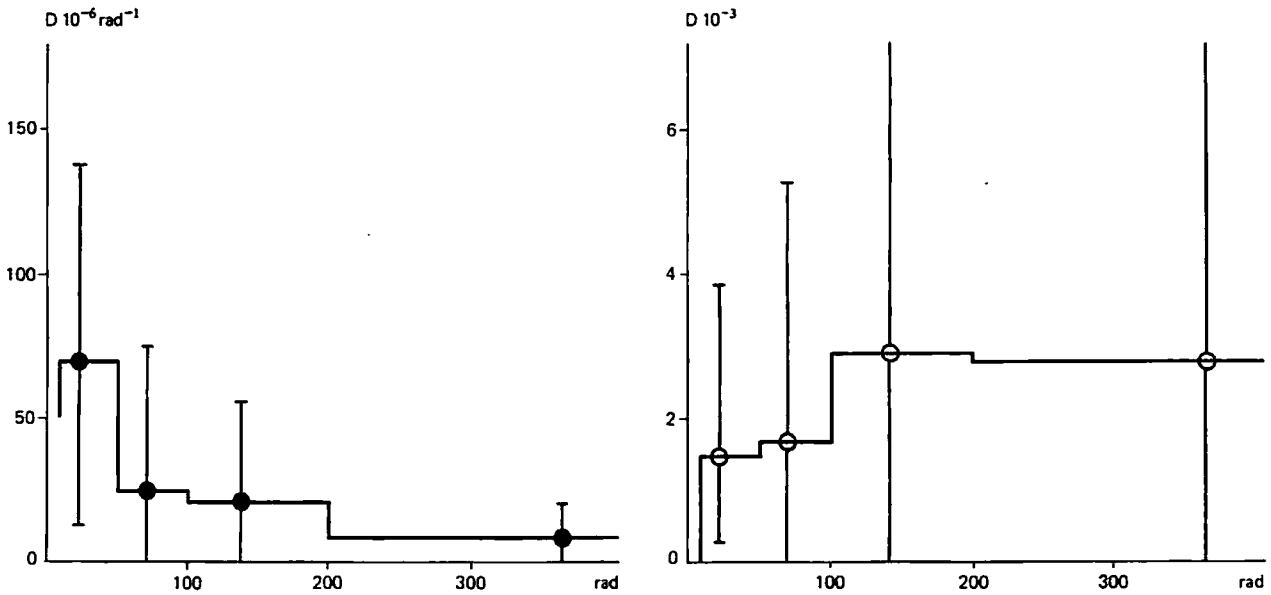

Figure II. Variation of lung cancer induction rate in Hiroshima with T65 kerma

Excess cancers as compared with 0-9 rad group
Left diagram—excess deaths per million man rad
Right diagram—excess deaths per thousand persons
(Ranges indicate 90% confidence limits)

203. The number of deaths observed in Nagasaki are too few for further detailed analysis. For Hiroshima, however, the difference between the effectiveness per unit kerma at low doses and at high doses is the same as was noted in the 1972 report (table 15). Thus, the mortality rate per rad falls from 70 (13-137) 10^{-6} rad^{-1} for those exposed at 10-49 rad, to 8 (neg.-21) 10^{-6} rad^{-1} following exposures at over 200 rad (fig. II). Similarly, the excess rate per thousand persons exposed does not continue to rise with increasing mean dose, although the wide confidence limits of all these values do not allow the assumption that a maximum mortality rate for these cancers has been reached at the mean absorbed doses (of about 200 rad) attained in the higher exposure groups. When the induction rate in the whole group of those exposed at over 10 rad is compared with that for those exposed only at higher levels (table 16), the rates per rad thus still differ by a factor of 3 when based on kerma, or by a factor of about 2 when based on weighted absorbed dose, on the assumptions made in paragraph 202. The likelihood of a falling induction rate with increasing mean absorbed dose is thus not excluded, but the average rate over a wide dose range appears to be in the region (10-25) 10^{-6} rad^{-1} (kerma or weighted dose).

204. Ishimaru *et al.* (64) have examined the possibility that those surviving exposure at high dose might have smoked more heavily than others, and that the apparent association of an increased lung cancer mortality with radiation might be due to this. They found no evidence to support this possibility, or that environmental factors other than radiation were responsible for the increase. The smoking history was available in 204 subjects from Hiroshima and Nagasaki in whom a lung cancer was verified at autopsy, 61 having been exposed at low radiation dose and 13 at high dose. The relative risks of lung cancer (in 1323 autopsies) were 8.6 and 3.0 in smokers and non-smokers who had been exposed at over 200 rad (T65 kerma) and 6.2 and 1.0 in smokers and non-smokers exposed at less than 1 rad. The relative risk (relative to unirradiated non-smokers and standardized for sex and age at death) was thus increased by about as much by radiations whether the subject was a smoker or not.

205. The histological character of the "lung" cancers was examined in the same series (24), which included 1700 autopsies on subjects exposed at 1 rad or over (with 127 at over 200 rad) and 1196 with exposures of less than 1 rad. The prevalence rate of lung cancer at autopsy was significantly increased in those who had been exposed at 200 rad or over, with a rate of 10.2 per cent at autopsy as compared with 5.1 per cent in those exposed at less than 1 rad, and 5.1 per cent also in those who had not been in the cities at the time of the bomb. Three types of lung cancer were increased in this highly exposed group, but the increase was only significant for small-cell anaplastic tumours. The excess numbers, relative to expectation based on the <1 rad group, are however too small to exclude equal increases in other tumour types (table 17), particularly the epidermoid and bronchogenic carcinomas, or even a proportionate increase of all types as seen in the control group.

TABLE 17. EXCESS NUMBER OF LUNG CANCERS AT AUTOPSY

(Compared with expected numbers as judged by types observed in the <1 rad group)

	Kerma group (rad)	
	>200	*1-199*
Epidermoid	1.2 (−1.0-6.0)	7.6 (−0.8-18.3)
Small-cell anaplastic	3.7 (0.7-9.2)	−1.8 (−7.3-6.1)
Bronchogenic adeno-carcinoma	2.0 (−0.6-7.2)	−4.0 (−10.9-5.2)
Bronchio-alveolar adeno-carcinoma	0.0 (−0.6-2.4)	3.1 (−1.7-10.3)
Large-cell carcinoma	0.0 (−0.3-2.7)	−0.9 (−3.1-3.9)
Combined and unclassified	0.6 (−0.4-4.3)	−0.3 (−3.3-5.2)
Total	7.5 (2.2-15.2)	3.7 (−10.8-20.4)

Source: Reference 24.
Note: The 90% confidence limits are indicated in parentheses.

206. The number of lung cancers induced, or at least the number causing deaths within 24 years of the exposure, appears to depend critically upon the age at exposure (14). For those who were aged 35 or over, the total number of deaths has been increasing about linearly with time since about 10 years after exposure, that rate of increase being somewhat (about 50 per cent) faster in those who were over 50 than in those aged 35-49. There has, however, been no increase in rate in those who were aged less than 20, and little, if any, in subjects aged 20-34 at exposure.

207. The increased mortality in Hiroshima and Nagasaki over 1950-1972 is slightly, but not significantly, greater in females than in males (mortality per 1000 persons exposed at 10 rad or over, as compared with 0-9 rad group):

Males	0.85 (neg.-2.27)	(43% were aged 35 or over)
Females	1.09 (0.37-1.97)	(38% were aged 35 or over)

B. LUNG CANCER IN WORKERS EXPOSED TO HIGH RADON LEVELS

208. In its 1972 report, the Committee discussed the evidence obtained from studies on uranium and other hard rock miners, of an increased incidence of lung cancer associated with the high radon concentrations in the atmosphere of many mines. It was stated, however, that the incidence of or mortality from lung cancer in groups of miners could only be related to the radon concentrations to which they had been exposed in the case of those working in the uranium mines of the Colorado Plateau in the United States, where extensive studies had been made both of the frequency of lung cancer and of the associated radon levels.

209. Since the time of the last report, two further populations of miners with increased incidence of lung cancer have been described, and the increase related to the corresponding radon levels. Each of the three major studies shows a dose-effect relationship between excess incidence of lung cancer and estimated exposure, the data being consistent in each case with a linear relationship between the excess cancer and the cumulative working level months (WLM)[5] of exposure to radon.

210. It remains difficult to separate adequately the contributory effects of radon and of smoking in causing the cancers, since there are too few non-smoking miners to form a sufficient control group, but Archer *et al.* (5) attempt to make a correction for the cigarette-smoking habits of miners. They find that, among smokers, 15.5 deaths from respiratory cancer should have occurred (among white underground uranium miners) as compared with 58 observed. In non-smokers, 0.5 deaths should have occurred as compared with 2 observed. While the proportionate increase in mortality from lung cancers is thus about the same in the two groups, they emphasize that the sample size of non-smokers is too small to be certain of this point. They point out, however, that in the absence of any interaction between radiation and cigarette smoking, the smoking habits could account for no more than a 49-per-cent increase in lung cancer rate, so that some interaction between the effects of radiation and of cigarette smoking appears probable and is being further investigated.

211. Ševc *et al.* (136) found that cigarette smokers formed about 70 per cent of a random sample of 700 uranium miners, and that this was equal to the frequency in the general male population in Czechoslovakia. They noted that there was no reason to suppose that consumption of cigarettes correlated with radiation exposure otherwise than through age, and that the comparison of lung cancer rates in miners with age standardized general vital statistics therefore permitted the exclusion of smoking as a major causal factor in the excess of lung cancers that they observed in miners.

212. Archer *et al.* (6) have now shown that the excess mortality from lung cancer increases about linearly with cumulative WLM in non-smokers, but to an extent which is only of the order of one eighth that which is observed in miners smoking 20 cigarettes per day.

213. At least in regard to miners who smoke, however, there are now three estimates of the lung-cancer risk rate

[5] "Working level" is defined as any combination of short-lived radon daughter products in one litre of air that will result in the ultimate emission of $1.3\ 10^5$ MeV of potential alpha energy. Working level month (WLM) is the exposure to one working level during 170 hours.

for different exposure levels from radon and two further estimates are available from other mining groups, giving a mean risk for a stated average exposure.

214. For uranium mines of the Colorado Plateau, the dose-effect relationship is consistent with a linear regression through zero. The total experience amongst white underground workers in uranium and other hard rock mines, from July 1950 to September 1968, showed an excess of 58.3 deaths from lung cancer in a population equivalent to 37 958 person-years. Assuming a mean exposure at the midpoints of the various exposure groups with stated limits, and a mean exposure of 5000 WLM in the group exposed at over 3720 WLM, the mean exposure would be of 740 WLM, implying an excess mortality of 38 10^{-6} per WLM during the period of observation. Average annual rates are about 2.9 10^{-6} per WLM year for those who have worked as miners for over 10 years, or 2.1 10^{-6} per WLM year for the whole group.

215. Studies from uranium mines in Czechoslovakia showed an excess rate corresponding to 170 10^{-6} deaths from lung cancer per WLM over an exposure period varying from 19 to 23 years (135), indicating an annual rate of about 8 10^{-6} per WLM year. Most of these exposures were received prior to improvement of ventilation of mines in about 1958. A further report on a group of these miners who started work in the uranium mines between 1948 and 1952 and have now been followed for 21-26 years (136) shows an excess rate of 230 10^{-6} per WLM, the dose-effect relationship again being consistent with a linear regression through zero. The rate varied with age:

Age at start of mining	*Excess rate and 95% confidence limits (10^{-6} WLM^{-1})*
Under 30	140 (100-180)
30 to 39	230 (160-300)
Over 40	370 (280-460)
All	230 (155-305)

indicating rates per million per WLM year of about 6, 10 and 16 in the three age groups. The authors suggest that these rates may be higher than those inferred for the Colorado miners because of a younger mean age of the latter at the start of mining. They emphasize that their own estimates of exposure rely on large numbers (over 120 000) of measurements of radon concentrations in mines in the period since 1948, with at least 100 determinations per year in each mine, and that the additional hard-rock exposure of the miners was very small.

216. In non-uranium mines in Sweden the excess mortality shows a linear regression, with slope equivalent to 3.4 10^{-6} excess deaths from lung cancer per WLM year. For fluorspar mines in Newfoundland the mean rate is estimated as 2.2 10^{-6} per WLM year, while for iron mines in the United Kingdom it is 6.0 10^{-6} per WLM year (144).

217. These estimates may be regarded as reasonably consistent in view of the difficulties and likely differences in ascertainment of lung cancer, and of associating radon measurements at certain positions in mines with alpha radiation dose to cells of the bronchial epithelium, as well as possible differences in smoking habits, urban or rural residence, typical duration of work in mining, age at starting and other circumstances. Moreover, it has been shown that differences in risk may apply to those with long or short total periods of exposure (135). To the precision required for risk estimation, however, a rate of 5-10 lung cancers per million per year and per WLM appears representative of available data.

218. A study of lung cancer in Ontario uranium miners in the period 1955-1974 (50) records a death rate from this malignancy which rises from about 0.3 per cent in the unexposed subjects to 3.7 per cent in those with 180 WLM of cumulated exposure. The authors emphasize, however, that these data cannot properly be used for risk estimation, owing to the limited total periods of survey (of within 20 years from the start of exposure) and for lack of information on smoking habits. The survey is of particular value, however, for showing consistency of the dose effect relationship at low dose with a linear regression which is taken to exclude any "threshold" greater than 10 WLM. It also indicates that, although the absolute excess of lung cancers was lower in those under 35 than over 35 at entry to mining, the relative increase was comparable in the two groups.

219. Several steps are involved in deriving the total risk of lung cancer from estimates of induction per WLM. Since lung tumours may develop with a long latency after the relevant exposure, the annual rates of incidence must be regarded as continuing over long periods of time, and the mean rates used for calculation of total mortality must be appropriate for the average of these periods of time. In the case of the least two of the estimates quoted above, this condition appears to be adequately satisfied. For the Czechoslovak miners, the rates correspond to averages over periods of 20 years or more. If this is regarded as comparable to the median latency for tumour development and diagnosis, and the total of cancers is doubled to allow for later developing malignancies, the final figure (of about 450 10^{-6} per WLM) should approximate the total expression of the radiation effect.

220. For the Swedish data also, although mean exposure times are not stated, the "latencies" observed from the start of mining to the diagnosis of the tumours observed, which range up to 40 years and average 26 years, show that the rates derive from populations with prolonged exposure. The annual rate might thus be multiplied by 40 (years) to allow for full expression, giving a total in the region of 140 10^{-6} per WLM.

221. The values quoted for miners in the Colorado Plateau represent rates averaged over somewhat shorter exposures since, for example, the data of Archer *et al.* (5) refer to 3366 miners and 37 958 person-years of exposure, giving an average exposure of about 10 years. From information given (81) on the excess deaths and person-years at risk in the various exposure groups, it appears that the risk for a given exposure rises with the mean period since the start of uranium mining, as shown in table 18. While the mean rate for all periods since

TABLE 18. MORTALITY IN URANIUM MINING

	Period since start of mining (years)					
	<5	*>5*	*>10*	*>15*	*>20*	*>25*
Excess deaths from respiratory cancer	0.6	8.6	20.6	17.6	5.3	5.7
Person year WLM product (10^6)	3.4	7.8	7.7	4.3	2.4	2.6
Excess deaths per 10^6 person year WLM	0.2	1.1	2.7	4.0	2.2	2.2
90% confidence limits	0.0-1.4	0.4-2.0	1.7-4.0	2.6-6.2	0.8-4.6	0.8-4.6

Source: Reference 81.

start of mining is 58.3/28.3 = 2.06 deaths per 10^6 person year WLM, that for miners who have worked for 10 years or more is 49.1/17.1 = 2.86 per 10^6 person year WLM. Or, if the rates for the various intervals are used to estimate the total of all deaths, say to 30 years from start of exposure, a value of about 70 10^{-6} per WLM is obtained. It is not clear, however, whether the apparent fall in rate after 20 years of exposure is significant, or what contribution would be made at periods longer than 30 years.

222. For a full, e.g. 40-year, expression of the total carcinogenic effect on lung tissue of radon and of its daughter products, therefore, an incidence of 200-450 10^{-6} per WLM can be regarded as probable. Since 1 WLM has been estimated as delivering about 1 rad of alpha radiation to bronchial epithelium (Annex B), the risk of exposure to low-LET radiation would on this basis be in the region of 50 (or from 20 to 150) 10^{-6} rad^{-1} if a weighting factor of 5-10 is assumed for alpha radiation at the high dose levels on which the estimates are based. If estimated in terms of mean lung dose, with 0.5 rad per WLM, the risk per rad would be twice as high, but this criterion seems less appropriate since the cancers are likely to arise from bronchial epithelium. It must be recognized, however, that these estimates depend on very indirect indications of tissue dose, as derived from air concentrations at monitoring sites in mines and strictly may apply only to miners who smoke. If smoking has a co-carcinogenic and not simply an additive carcinogenic effect the same increase cannot necessarily be assumed for non-smokers. Uncertainties as to the lung tissue over which dose should be averaged, the relationship between radon concentration and tissue dose, and the value of RBE appropriate for lung carcinogenesis from moderate doses of alpha radiation add to the uncertainty of the estimate (ref. 51 and para. 215).

C. SUMMARY

1. Comparison of estimates

223. There is an apparent discrepancy between the low mean induction rates in Hiroshima and Nagasaki, 10-25 10^{-6} per rad of kerma or of weighted absorbed dose, and the higher values, 40-180 10^{-6} per rad, that have been inferred from the mortality in uranium and other miners. There are, however, a number of factors that might explain this discrepancy:

(a) The rate per unit kerma is not, and that per unit absorbed dose (weighted according to data on leukaemia induction) may not be, the relevant basis for risk estimation. However, even expressing the rates as per unit absorbed dose (with RBE= 1) would only increase the Japanese estimates by about 75 per cent;

(b) The Hiroshima population was of all ages, and the carcinogenic effect appears to have been expressed predominantly in those aged over 35 at exposure. Since 40 per cent of these populations (exposed at over 10 rad) were over that age, the observed rates should probably be multiplied by a factor of up to 2.5 to correspond to the rates observed in uranium miners;

(c) The Hiroshima rates are based on information in the period from 5 years to 27 or 29 years from exposure and, since deaths continue to occur in the exposed groups, should be increased (perhaps by up to 50 per cent) to correspond to the 40-year period considered for uranium miners;

(d) It has been noted (13) that many deaths from lung cancer are not identified as such on death certificates and that adjustment for such errors would raise the rates in Hiroshima by about 50 per cent;

(e) The induction rate estimated for those exposed at 10-49 rad in Hiroshima was 70 (13-137) 10^{-6} per rad kerma (table 15), and would be equivalent to about 120 (23-240) 10^{-6} per rad unweighted absorbed dose. This rate is much greater then those estimated at higher dose but has wide confidence limits. It is improbable, however, that this rate in Hiroshima occurs at a level which corresponds to those on which the uranium miners mortality are based, since the former was associated with a 0.2-per-cent excess incidence of lung cancer (fig. II), while in the studies of Ševc *et al.* (136), the data are consistent with the higher incidence rate per WLM up to excess mortalities of 10 per cent;

(f) It might be questioned whether, for the lung as for the breast, spontaneous cancer rates in Japan are unusually low, and that a lower induction rate might be in some way associated. In females the annual rate of lung cancer registration in two Japanese cancer registries was 6.0 and 5.2 cases per 100 000, as compared with a mean rate of 7.6 ± 5.5 (SD) in 54 other registries with comparable criteria. The annual rate in males was somewhat lower than that in many other countries, with

age-standardized rates in these registries of 15.6 (in 1962-1964) and 15.3 (in 1966), as compared with 35.5 ± 19.4 per 100 000 at comparable periods in the other registries, but Japanese rates have been noted (para. 41) to be increasing;

(g) Ishimaru *et al.* (64) record a history of cigarette smoking in 52 per cent of a series of 1323 people from Hiroshima and Nagasaki (males and females) from whom a smoking history was available, whereas Ševc records 70 per cent of a random sample of miners as being cigarette smokers. The difference, presumably due in part to the proportion of women in the Japanese populations, might account for some of the discrepancy in induction rates, but the data of Moriyama and Kato (97) do not indicate a clear difference in induction rates in the two sexes in Hiroshima;

(h) On the other hand, estimates of the rad equivalent of the WLM at the tissues of interest have varied rather widely and the estimate of 0.5 rad mean lung dose may be too low, or if the dose to bronchial epithelium (para. 222) were the appropriate value to use, the risk estimates for miners would be halved;

(i) Finally, the values of 5 and 10 taken for RBE (in paragraph 222) for calculation of mortality per rad of low-LET radiation in miners may be unduly low at the dose levels involved and an RBE of 20 would bring these estimates into the range of (20-50) 10^{-6}. However, since these dose levels were associated with high incidences of lung cancer, this appears improbable.

2. Conclusions

224. Apart from the findings in Hiroshima and Nagasaki and in miners, no other sources of information are available to confirm the higher or lower value of the induction rate. In its 1972 report, the Committee noted the excess of 41.8 deaths from lung cancer among 13 940 patients treated for ankylosing spondylitis (within a mean period of 13 years). A further study of such patients treated with only a single course of radiotherapy has shown an excess mortality from lung cancer in 0.26 per cent of 14 109 patients followed for a mean period of 9.5 years from the time of the treatment. The excess mortality from lung cancer was 0.46 per cent during the period starting 6 years after the treatment in 6838 patients (143) who were followed for a further mean period of 11.3 years from this time (36). No risk estimates can, however, be derived with confidence, since the mean lung dose will depend critically upon the position and size of the radiotherapy fields, and is at present under investigation. The Committee's 1972 report referred to a tentative estimate of bronchial dose by Dolphin and Marley (39) of 80 rad, derived by inference from the mean spinal marrow dose of 880 rad. This estimate, if applicable to patients who had a single course only with estimated mean *total* marrow dose of 321 rad, would imply a risk for the mean period 6-17 years of $0.0046/80 \cong 60\ 10^{-6}$ rad^{-1}. The mean lung or bronchial dose will, however, depend critically upon the position and size of the fields used in treatment, and must await a more accurate determination.

225. In view of the unusually short and fatal course of lung cancer, particularly of the anaplastic type (para. 205), the excess incidence of this disease is unlikely to differ materially from the mortality. The incidence rates in Hiroshima and Nagasaki in the period 1959-1970 corresponded to $13\ 10^{-6}$ and $12\ 10^{-6}$ per rad kerma respectively. The corresponding rates per unit absorbed dose of low-LET radiation would be about $20\ 10^{-6}$ rad^{-1} in Nagasaki, and 10, 16 or $25\ 10^{-6}$ rad^{-1} in Hiroshima, according to whether an RBE of 20, 10 or 1 is used for the high-LET component of the absorbed dose.

226. From the rather discordant sources of information available, the risk of lung cancer induction by low-LET radiation would appear to be in the region of $50\ 10^{-6}$ rad^{-1} for exposure at ages greater than about 35, and presumably about half this rate as the average risk for exposure of a whole population of all ages. Further guidance as to this estimate should result from determination of a mean lung dose in the irradiated spondylitics, since lung cancer incidence is clearly raised in these patients but not in unirradiated patients with this disease (120).

VI. BONE TUMOURS

227. In its 1972 report, the Committee referred to the absence of evidence of induction of bone cancer in survivors at Hiroshima and Nagasaki, where there appeared to be no excess of diagnoses to 1965 (165). There is still no good basis for estimating the risk of bone cancer induction by external radiation, except that results of scalp irradiation for ringworm suggest that it is small in children. Modan *et al.* (92) record 2 cancers of bones of the head (with about 0.5 expected) in 10 902 children. Shore *et al.* (139) record 4 tumours of scalp and jaw, 1 of which was malignant (138), in 2215 irradiated children with none expected. Assuming that the skull forms about 25 per cent of the total bone mass in children (reference 62, quoting 40 per cent at birth and 15 per cent in the adult) and from the dose estimates given for each survey (52, 131, 159) risks per unit absorbed dose for bone cancer of 3 (neg.-10) 10^{-6} rad^{-1} and 5 (0.2-21) 10^{-6} rad^{-1} can be derived. In the recent survey of 14 109 patients irradiated for ankylosing spondylitis and followed for a mean period of 9.5 years (36), 4 deaths occurred from malignancies arising in heavily irradiated bone areas. Since only 1.3 such deaths were expected, this observation indicates a significant induction of bone tumours in the adult. No estimate is yet available for the mean dose to bone from these treatments (as distinct from the mean bone marrow dose of 321 rad) so no risk estimate can be derived; and it could only be very approximate in view of the small excess number of cancers. Moreover, the distribution of "spontaneous" osteosarcomas in man and probably also that of radiation-induced sarcomas, varies in different bones, and the long bones of the limbs will have been little exposed in the spondylitis treatments. The excess mortality, of only 0.02 per cent of patients however, suggests a low induction rate at least in the spine.

228. The Committee also reported on the incidence of osteosarcomas following intravenous therapeutic administrations of Peteosthor, a preparation containing ^{224}Ra. The risk estimates for bone from this source have been extended in a valuable way by Spiess and Mays (146) who have identified the difference in risks for those who were juveniles (younger than 20) or adults at the time of treatment. They also show that the risk appeared to be higher from a given total dose if the administrations were given over a time span of a year or more than if given during a short period, i.e. of a few months only. By June 1970, the average time since patients had received their first injections had been about 22 years for juveniles and 19 for the adults, and sarcomas had developed in 35 of the 208 juveniles for whom dose and injection span were known, and in 12 of 607 adults (who had in general received lower doses).

229. For juveniles, the estimated risk rises from about $40\ 10^{-6}$ rad^{-1} (mean bone dose) for injections given during a short span to about $220\ 10^{-6}$ rad^{-1} for longer time spans. For adults, the risk rises from 30 to $170\ 10^{-6}$ rad^{-1}. In each case the data are consistent with the risk E (deaths per million per rad) rising from the lower to the higher value with an interval diminishing with a half-period of about 8 months:

$$\text{For juveniles, } E = 40 + 180\,(1 - e^{-0.09m})$$
$$\text{For adults, } E = 30 + 140\,(1 - e^{-0.09m})$$

where m is the time span in months during which the injections were given (146).

230. Two points need emphasis with regard to these risk data. Firstly, since the dose is of alpha radiation (see Annex I, paragraph 269), the appropriate risk estimates for bone from radiation of low LET might be lower by a factor of 5-20. Secondly, there is now ample evidence that osteosarcomas arise predominantly from endosteal cells and that the relevant dose for sarcoma risk estimation is therefore that to these cells, which lie at a distance of up to 10 μm from bone surface, rather than the mean dose averaged through bone, as used in the risk estimates quoted. Radium-224 has a short half-life of 3.64 days and its radiation and that of its daughter products is largely delivered while these radionuclides are still present on bone surface. This contrasts with that from ^{226}Ra, which becomes distributed throughout bone during its period of radioactive decay. The dose to endosteal cells from ^{224}Ra is about 9 times that as averaged throughout bone, whereas that from ^{226}Ra is about two thirds the mean bone value (127). The appropriate risk estimates for sarcoma induction by irradiation of endosteal cells from ^{224}Ra in juveniles are thus about $25\ 10^{-6}$ rad^{-1} (of alpha radiation) to endosteal cells for long spans of injection, and $20\ 10^{-6}$ rad^{-1} in adults. An approximate figure for prolonged bone irradiation from low-LET radiation would thus probably be in the region of (1-50) 10^{-6} rad^{-1}.

231. In its 1972 report, the Committee discussed the data available from groups of people with ^{226}Ra burdens and the lack of bone sarcomas at estimated cumulative mean bone doses of 700 rad or less. It was pointed out that the number of people studied at doses lower than 700 rad corresponded only to $4.6\ 10^{4}$ man rad and that only 1.8 sarcomas would be expected in this group, as judged from the incidence at higher doses, if incidence were linearly proportional to dose.

232. Meanwhile, however, Rowland *et al.* (127) have noted that the incidence of osteosarcomas in the groups studied is better represented by the relationship in which incidence is proportional to the square of the dose than to the dose itself, each relationship involving also an exponential term to correspond with the decreased incidence at higher doses. The former relationship would imply an even lower expectation of sarcoma at low doses. For example, according to the equation given in paragraph 233, the expectation in the group at doses lower than 700 rad would be only 0.3 sarcomas.

233. The best fit for incidence of sarcomas (I = fractional incidence) was to the equation

$$I = 3.9\ 10^{-8}\ D^2 e^{-D/4.85\ 10^3}$$

where D is the total rad dose to bone from exposure to diagnosis of a tumour. The incidence of carcinomas (of paranasal sinuses and mastoid air cells) was adequately fitted by

$$I = 3.1\ 10^{-5}\ D e^{-D/1.24\ 10^4}$$

234. It is of interest that sarcomas have occurred following mean bone doses as low as 90 rad from ^{224}Ra, but only at doses above 1160 rad from ^{226}Ra. However, when these limits are expressed as dose to endosteal cells rather than as mean bone doses, this discrepancy disappears since sarcomas are seen at endosteal doses above 810 rad from ^{224}Ra and above 760 rad from ^{226}Ra (127).

235. In a review of 261 cases of bone tumour which were regarded as having been induced by therapeutic radiation, Yoshizawa *et al.* (169) note that 50 per cent of the induced malignancies were described as osteosarcomas, 25 per cent as fibrosarcomas and 7 per cent as chrondrosarcomas. A further 8.5 per cent included spindle cell sarcomas and mixed polymorphic cell sarcomas.

SUMMARY

236. The risk of inducing malignancies of bone by low-LET radiation thus appears to be low, and in the region of (2-5) 10^{-6} rad^{-1} to endosteal cells (table 19) for absorbed doses of a few hundred to 1500 rad in locally irradiated bone. Risk estimates for alpha radiation at doses of a few hundred to many thousand rads (table 19) are consistent with a risk of this order assuming an RBE of about 10. Spiess and Mays found induction rates per unit absorbed dose to be about equal in males and females, and about 30 per cent higher in juveniles than in adults.

TABLE 19. BONE-TUMOUR INCIDENCE RISK ESTIMATES

Reference	Population studied	Period of study (years since irradiation)	Source of irradiation	Endosteal dose (rad)		Risk in period of study per unit of endosteal dose (10^{-6} rad^{-1})	
				Mean	Range		
92	Children	About 18	Radiotherapy to scalp	about 100[a]	to 1 500	3 (neg.-10)	low LET
139	Children	20	Radiotherapy to scalp	about 100[a]	to 800	5 (0.2-21)	low LET
146	Juveniles and adults	About 23	^{224}Ra	10 000 1 850	± 7 500 ±1 500	25 20	high LET
41a, 45a	Adults	About 35	^{226}Ra	about 2 000	to 30 000	9 at 10 rad[b] 850 at 100 rad	high LET
						60[c]	high LET

[a]Assuming 25 per cent of bone to be irradiated at a mean dose of 400 rad.
[b]Based on quadratic formula (para. 233).
[c]Based on linear formula (para. 231).

VII. OTHER CANCERS

237. While some very approximate indication can be given for the risk of cancer induction in certain other organs by radiation, the total carcinogenic risk cannot yet be derived by summing the individual contributions to this risk from every organ. A clearer guide to the size of the total risk is obtained by estimating the total mortality from all forms of malignant disease following effectively whole-body radiation at known dose levels, for example in the exposed populations of Hiroshima and Nagasaki, and comparing this with the expected number of such cancers. With reservations owing to the partial-body nature of exposure, some estimate can also be derived from patients treated for ankylosing spondylitis. In each case, correction has to be applied to allow for tumours that may become diagnosable after the available period of follow-up, although in some studies, for example of the effects of foetal irradiation, the full number of tumours appears to have been reached.

238. In the case of malignancies resulting from occupational exposure of radiologists, this method cannot be adopted because the exposures are not known. Here it is possible, however, to record the total excess of deaths from malignant disease other than leukaemia, and to compare this total with the excess due to leukaemia. The ratio is of value, firstly because long periods of follow-up have occurred since the exposures that are likely to have been relevant, and secondly, because the radiation induction of leukaemia can be estimated from other sources, so that that for other malignant diseases can be derived.

239. From the JNIH-ABCC Life Span Study, the mortality rates are shown in figure III for successive periods, both for leukaemia and for all other malignancies. There is a strong suggestion that the excess mortality from leukaemia is now ceasing, and a possible indication that the excess rate from other malignant disease may have reached its peak. This would, if so, be consistent with the indications noted above that the median latency for diagnosis of radiation-induced cancer may be about 25 years.

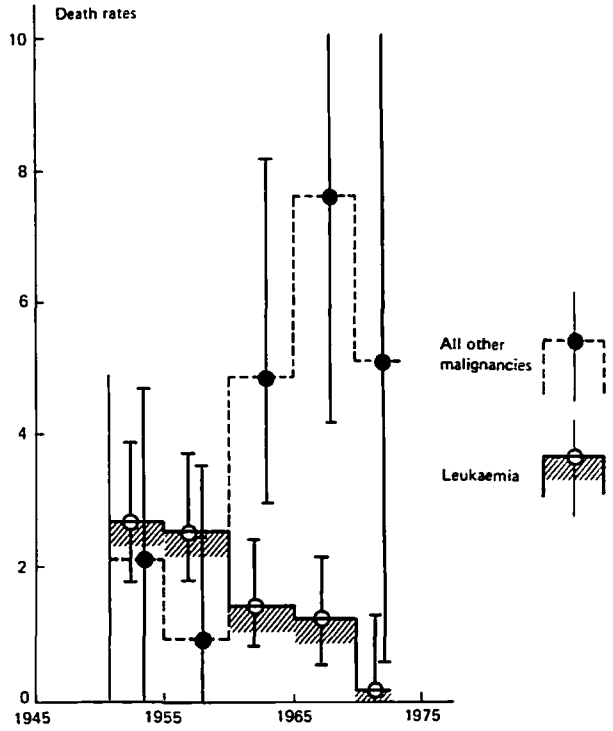

Figure III. Variation of death rates from leukaemia and from all other malignancies with time since exposure

Rates, deaths per million man rad during successive periods of JNIH-ABCC survey
Leukaemia: open circles and hatched columns
All other malignancies: filled circles and dashed columns
(Ranges indicate 90% confidence limits)

240. The further increases in the period (of 21 months) between the 1950-1972 and the 1950-1974 estimates (see table below) are consistent with those indications, neither the increase in leukaemia nor indeed that in other malignancies being much (or significantly) greater than that expected on the basis of the 0-9 rad group. (If this expectation is estimated simply in proportion to person-years at risk, but without any correction for age and sex distribution, the 1972-1974 increases for leukaemia and other malignancies became 3.7 and 145.3, respectively. The corresponding excesses of the ⩾10 rad group over the 0-9 rad group are then 6 – 3.7 = 2.3 and 156 – 145.3 = 10.7).

Hiroshima and Nagasaki

Males and females, all ages

	Dose group (rad):					
	0-9			*>10*		
	1950-1972	*1950-1974*	*1972-1974*	*1950-1974*	*1950-1974*	*1972-1974*
Person-years (10^3)	1 092	1 166	74	476	522	46
Deaths from:						
Leukaemia	48	54	6	84	90	6
Other malignancies	2 232	2 467	235	1 075	1 075	156

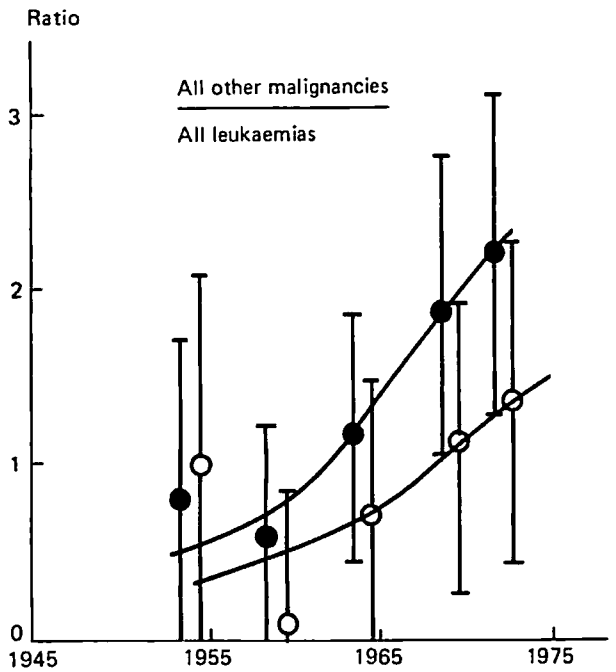

Figure IV. Ratio of numbers of deaths from all other malignancies other than leukaemia to those from leukaemia

Ratios are of all excess deaths during the period from 1950 until dates indicated

Upper curve (filled circles): excess deaths as compared with Japanese National Statistics

Lower curve (open circles), excess deaths as compared with frequencies observed in persons exposed at 0-9 rad

241. Figure IV shows the ratio of excess deaths from other malignancies to those from leukaemia. The upper curve, obtained by comparison with Japanese National Mortality Statistics, may be the more valid, in the sense that some deaths attributable to malignant disease may have occurred even in the group exposed at only 0-9 rad. For example, the mortality ratio for leukaemia was 1.5 even in this group. On the other hand, the 0-9 rad group is much more comparable with those exposed in the methods of study and ascertainment, as well as in place of residence.

242. It is probable that this ratio of mortality rates may differ for those exposed in different dose groups, since the form of the dose-effect relationship is unlikely to be similar for all forms of malignancy. The precision with which the excess number of deaths is determined in lower dosage groups, particularly for solid cancers, however, is insufficient for this estimation to be made adequately.

243. In a further report of the Life Span Study recording mortality data from October 1950 to September 1974 (14), the excess mortality rates are estimated from the slope of the linear regression of deaths per person-year on estimated dose (T65 kerma). On this basis, the relationship between the excess of solid cancers to that of leukaemia is similar to that derived (fig. IV and table 20) by comparison with the rates observed in th 0-9 rad group, as follows:

	Period surveyed					
	1950-1954	*1954-1958*	*1958-1962*	*1962-1966*	*1966-1970*	*1970-1974*
Excess rate (10^{-6} y^{-1} rad^{-1}):						
Leukaemia	4.06	2.28	1.78	0.88	1.13	0.49
Other malignancies	1.61	−0.38	2.35	2.99	3.32	4.19
Cumulative total, October 1950 to September of final year of period:						
Leukaemia	4.06	6.34	8.12	9.00	10.13	10.62
Other malignancies	1.61	1.23	3.58	6.57	9.89	14.08
Ratio of cumulative totals, other malignancies/leukaemia	0.40	0.19	0.44	0.73	0.98	1.33

TABLE 20. EXCESS MORTALITY FROM LEUKAEMIA AND FROM ALL OTHER CANCERS IN HIROSHIMA AND NAGASAKI BY PERIOD

Dose groups 10->200 rad T65

Males and females, all ages

Period	Duration (years)	Man rad year ($\times 10^6$)	LEUKAEMIA				ALL OTHER CANCERS				Ratio other cancers/ leukaemia at end of period
			Observed	Expected	Excess	Excess rate ($10^{-6}\ y^{-1}\ rad^{-1}$)	Observed	Expected	Excess	Excess rate ($10^{-6}\ y^{-1}\ rad^{-1}$)	
			Compared with 0-9 rad group								
1950-1954	4.25	8.24	24	4.5	19.5 (11.8-29.6)	2.37 (1.43-3.60)	146	126.8	19.2 (neg.-44.3)	2.33 (neg.-5.36)	0.99 (neg.-2.22)
1955-1959	5	9.26	27	7.0	20.0 (11.6-30.7)	2.16 (1.25-3.31)	193	209.0	−16 (neg.-13.6)	−1.73 (neg.-1.47)	0.08 (neg.-1.00)
1960-1964	5	8.77	16	2.2	13.8 (7.6-22.3)	1.57 (0.86-2.54	258	223.0	35.0 (4.5-67.7)	3.99 (0.51-7.71)	0.72 (neg.-1.61)
1965-1969	5	8.25	4	4.8	9.2 (3.3-17.5)	1.12 (0.40-2.13)	301	268.1	32.9 (neg.-68.1)	3.99 (neg.-8.26)	1.12 (0.14-2.09)
1970-1972	3	4.68	3	2.7	0.3 (neg.-5.6)	0.06 (neg.-1.20)	177	162.0	15.0 (neg.-42.4)	3.21 (neg.-9.06)	1.37 (0.30-2.44)
			Compared with Japanese National Statistics								
1950-1954				1.7	22.3 (14.8-32.1)	2.71 (1.80-3.90)		128.4	17.6 (neg.-39.1)	2.14 (neg.-4.75)	0.79 (neg.-1.73)
1955-1959				2.8	24.3 (16.3-34.4)	2.62 (1.76-3.71)		184.0	9.0 (neg.-33.5)	0.97 (neg.-3.62)	0.57 (neg.-1.24)
1960-1964	as above	as above	as above	3.3	12.7 (6.7-21.0)	1.45 (0.76-2.39)	as above	215.2	42.8 (17.0-70.8)	4.88 (1.94-8.07)	1.17 (0.43-1.90)
1965-1969				3.7	10.3 (4.8-18.2)	1.25 (0.58-2.21)		238.4	62.6 (34.7-92.7)	7.59 (4.21-11.24)	1.90 (1.09-2.71)
1970-1972				2.3	0.7 (neg.-5.5)	0.15 (neg.-1.18)		153.0	24.0 (2.7-47.5)	5.13 (0.58-10.15)	2.22 (1.31-3.13)

Source: Reference 97.

Note: The 90% confidence limits are indicated in parentheses.

244. It has been pointed out (para. 63) that the frequency with which leukaemia is induced by radiation varies with age at the time of exposure, with a moderate rate of induction at age 0-9 years, a lower rate for ages 10-19 and higher rates at greater ages. It is important to note that the induction of other malignancies as a whole varies in a similar manner with age, and that the relative increase at older ages is greater than for leukaemia. The current Life Span Study data, therefore, show that the ratio of deaths from other malignancies to those from leukaemia, as occurring in the total period from 5 to 29 years from exposure, differs for different ages at exposure (see table below). The ratio discussed in paragraph 242 and referred to in the following paragraphs will therefore depend on the age structure of the population exposed.

Hiroshima and Nagasaki, 1950-1974

Male and female

	Age at exposure (years)					
	0-9	*10-19*	*20-34*	*35-49*	*>50*	*All*
Mortality per unit kerma (10^{-6} rad^{-1}):						
Leukaemia	76 (66-85)	23 (17-29)	54 (38-53)	44 (34-53)	82 (66-99)	46 (42-50)
Other malignancies	33 (25-42)	20 (7-34)	59 (30-68)	74 (16-132)	153 (12-295)	53 (35-71)
Ratio, other malignancies/ leukaemia	0.4	0.9	1.1	1.7	1.9	1.2

245. The findings of Doll and Smith (36) on the irradiation of ankylosing spondylitis patients, show a similar relationship between the induction rate of cancers, and probably also of leukaemia, and the age at exposure. Their data refer only to cancers of certain organs, essentially those in the heavily irradiated parts of the body; relatively few treatments were given at ages below about 20. Their values for excess risk at older ages, however, show a clear increasing trend with age for cancers of these heavily irradiated sites (χ^2_1 trend = 15.1) and for leukaemia (χ^2_1 trend = 6.7). The excess rates for cancers at >6 years after treatment and for leukaemia at > 2 years are as follows:

	Age at treatment (years)					
	<25	*25-34*	*35-44*	*45-54*	*>55*	*All*
Excess rate (10^{-5} y^{-1}):						
Cancers	14	34	127	182	339	91
Leukaemia	4	13	19	43	52	90
Ratio, cancers/ leukaemia	4	3	7	4	6	4.7

246. If it is assumed that the median latency for deaths from malignant disease other than leukaemia is 25 years, and that the mortality from leukaemia has ceased by this time, then the final expected ratio of excess deaths from cancers to those from leukaemia should finally reach twice the value reached by 25 years, or about 3 on the basis of the Japanese data (fig. IV).

247. This estimate of the ratio can be compared with the value 4.3 derivable from the mortality studies on American radiologists, among whom an estimated excess of 11.3 deaths from leukaemia occurred during the period 1935-1958, as compared with an excess of 48.2 deaths from all other cancers (134). For ankylosing spondylitis, it is difficult to estimate the proportion of organs sensitive to radiation carcinogenesis which lay within the radiation fields, as compared with the proportion of marrow in those fields. From the publication of Court Brown and Doll in 1965 (29), however, the ratios of excess deaths from all other malignancies to those from leukaemia were 3.1 ± 1.1 (S.E.) for patients completely followed up at that time and 5.5 ± 1.4 for those with incomplete follow-up. In the further report on patients who had received only one course of treatment (36) and for whom the relevant time of exposure is therefore unequivocal, the mean ratio rises to a value of 3.0 by a mean time of 13 years and to 3.7 at 25 years from the time of irradiation. The ratio based on numbers of deaths, however, is subject to bias owing to the decreasing number of patient-years at risk at the longer intervals after exposure, when leukaemia deaths have ceased to occur but when deaths from induced cancer continue. If allowance is made for this (by using the ratio of cumulant rates rather than of cumulant numbers of deaths), the ratio has a value of 3.6 at 13 years and 5.3 at 25 years. Following pelvic x irradiation for metropathia haemorrhagica, Smith and Doll (142) have found a ratio of excess deaths from cancers to those from leukaemia of 3.9 (to a mean of 19 years from single courses of irradiation). Here again, however, the ratio will depend on the proportion of marrow and of organs sensitive to radiation carcinogenesis within the pelvis. In the light of these values, however, and particularly of the ratios derived from effectively whole-body irradiation, it appears probable that the ultimate total number of deaths from *all* malignant disease will be 4-6 times that from leukaemia alone.

248. This estimate might be falsified if, in populations under study, deaths started to occur from any group of tumours for which the latency, from exposure to death, was unusually long. As noted already, it is difficult to

establish mean latencies for any type of solid tumour, because of the very long periods of follow-up required for full ascertainment. There is some suggestion that tumours of skin, and perhaps also of pharynx and larynx, may have long latencies, but this is uncertain. It is clear, however, that some malignant tumours have exceptionally long mean survival times from diagnosis to death, and this applies particularly to cancers of the thyroid of the type induced by radiation, and probably also to tumours of breast. The high induction rate for such cancers by radiation might possibly, therefore, cause a bimodal distribution with time of deaths from solid tumours, although the probable low fatality rate from these thyroid tumours with adequate treatment makes this unlikely. For the breast, the data of Wanebo *et al.* (158) suggest an induction rate in the Adult Health Study population examined between 1958 and 1966 which is several times the mortality recorded in the Life Span Study by 1972. This ratio, however, could well be consistent with the fact that many breast tumours may be fully removed at operation. There is thus no *a priori* reason to expect any large number of deaths from a separate group of malignant diseases to start to occur, although the proportion of deaths that are due to breast cancer and perhaps to thyroid cancer may well rise.

249. In any case, the median latency for fatal induced cancers in the populations studied at Hiroshima and Nagasaki, which had an initial mean age of about 30 at the time of exposure, could not greatly exceed 25 years, since the mean expectation of life would in itself start to exclude a much longer median latency unless the distribution of latencies was very skewed positively; and it is of interest that that of leukaemia appears to be negatively skewed.

250. The distribution of malignancies fatal within 27.5 years of exposure at Hiroshima and Nagasaki is shown in table 21. As compared with Japanese National Statistics, the individual fatal malignancies shown on this basis to be significantly increased in frequency were leukaemia, lung cancer and breast cancer. There was a probable increase in cancer of digestive organs other than the stomach and clear evidence of increase of cancers not separately listed. Of the total increase in deaths from solid tumours, lung cancers accounted for 28 per cent, those of the breast for 11 per cent and those of digestive organs other than the stomach for about 18 per cent. Rather over half of all fatal induced solid tumours therefore probably arose from these tissues.

TABLE 21. EXCESS MORTALITY FROM ALL CAUSES IN HIROSHIMA AND NAGASAKI, 1950-1972

Males and females, all ages

(Values for all exposed at ⩾ 10 rad; rates are per unit kerma)

		Compared with 0-9 rad group			*Compared with Japanese National Statistics*		
Cause of death	*Observed*	*Expected*	*Excess*	*Excess rate (10^{-6} rad^{-1})*	*Expected*	*Excess*	*Excess rate (10^{-6} rad^{-1})*
Leukaemia	84	21.0	63 (48-80)	36 (27-46)	13.7	70 (56-87)	40 (32-50)
All other malignant neoplasms	1 075	987.6	87 (24-153)	50 (14-87)	918.8	156 (103-212)	89 (59-121)
Cancers of:							
Stomach	417	411.8	5 (−34-47)	3 (−20-28)	419.6	−3 (−36-33)	−2 (−28-25)
Other digestive organs	261	255.3	6 (−26-39)	3 (−13-20)	232.8	28 (2-56)	16 (1-32)
Trachea, bronchus and lung	100	76.2	24 (5-44)	13 (3-24)	56.5	44 (28-62)	25 (16-36)
Other respiratory organs	29	26.0	3 (−7-15)	2 (−5-10)	17.2	12 (4-22)	7 (2-13)
Breast	37	24.0	13 (2-26)	7 (1-14)	19.0	18 (9-30)	10 (5-17)
Cervix and uterus	86	77.5	8 (−9-28)	4 (−4-14)	79.1	7 (−8-24)	4 (−5-14)
Other malignant neoplasms	145	117.0	28 (6-53)	16 (3-30)	94.6	50 (31-72)	29 (18-41)
Benign or unspecified neoplasms	53	52.6	0.4 (−13-16)	0.2 (−6-8)	42.9	10 (−1-24)	6 (−1-14)
All diseases except neoplasms	3 970	3 947.7	22 (−101-148)	13 (−60-88)	4 592	−622 (−725--517)	−354 (−413--294)

Source: Reference 97.
Note: The 90% confidence limits are indicated in parentheses.

251. Mortality rates for cancer of the stomach, oesophagus, urinary organs, and lymphatic and haematopoietic tissues are also significantly increased in exposed members of the Life Span Study during the period 1950-1974 as discussed below. Table 22 shows the estimated mortalities per unit kerma in this period, and indicates also the total rates for all malignancies. Although individual estimates are imprecise, it appears that the types of malignancies listed may account for over 90 per cent of all deaths from malignant disease that have occurred, and suggests that fatal malignancies of all other organs, for which increased rates are not yet detectable, may together contribute only a small proportion of all fatal radiation-induced malignancies. This would be consistent with the low induction rate of bone cancers, and the low fatality rate of thyroid cancers as discussed above, and with the probably low rates for other organs. It must be recognised, however, that some bias towards high estimates for individual types of cancer may be introduced, since significant induction might be suspected if random high, but not random low, incidences occurred.

252. For a number of these other organs or tissues, however, radiation has been shown to induce malignant tumours after moderate doses of a few hundred rads. While no convincing estimate can be made of the carcinogenic risk for most of them, it is often possible to show that the risk is unlikely to be high. The position can be reviewed briefly with regard to several such organs or tissues.

TABLE 22. EXCESS MORTALITY FROM MALIGNANCIES IN HIROSHIMA AND NAGASAKI, 1950-1974

Males and females, all ages

(Excess rate per unit kerma, 10^{-6} rad^{-1})

Malignancy	*Hiroshima*	*Nagasaki*	*Both cities*
Leukaemia	56 (51-61)	35 (29-41)	46 (42-50)
Other (solid) malignancies:			
Lung	13 (5-21)	3 (neg.-11)	8 (3-14)
Stomach	19 (3-36)	10 (neg.-25)	15 (4-27)
Oesophagus	9 (4-14)	−2 (neg.-3)	5 (1-8)
Large bowel	4 (neg.-8)	0.5 (neg.-4)	2 (neg.-5)
Other digestive organs	9 (0-18)	3 (neg.-13)	6 (neg.-13)
Bladder and urinary organs	4 (neg.-8)	2 (neg.-6)	3 (0.5-6)
Lymphatic and haematopoietic organs	5 (1-8)	4 (0-9)	4 (1-7)
Breast (females only)	10 (2-18)	6 (neg.-17)	9 (2-15)
Cervix and uterus (females only)	10 (neg.-24)	−9 (neg.-6)	3 (neg.-12)
Residue (by difference)	5	0	3
Total solid malignancies	77 (51-102)	21 (neg.-47)	53 (35-71)

Source: Life Span Study 1950-1974 (14).

Note: The 90% confidence limits are indicated in parentheses.

A. BRAIN

253. Although tumours of the brain do not metastasize and may not therefore be classified as "malignant", they commonly constitute a hazard to life because of their situation in a way that non-malignant tumours of other organs ordinarily do not. For this reason, estimates in this section (paras. 253-256) are of total brain tumour induction, where this information is available.

254. Modan *et al.* (92) record the development of eight brain tumours (six definite and two probable) during their follow-up from 12 to 23 years of 10 902 children irradiated for tinea capitis. Irradiation was by 5 fields to the scalp, with an estimated dose to brain of 120-140 rad at the surface, and 95-120 at a depth of 2.5 cm. On the basis of two control studies, 1.5 certain or probable tumours would have been expected. This incidence for a mean dose of, say, 120 rad would correspond to an induction rate of 5 (2-10) 10^{-6} rad^{-1}.

255. In its 1972 report, the Committee recorded the follow-up study by Albert *et al.* (1) of 2043 children treated for tinea capitis by radiation epilation of the scalp and in whom the occurrence of malignancies was compared with that in 1413 children who had had the same infection untreated by radiation. These authors (139) now record the development of 6 intracranial tumours in 2215 irradiated children with none in 1395 controls. The crude incidence rate is quoted as 2.8 10^{-3}. The estimated brain dose varied from 70 to 175 rad with a mean of 140 rad, so that this rate per unit absorbed dose corresponds to 20 (9-39) 10^{-6} rad^{-1} for a mean follow-up of 20.5 years. A long latent period may however elapse before diagnosis of radiation-induced intracranial tumours and a mean value of about 27 years was noted by Munk *et al.* (98). Indeed, Shore *et al.* estimate from their data by actuarial methods that the risk of intracranial tumour development to 29 years would be about 2.5 times that already observed in their series.

256. The sensitivity of the foetal brain may, however, be high, since MacMahon (83) found tumours of the nervous system to constitute 24 per cent of "all malignancies" apparently induced by intra-uterine irradiation. If, as the Committee noted in its 1972 report, the total induction of malignancies in the foetus corresponds to a rate of 200 10^{-6} rad^{-1}, this would suggest a high risk to the foetal brain. However, since only 19 cases were observed as compared with 14.3 expected, the estimate, of 50 (neg.-145) 10^{-6} rad^{-1} has wide confidence limits and is not inconsistent with that for the brain during childhood. Moreover, it has been noted that many pelvimetries are carried out when the foetus is in a breech presentation, when the absorbed dose in the foetal brain is likely (106) to be considerably higher than the mean foetal dose.

B. SALIVARY GLANDS

257. Modan *et al.* (92) record 4 malignant tumours of salivary (parotid) glands in their follow-up of 10 902 children irradiated for tinea capitis, with none in either of the control series. The dose to the salivary glands was not estimated. The mean thyroid dose of 6.5 rad, however, is similar to that of 6 rad estimated in the New York study of tinea capitis irradiation in children, for whom a parotid dose of 39 rad has now been estimated by Harley *et al.* (52). If this parotid dose is taken as applying also in Modan's series, the induction rate for salivary cancers would be 9 (3-22) 10^{-6} rad^{-1}.

258. Four salivary tumours were observed in the New York series (139) of which one was malignant (138), none being seen in the control series. The authors quote a crude rate of 1.8 10^{-3} for all such tumours, which would imply risk rates for salivary cancers of 12 (1-35) 10^{-6} rad^{-1} to 20 years.

259. Following neck irradiation in infancy or childhood, Saenger *et al.* (128) reported an excess of 2 salivary cancers in association with 11 thyroid cancers. Hempelmann (58) reports 4 salivary tumours, all now regarded as benign, in association with 24 thyroid cancers. If the salivary glands were as frequently exposed as the thyroid in the radiation fields used for neck irradiations in childhood, these observations would suggest an induction rate for salivary cancers of less than one tenth that for the thyroid, or in the range (5-10) 10^{-6} rad^{-1}.

260. Belsky (16) reports a significant excess of salivary cancers in A-bomb survivors in Hiroshima and Nagasaki exposed at over 300 rad kerma, with two cases observed as compared with 0.12 expected. Since 1340 persons (16 172 person years) were exposed in this group, this excess rate is of $1.4\ 10^{-3}$; or, if the mean kerma in the group was between 400 and 500 rad, about $3\ 10^{-6}$ rad^{-1} over a period of 12 years (1957-1970). This estimate would have confidence limits (1-8) 10^{-6} rad^{-1}. No excess was observed (3 observed, 3.6 expected) in those exposed at 1-299 rad, but absence of effect in this group is not inconsistent with the significant excess in the higher dose group. The rate in the latter would be about the same if estimated as per rad weighted absorbed dose (with $W = 7$ at this dose level), or somewhat higher (by about 40 per cent) per rad unweighted absorbed dose.

261. Takeichi *et al.* (152a) now report a total of 17 cancers of salivary glands that have been diagnosed in hospitals in Hiroshima during a 19-year period in A-bomb survivors exposed within 5000 m of the ground zero. The number expected was 1.7, as judged by the estimated numbers of survivors and the rate ($1.2\ 10^{-6}$ y^{-1}) in those who were over 5000 m distant. The excess rate in those exposed at less than 1500 m was 21 (9-41) 10^{-6} y^{-1} while for those exposed at between 1500 and 5000 m, it was 7 (4-14) 10^{-6} y^{-1}. Risk rates cannot be derived, however, since mean doses are not known for the total population of survivors. For members of the Life Span Study, the total air dose at 1500 m in Hiroshima was about 32 rad (67), and the mean dose over all shorter distances would be about 135 rad. If these dose levels apply also for all survivors, it would suggest a low induction rate of a few cases per million per rad in 19 years, but shielding factors become important at short ranges and are not known for survivors as a whole.

262. All these estimates are thus somewhat lower than the values derived in paragraphs 257-259, perhaps because the record is of cases following exposure at all ages, and diagnosed only between 13 and 25 years from exposure. All estimates have wide confidence limits, however, and would be consistent with a risk rate in the region $10\ 10^{-6}$ rad^{-1} to 20 years following exposure in childhood, with perhaps twice this value after prolonged follow-up, and with no evidence of any greater rate after exposure in adult life.

263. No evidence is available as to the mortality from any radiation-induced salivary tumours. The 15-year survival of naturally occurring cancers of the salivary glands is, however, high (70 per cent, see paragraph 18 and reference 23). The average risk rate per unit absorbed dose for fatal salivary cancers may thus be about $5\ 10^{-6}$ rad^{-1}.

C. MUCOSA OF CRANIAL SINUSES

264. As already stated, there is clear evidence of the carcinogenic effect of radiation on the mucosa of the mastoid and other air sinuses, but risk estimates cannot be derived since no determinations have been made of radon accumulation in these sinuses. It seems clear, however, that the risk must be small. Such cancers are fewer in numbers than are osteosarcomas in patients following incorporation of ^{226}Ra with only about two fifths the frequency of the sarcomas (127), so that the contribution to fatal malignancies from this source would, in the case of whole body radiation, be even smaller than that from bone cancers, assuming equal mortality from each type of tumour. There is some indication that the number of these carcinomas is now increasing more than is that of the sarcomas, corresponding to a longer latency until these tumours become detectable. The mucosa is closely applied to bone, so is likely to receive a dose at least equal to that delivered to endosteal cells, or larger if accumulated radon makes any substantial contribution.

265. The relationship between incidence and mean bone dose from ^{226}Ra, quoted in paragraph 233, would imply a risk rate of (2-5) 10^{-6} rad^{-1} if an RBE of 10 or 20 was taken for the alpha radiation from radium and if no added dose was derived from radon retention. If additional irradiation resulted from radon accumulation, the risk rate would of course be lower. While it seems likely, therefore, that these areas of mucosa may have a risk comparable with or lower than that from the whole endosteum, no inference can be drawn as to the relative sensitivity of two tissues per unit area or per unit mass of cells.

D. DIGESTIVE ORGANS

266. The mortality statistics of the Life Span Study to 1972 (97) showed a possibly significant excess of cancers of digestive organs other than the stomach, but did not indicate any high incidence for the stomach itself. Thus by the end of 1972, 261 deaths had been attributed to cancers of digestive organs other than the stomach, as compared with 232.8 expected on the basis of Japanese National Statistics. This excess of 28.2 has 90% confidence limits of 2.2 and 56.4.

267. Nakamura has now identified a significant increase in cancer of the stomach in irradiated populations in Hiroshima (101). The Life Span Study data (14) for both cities (for the 24 years to September 1974) confirm an increased mortality from cancers of the digestive organs, with significant increases for oesophagus as well as stomach in Hiroshima, possible increases for large intestine, and an increase for the group of other digestive organs (see table 22).

268. Tumor Registry data for the period of 1959-1970 suggest a significantly ($P \leq 0.02$) increased incidence in Hiroshima of cancers of the stomach, oesophagus, liver and large intestine, and perhaps in Nagasaki of cancers of the pancreas ($P = 0.06$) and large intestine ($P = 0.085$):

	Hiroshima	*Nagasaki*
	(Incidence rates per unit kerma, 10^{-6} rad^{-1})	
Stomach	18 (3-34)	10 (−5-26)
Oesophagus	6 (1-10)	–
Liver	4 (2-7)	4 (−2-10)
Large intestine	6 (1-11)	3 (−1-6)
Pancreas	0 (−4-5)	4 (0-8)

It must be emphasized, however, that incidence rates, as based on procedures of tumour registration, are liable to various possibilities of bias. These are not reflected in

the confidence limits or probabilities of significance given here, which are determined only by the random errors involved in estimating these rates (by contingency table methods (66)).

269. The studies of Court Brown and Doll (29) on patients treated for ankylosing spondylitis by irradiation showed an excess of deaths (occurring at more than 6 years after treatment) from cancer of several organs of the digestive tract which were heavily irradiated, although at unascertained dose. For the groups of patients completely followed up to 1 January 1960, or incompletely followed up to 1 January 1963, values were as follows:

	Complete follow-up (141 796 person years)			*Incomplete follow-up (165 631 person years)*		
	Observed	*Expected*	*Excess*	*Observed*	*Expected*	*Excess*
Cancers of:						
Pharynx	4	0.70	3.3 (0.7-8.5)	5	1.05	3.95 (0.9-9.5)
Oesophagus	3	2.25	0.75 (neg.-5.6)	3	3.37	−0.6 (neg.-4.3)
Stomach	28	16.0	12.0 (3.9-22.4)	38	23.6	14.4 (4.9-25.1)
Pancreas	9	3.8	5.2 (0.9-11.9)	12	5.7	6.3 (1.2-13.7)

270. In a follow-up of the patients who had only one course of radiotherapy for ankylosing spondylitis, Doll and Smith (36) observed numbers of deaths from stomach, pancreas, large intestine and probably oesophagus, which were significantly increased as shown either in the total series (of 14 109 patients with mean follow-up of 9.5 years) or in deaths at 6 or more years after treatment (6838 patients with a further follow-up to a mean time of 17.3 years from exposure as follows:

	All deaths			*Deaths after 6 years*		
	Observed	*Expected*	*Excess*	*Observed*	*Expected*	*Excess*
Cancers of:						
Stomach	45	34.2	10.8 (0.4-24)	36	24.6	11.4 (2.1-23)
Oesophagus	10	5.6	4.4 (−0.2-11)	9	4.3	4.7 (−0.4-11)
Pancreas	18	9.5	8.5 (1.2-17)	12	7.5	4.5 (−0.6-12)
Large intestine	28	17.3	10.7 (2.6-21)	18	13.1	4.9 (−1.5-13.6)

271. In the earlier report, a significantly increased number of deaths from cancers of the large intestine was also reported (25 observed and 14.8 expected) but the authors hesitated to ascribe this excess to radiation in view of the known increase of cancer of the colon in ulcerative colitis, and the association of ulcerative colitis with ankylosing spondylitis. Similarly, it was thought that the increased rate of stomach cancer might possibly be attributable to drugs taken in the relief of pain in ankylosing spondylitis.

272. Now, however, a series of patients with ankylosing spondylitis, but not treated by radiotherapy, has been found to have no increased cancer incidence as compared with a normal population (120). During a mean observation period of 7.9 years on 1021 patients, the total number of deaths from malignant disease was 18, compared with 19.1 expected. Of these, 3 were from stomach cancer (2.6 expected) and none from cancer of large intestine (1.4 expected; one colon cancer occurred during a further 3-year period which added 8 per cent to the person years surveyed). It does appear likely therefore that the increases in cancer rate for stomach and large intestine, as well as for oesophagus and pancreas, may be attributable to radiation, and that risk estimates may be obtainable from this source when the absorbed doses to these organs from the courses of treatment have been derived.

273. Brinkley and Haybittle (18) noted an increase of fatal cancer of colon and rectum (7 observed, 1.5 expected) in 227 patients within an average period of 16 years after pelvic irradiation for benign disorders. About half of the large intestine is likely to have been in the irradiation field and to have received a mean dose in the order of 800 R (54). Certainly 3, probably all 4, of the cancers of the large intestine arose from the area included within the field. No cancers were observed as having occurred in the small intestine, of which about half is likely to have been in the field. The observations suggest a substantial induction rate in large intestine and rectum, perhaps of the order of 25 10^{-6} rad^{-1} from half the intestine, but these indications are necessarily very approximate.

274. Smith and Doll (142) observed an increased number of deaths from cancer of the intestine in 2067 patients followed for a mean period of 19 years after treatment for metropathia haemorrhagica by pelvic x irradiation. From cancer of the intestines, 24 deaths occurred at 5 years or more after irradiation, with 13.86 expected; and for cancer of the rectum, 8, with 5.23 expected. It is of interest that of the intestinal cancers, 3 were of small intestine (143). With 0.4 expected, 3 or more would only occur by chance with $P = 0.008$. For cancers of the large intestine and rectum, the excess of $29 - 18.69 = 10.31$ (2.1-20.8) would only occur by chance with $P = 0.028$.

275. While these data indicate the likelihood of cancer induction in both small and large intestine, no reliable risk estimate can be derived because of the small numbers of cases and the uncertainty as to the proportion of small or large intestine lying within the

pelvis and exposed in the primary beam. If it is assumed, however, that only about one third of each intestine (small or large), but all the rectum, was directly exposed at a mean dose of 400 rad, approximate risk estimates would be: small intestine 10 (2-25) 10^{-6} rad^{-1}; large intestine 25 (2-60) 10^{-6} rad^{-1}; rectum 3 (0-10) 10^{-6} rad^{-1}.

276. In summary, therefore, it is clear that radiation induces cancers of the gastro-intestinal tract and digestive organs, although the total risk rate for all these tissues is not high, the estimate for Hiroshima and Nagasaki mortality 1950-1974 being about 25 (10-45) 10^{-6} rad^{-1} kerma. Estimates for individual sections of the gut are in the region of 5 10^{-6} rad^{-1} for oesophagus, small intestine and perhaps rectum. The rate for large intestine is similar on Japanese data, but is somewhat higher as inferred from pelvic irradiation (paras. 273-275), but these estimates depend upon assumptions as to the proportion of bowel present in the primary beam. A value of (5-10) 10^{-6} rad^{-1} would however be consistent with these data also. For the stomach a rate of (10-20) 10^{-6} rad^{-1} is suggested by the current Japanese information, but a further estimate for low-LET radiation will be available as soon as dosimetric estimates are obtained for the stomach irradiation during the treatment of ankylosing spondylitis. This applies also to the pancreas, for which a significant excess of cancers is detectable following this therapy. Estimates for the liver are discussed below (paras. 283-285).

E. PELVIC ORGANS

277. Palmer *et al.* (107) also noticed an excess of rectal cancers following the irradiation of the pelvis by radium or x rays or both in 651 patients with uterine fibroids and 80 with other benign pelvic disorders. Seven rectal cancers occurred within a mean follow-up period of 16.1 years as compared with 2.1 expected. No risk estimate can be derived, both because of uncertainty as to dosage and because ascertainment was by letters sent to previously irradiated patients to which replies were received in rather less than 50 per cent of cases. Local doses were quoted as of 2700 R, and 650-700 R, at 2 and 5 cm from the radium source in the cervix, and of "the equivalent of 1600 to 1800 mg.hr" if x rays alone were used. The cancers observed and expected were:

	Observed	*Expected*	*Mean latency (years)*
Fundus uteri	29	4.9	9.7
Cervix	11	6.5	8.5
Ovary	8	2.6	10.1
Rectum	7	2.1	10.7
Bladder	3	0.8	14.0
Vagina	2	0.2	12.7
Vulva	1	0.3	14.5

278. The excess number for the rectum is thus about equal to those for the cervix and ovary, although the doses will not necessarily have been the same. This excess is about one fifth of that for cancer of the fundus uteri, in which malignancies occurred in 4 per cent of patients compared with 0.7 per cent expected, after doses which presumably were about 700 rad. The estimated excess incidence of all pelvic cancers was 6 per cent, whereas that following irradiation for cervical cancer in 471 patients, at dose levels higher by factors of 2 or 3, was only 0.35 per cent. The latter estimate is imprecise, as only 13 cancers were found as compared with 11.4 expected, but does suggest that the induction of these tumours may be lower at high doses.

279. Palmer *et al.* (107) quote five surveys including a total of 3968 patients in whom 27 uterine, 10 cervical and 8 ovarian cancers were observed following pelvic irradiation, but they note that mean periods of follow-up were commonly less than 10 years and no data are given of the local dosimetry or control series.

280. Following pelvic irradiation for metropathia haemorrhagica, Smith and Doll (142) observed the following numbers of deaths from pelvic malignancies, occurring at 5 or more years after irradiation:

Site	*ICD Code*	*Observed*	*Expected*
Uterus	(171/174)	16	10.34
Ovary	(175)	8	7.66
Bladder	(181)	3	2.15
Other pelvic	(176)	0	0.85

These data suggest ($P = 0.08$) an excess of fatal uterine cancer, with an estimated risk—for death between 5 and 19 years after 400 rad—of 6.8 (0-16.9) 10^{-6} rad^{-1} if the incidence of uterine cancer is not increased in patients with metropathia haemorrhagica. Data for other pelvic organs indicate that risks higher than 8 10^{-6} rad^{-1} for ovary and 7 10^{-6} rad^{-1} for bladder are improbable ($P < 0.05$).

281. Data for Hiroshima and Nagasaki (14) still show no significant increase in mortality from cancer of cervix and uterus, and appear to exclude a risk rate per unit kerma higher than about 10 10^{-6} rad^{-1}—the estimates for excess mortality in both cities to 1974 being 3 (−7-12) 10^{-6} rad^{-1}. The mortality rate per unit kerma for cancers of bladder and urinary tract is, however, just significantly in excess of expectation, with a value of 3 (0.5-6) 10^{-6} rad^{-1}. Tumor Registry data for 1959-1970 confirm an increasing incidence with increasing exposure for bladder (and urinary organs) cancers in both cities, and—for certain dose groups in Hiroshima—suggest this also for the ovary (tube and ligament) and for the cervix. No significant excess is observed for cancers of the prostate or rectum. Estimates rates during this 12-year period have been:

	Hiroshima	*Nagasaki*
	(Incidence rate per unit kerma, 10^{-6} rad^{-1})	
Bladder	4 (0-8)	4 (0-8)
Ovary	7 (2-12)	0 (−3-3)
Cervix	13 (2-24)	−3 (−17-11)

282. A suggestion of sensitivity of the bladder to cancer induction by radiation at much higher doses is given by data of McIntyre and Pointon, who observed 16 epithelial cancers of the bladder, with 9 expected, in 8950 patients treated for cancer of the cervix (89). Ascertainment was likely to have been better than

50 per cent, but was certainly not known to be complete. The dose to the bladder, of 4000 rad or more, is too high to allow any useful risk assessment of the carcinogenic effects of moderate doses.

F. LIVER

283. Only a tentative risk assessment appears to be possible for the liver. Cancer of the liver has repeatedly been observed following Thorotrast administration but, as stated earlier, much of the energy of the decay of the contained thorium is expended in necrotic tissue and in the Thorotrast deposits themselves. Estimates have however been made (75) of the mean dose to liver from a given injection of Thorotrast, with corrections for self-absorption depending upon the mass injected. In the light of these dosimetric estimates, it appears from a number of epidemiological surveys (see table 23) that the excess frequency of liver cancer is in the region of 5 per cent within 20 years of injections involving liver absorbed doses of about 500 rad by this time. This would imply a risk rate of $100\ 10^{-6}$ rad^{-1} of alpha radiation if the carcinogenic effect of Thorotrast was due essentially to its radiation, rather than to its chemical, effect. It is suggested that this is so in the light of observations on animals injected with a "thorotrast" in which the ^{232}Th content is enriched with ^{230}Th. These surveys would suggest that the lifetime carcinogenic risk of liver irradiation of low LET would be in the region of $(10\text{-}20)\ 10^{-6}$ rad^{-1} if an RBE of 10 or 20 were applicable to alpha radiation from ^{232}Th at these dose levels. It remains uncertain however, how much of the estimated dose is "wasted" radiation, either because of irradiation of already necrotic cells, or because the tumours have already been induced while exposure is continuing. It also remains uncertain whether any of the cancers observed are chemically or mechanically induced by the thorium oxide preparation (see also Annex I, paragraph 253).

TABLE 23. OCCURRENCE OF LIVER CANCERS FOLLOWING THOROTRAST INJECTION

Reference	*Country*	*Approximate mean follow-up (years)*	*Mean dose of Thorotrast (ml)*	*Mean volume of Thorotrast injected (ml)*	*Accumulated dose in 20 years (rad)*
141	Portugal	30	26	6.4	530
42	Denmark	28	23	3.6	470
69	United States	10	24	–	–
72	Germany, Fed. Rep. of	30	30	7.0	570
96	Japan	33	16	4.5	370

284. The induced tumours are mainly cholangiocarcinomas and haemangioendotheliomas, with smaller numbers of hepatomas arising from liver cells themselves. This distribution may of course reflect the relative sensitivity of epithelial and parenchymal tissues to cell killing by radiation rather than to tumour induction alone.

285. The incidence of liver cancer in Hiroshima and Nagasaki, as observed in Tumor Registry data for 1959-1970, increases with increasing estimated kerma, the excess incidence during this period being $4\ (2\text{-}7)\ 10^{-6}$ rad^{-1} in Hiroshima and $4\ (\text{neg.-}10)\ 10^{-6}$ rad^{-1} in Nagasaki.

G. MALIGNANT LYMPHOMA AND MULTIPLE MYELOMA

286. An apparent increase in both these types of tumour was noted in the Committee's last report, with the reservation that more data were needed to conclude that A-bomb survivors were at increased risk of developing these forms of malignancy.

287. Data published by Nishiyama *et al.* (104) show that 23 cases of malignant lymphoma were recorded in 1945-1965 among 44 509 survivors in the extended Life Span Study sample at Hiroshima and Nagasaki. This number can be compared with 18.0 expected on the basis of findings in 34 675 survivors exposed at less than 1 rad in both cities, adjustments being made to standardize for population distribution and for the skewed distribution of age in the population at the time of the bomb owing to the paucity of civilian males of military age. For multiple myeloma, 6 cases were observed with 2.6 expected on this basis, an excess of 3.4 (0.0-9.2). The numbers in the two cities were:

	Malignant lymphoma		*Multiple myeloma*	
	Observed	*Expected*	*Observed*	*Expected*
Hiroshima				
1-99 rad	7	11.0	3	1.6
⩾100	8	1.3	1	0.2
Nagasaki				
1-99 rad	6	4.7	2	0.7
⩾100	2	1.0	0	0.15
Total	23	18.0	6	2.6

288. The total excess of cases of malignant lymphoma is thus only 5.0 (0-14.6). It is suggestive, however, that the greatest excess occurred in the highest exposure group at Hiroshima. In this group of 3138 survivors there were 4 cases of lymphosarcoma (0.4 expected on a basis of those exposed at less than 1 rad at Hiroshima), 1 case of reticulum cell sarcoma (0.5 expected) and three cases of Hodgkin's disease (0.2 expected). Since this group corresponds to about $0.76\ 10^{6}$ man rad, the excess per unit kerma for all malignant lymphomas would, during the period of observation, represent about $9\ (4\text{-}18)\ 10^{-6}$ rad^{-1}, or $12\ (5\text{-}23)\ 10^{-6}$ rad^{-1} absorbed dose, assuming absorbed-dose/kerma ratios as for the

stomach (53). If the high-LET component were weighted by about 10 (para. 55), the rate would be 10 (4-20) 10^{-6} rad^{-1}.

289. Court Brown and Doll (29) found an excess of 4.7 (1-11) deaths from cancers of lymphatic and haematopoietic tissues to be associated with 30 (21-41) deaths from leukaemia at periods of 6 years or more after treatments for ankylosing spondylitis. This ratio of rates appears to be broadly consistent with estimates for lymphoma noted in paragraph 288 and for leukaemia in chapter II of this annex, assuming that the relevant lymphatic and marrow tissues received about equal doses in these treatments.

290. Malignant neoplasms of lymphatic and haematopoietic tissues (apart from leukaemia) have now been identified as contributing a small increasing mortality in the Life Span Study cohort from 1950-1974, the excess rates per unit kerma over this period being: (10^{-6} rad^{-1}):

Hiroshima	5 (1-8)
Nagasaki	4 (0-9)
Both cities	4 (1-7)

291. In the study of Doll and Smith on patients treated with a single course of radiotherapy for ankylosing spondylitis (36), no dose estimates are yet available for lymphatic tissues (excluding those from Hodgkin's Disease which were not increased), but the excess deaths from malignant tumours of these tissues can be compared with those from leukaemia in the same series, suggesting that lymphatic malignancies are less frequent and develop later than leukaemia:

		Excess deaths	
Number of patients	*Mean period during which deaths occurred (years)*	*From leukaemia*	*From malignancies of lymphatic tissues*
14 109	0-9.2	24.5 (16-35)	8.2 (0.3-16)
6 838	6-17.3	10.4 (5-18)	7.6 (2.5-15)

292. Matanoski *et al.* (89a) have recorded an increase in standardized mortality ratio (SMR) for certain tumours arising from lymphoid tissues in members of the Radiological Societies of North America, as compared with those found during the same periods in members of pathologists' and oto-rhino-laryngologists' societies. The increases were observed for lymphosarcoma and reticulum cell carcoma (ICD 200) for 1920-1929 and 1930-1939, although not for 1940-1949; and for Hodgkin's Disease (ICD 201) for the last of these periods only. For other neoplasms of lymphatic and haematopoietic tissues (ICD 202), increases occurred during the last two of these periods, and particularly during 1940-1949 when the SMR was 5.7 for radiologists as compared with 1.0 for pathologists and 2.2 for oto-rhino-laryngologists. Risk estimates cannot be derived from these data, however, in the absence of adequate estimates of the doses received at work.

H. SKIN

293. Malignant tumours of skin were the first cancers reported to have been induced by radiation (46), but no estimate yet appears to be available of the frequency with which they are induced. The absence of reports of skin tumours occurring either in the populations exposed at Hiroshima and Nagasaki, or in the closely studied populations on Rongelap Island or following neck radiation in infancy, strongly suggest that such tumours must be infrequent at moderate dosage. In these populations, the low mortality from skin tumours would presumably not prevent their occurrence being detected on examination, even if they had been excised or cured by radiation therapy. It can be argued that infrequent reporting of skin tumours following radiation therapy in adults does not constitute evidence against the sensitivity of the skin as a whole for moderate doses, in view of the small fields, high levels of skin irradiation and often of the short survival of patients after treatment. These observations, however, do not apply to populations exposed to moderate whole-body radiation.

294. Some indications that the skin has low sensitivity to carcinogenesis by radiation is suggested by the findings of Modan *et al.* (92) of only one skin cancer (on the scalp) in the 10 902 children given scalp irradiation (with 5 fields at 350 R per field). No skin tumours were seen in the control series. It is likely, in view of the known variation of head circumference and the body surface area with age, that about 4 per cent of the total skin area may have been irradiated, so that a low rate would apply even for whole skin irradiation. Modan *et al.* emphasize, however, that skin tumours, being associated with a low mortality, may have been missed if they occurred during the early years after irradiation before the National Tumour Registry was established.

295. Albert and Omran (1) record the occurrence of two basal cell carcinomas of the scalp within 12 years of irradiation of 2043 children of average age 7.5 years, with none in their control group of 1413 children. Since the scalp dose was of 500-800 rad, this implies a low risk level of 1 or 2 skin cancers per million per rad for irradiation of this area. Further follow-up to a mean time of 20.5 years (139) now shows 10 skin tumours to have occurred within the unshielded areas (in contrast to only one in the control group), the majority being basal cell carcinomas. The total incidence of epithelial cancers corresponds to an induction rate per unit absorbed dose of about 5 (2-10) 10^{-6} rad^{-1} by 20 years for this area exposed in childhood, although with no excess mortality from this cause.

296. Rowell (126) notes the occurrence of 5 skin cancers (one squamous and four basal cell) in 100 patients treated for benign dermatoses during 1930-1964 and examined in 1964. Patients were selected for examination if the treatment doses had exceeded 1500 R to hands or 1600 R to face, nails or feet. Skin cancers occurred in 1 of 59 patients whose hands were treated, and in 4 of 25 patients who had treatment to the feet. The mean doses are not stated, but the tumours developed after exposures of 2000-3200 R. The fields, if used for treatment of dermatoses, may have involved the whole of hands or face but would still represent only a small percentage of body area, and a 5-per-cent tumour incidence following, say, 2500 R to a few per cent of the skin surface would suggest a substantial sensitivity of the skin to carcinogenesis at these dose levels. It is clear, however, that more and larger series require to be studied.

297. Delarue *et al.* (31) record the occurrence of only one skin cancer in the area likely to have been exposed during multiple fluoroscopies done in management of pneumothorax treatment of 308 patients. Since an average of 142 examinations were made, at a mean skin dose of 6-12 rad for each, this corresponds to an incidence rate of about 4 (0.2-18) 10^{-6} rad^{-1} following exposure presumably of about 3-5 per cent of the total skin area.

298. In patients who received a single course of radiotherapy for ankylosing spondylitis, Doll and Smith (36) have recorded no deaths from skin cancer, with 1.6 expected, in the 6838 patients followed from 6 years after the course for a further mean period of 11.3 years. A typical treatment is likely to have involved a total skin dose in the region of 1000-1500 rad to 3-5 per cent of the total skin area. Since the upper limit of the 90% confidence zone (with 0 observed and 1.6 expected) would correspond to a possibility of 1.4 cases, the maximum estimated annual rate for whole-skin exposure at these dose levels would be about 0.5 10^{-6} y^{-1} rad^{-1}, implying a relatively low mortality even if the rate operated over several decades.

299. Ševcová *et al.* (137) observed the incidence during a 5-year period of skin cancer in uranium miners at a rate of 18.7 (8.0-38.0) 10^{-4} (95% confidence limits), as compared with an expected rate of 4.1 10^{-4} for Czech males of the same age distribution. The rates in other uranium workers (not miners) were 4.8 (0.6-17.0) 10^{-4} observed and 7.2 10^{-4} expected. The tumours in the miners were predominantly basal cell cancers of the cheek and forehead. The estimated absorbed dose to basal cell layers of the epidermis from the alpha radiation from radon daughters was estimated as 6 rad per year, as derived from epidermal thickness data of Whitton (161) and from measured average skin contaminations of 6 pCi cm^{-2} under current exposure conditions. Having regard to average lengths of mining experience prior to skin cancer diagnosis (14.2 years) and the probable occurrence of higher contamination levels previously, the accumulated dose to basal cells was estimated as 100 rad or more. On this basis, the induction rate for facial skin can be estimated as 3 10^{-6} rad^{-1} y^{-1} or less. Alternatively, since an estimated dose rate of 6-10 rad^{-1} y^{-1} was leading to an incidence of 290 10^{-6} y^{-1}, the total induction rate could be regarded as at least 30-50 10^{-6} rad^{-1} of alpha radiation, and this estimate should be increased owing to the relatively short mean times of exposure and survey and the known long latency for many skin cancers.

300. It may be questioned however whether the ascertainment of skin cancer in the mining populations, surveyed for the development of this condition, might have differed in efficiency from that for the general population as derived from nationwide oncological notifications, but the rates recorded for the non-mining uranium workers, from registrations at the same health institute, were in fact somewhat lower than those expected on the nationwide basis. All tumours were removed surgically and no signs of recurrence had been observed at the time of reporting. It may be noted that no excess incidence of laryngeal cancer was observed in Czechoslovak uranium miners by Plaček and Ševc in 1975 (113).

301. Any estimates of this type, however, are necessarily approximate and should be treated with considerable reserve in view of the long latencies that have been reported for radiation-induced tumours of the skin. Pegum (110) has noted a mean latency of 31 years after treatment of tinea capitis; Andrews (4), a mean value of 27 years in patients following radiotherapy; and Petersen (111), one of 27.5 years in 21 patients; while Spittle (para. 12, table 1) observed the very long mean latency of 41.5 years for basal cell cancer in a group of patients after treatment of tinea capitis by radiotherapy.

302. It is important, however, to note the low mortality associated with skin cancer. Andrews (4), for example, has observed a mortality of only 6 per cent during 10 years after diagnosis. It is likely, therefore, that the contribution of the skin to a fatal radiation-induced cancer rate must be low.

VIII. MALIGNANCIES IN PRE-NATALLY EXPOSED CHILDREN

303. In its 1972 report, the Committee described in detail the results of studies of Stewart and Kneale (149, 150) and of MacMahon and Hutchinson (84), showing an increased risk in the development of malignancies during the first 10 years of life of children who had been irradiated *in utero* during pelvimetric or other x-ray examinations involving the pelvis of the mother. It was stated that, although children born from mothers x-rayed while pregnant seem to have an increased risk of cancer after birth, a possibility still remained that the association, or at least part of it, was caused by factors other than radiation, and that further studies were needed to clarify this point.

304. This uncertainty was partly because of a discrepancy in the frequency of such malignancies following irradiation *in utero* in the studies referred to and in those of Jablon and Kato (65) of children whose mothers were pregnant at the time of the A-bomb explosions in Hiroshima and Nagasaki. A second possible criticism of the evidence, however, was that a subgroup of mothers might have been more frequently x-rayed than others because of hereditarily determined abnormalities (for example, of the pelvis) and that this subgroup might have a preponderance of children who developed malignant disease as a result of some associated and transmitted congenital abnormalities.

305. Mole (93) has now pointed out, by a further analysis of the data of Stewart (151, 152), that pelvic x rays are much more frequently carried out (in 55 per cent of cases) on mothers with twin pregnancies, than on mothers with other, or "singleton", pregnancies (of whom only 10 per cent are x-rayed during the pregnancy). Despite this, the excess frequency of malignancies in twins who were irradiated *in utero* is no higher than that in singletons so irradiated. The factors which called for a greater frequency of pre-natal x rays,

at least in this type of pregnancy, do not therefore appear to be associated with an increase in childhood malignancies. Thus, in singletons, leukaemia developed in $3.4\ 10^{-4}$ of all live-born children who had been x-rayed *in utero*, but in only $2.3\ 10^{-4}$ of those not x-rayed. In twins, leukaemia developed in $2.6\ 10^{-4}$ of those x-rayed and in $1.2\ 10^{-4}$ of those not x-rayed. The difference in rate apparently attributable to radiation is thus about equal in singletons and twins, being $(1.18 \pm 0.15)\ 10^{-4}$ in the former and $(1.43 \pm 0.46)\ 10^{-4}$ in the latter.

306. For other malignancies a similar result was observed. In x-rayed singletons the rate was $3.9\ 10^{-4}$, and $2.7\ 10^{-4}$ in those not x-rayed. In x-rayed twins the rate was $3.1\ 10^{-4}$, and $2.0\ 10^{-4}$ in those not x-rayed. The difference in rate attributable to radiation is $(1.24 \pm 0.17)\ 10^{-4}$ in singletons, and $(1.14 \pm 0.53)\ 10^{-4}$ in twins. Provided the higher still-birth rate in twins (5.7 per cent) than in singletons (2.1 per cent) did not introduce bias by including an excess of still-born twins who would have developed leukaemia or solid cancers, the evidence clearly supports a likelihood that the increase in malignancies was attributable to radiation rather than to selective factors.

307. Newcombe and McGregor (102) and Holford (59) have discussed the apparently linear relationship observed by Stewart and Kneale (150) between excess cancer risk and number of films per examination and regard the data as showing a close correlation to a simple linear relationship with dose, down to doses in the range of 0.2-0.25 rad.

308. Mole (93) discusses the apparent discrepancy between the excess of childhood cancers following diagnostic x rays *in utero*, and the apparently lack of any such significant excess in Japanese A-bomb survivors who had been irradiated *in utero* (65, 73). He suggests that the higher foetal doses received in Hiroshima and Nagasaki may have been associated with cell-killing effects which may have reduced the subsequent incidence of cancers that would otherwise have been expected. He points out also that, with only 1 childhood malignancy observed after irradiation *in utero* in these cities, as compared with 0.4 expected on the basis of Japanese National Statistics, the confidence limits of the resulting risk estimate would in any case have been wide and might be consistent with the Committee's estimate, in its 1972 report, of the risk of malignancies following foetal irradiation. With 34 900 man rad to mothers and with absorbed doses to the foetus as given by Auxier *et al.* (9), the foetal risk per unit kerma would be 43 (neg.-316) 10^{-6} rad^{-1}, or 25 (neg.-186) 10^{-6} rad^{-1} if the high-LET component of absorbed dose were weighted as in paragraph 55. Such estimates are not necessarily inconsistent therefore with the Committee's risk rate per unit absorbed dose for foetal irradiation, as given in its 1972 report, of 230 10^{-6} rad^{-1} (for doses in the range of 0.2-20 rad). In summary therefore, the risk per unit absorbed dose of fatal induced malignancies by foetal irradiation may be in the region of 200-250 10^{-6} rad^{-1}, half of these malignancies being attributed to leukaemia and one quarter to tumours of the nervous system (see also Annex I, paragraph 303).

IX. CONCLUSIONS

A. CARCINOGENESIS IN DIFFERENT ORGANS

309. The evidence on radiation carcinogenesis in man that has been reviewed in this Annex indicates a progressive increase in information as to the tissues and organs in which malignancies may be induced at absorbed doses in the region of a few hundred rads or less. It also allows approximate estimates to be made of the risk of inducing a malignancy at these dose levels for an increasing number of such organs if selectively irradiated, or for the whole body if more uniformly exposed.

310. The risk of the development of a malignancy following irradiation of individual tissues at dose levels of the order of 100 rad may vary with the LET of the radiation, sometimes with the age and sex of the subject exposed (see Annex I, paragraph 289), and probably also with the dose rate or "fractionation" with which the dose is delivered (see Annex I, paragraph 179).

311. The risk estimates obtainable for individual organs or tissues cannot be determined with great accuracy, but for several tissues, such as those of the bone marrow and the thyroid gland, approximate estimates are obtainable from several different sources and are mutually consistent within the accuracy of their determination. It is thus becoming possible to classify different body tissues into groups with different degrees of sensitivity to induction of malignancies by radiation. It must be emphasized, however, that such classifications, and the values for the induction rates themselves, are derived from the results of exposure at high dose levels, ordinarily in excess of 100 rad (of low-LET radiation). As stated above for leukaemia (paragraph 96) the corresponding rates per unit absorbed dose at doses of a few rad, while unlikely to be higher, may be substantially lower.

312. The thyroid and the female breast appear to have high rates of cancer induction by radiation at levels usually in excess of 100 rad, at least for certain ages at exposure. Average risk rates for all ages appear to be in the region of 100 10^{-6} induced cancers per rad absorbed dose of low-LET radiation. The low mortality rate for radiation-induced thyroid cancers and the moderately low rate for breast cancers probably bring the corresponding average risk rates for fatal cancer induction for these two issues to about 10 10^{-6} and 50 10^{-6} rad^{-1} respectively.

313. The induction rate for lung cancer also is high for males of over 35, insofar as a value can be derived from experience of uranium mining and probably also for females at these ages. Rates at other ages are difficult to establish but seem clearly to be lower, and a mean rate for all ages in the region of (25-50) 10^{-6} rad^{-1} of low-LET radiation seems probable.

314. The induction of leukaemia, of the acute and chronic granulocytic forms, occurs with a risk which appears to fall, probably from about 50 10^{-6} rad^{-1} at moderately high doses, to the region of 20 10^{-6} rad^{-1}

as the dose level is reduced. For radiation-induced leukaemia, the mean interval between exposure and death is in the region of 10 years, and is much shorter than the mean interval for other malignancies, which typically appears to be 25 years or more; The total induced mortality from leukaemia can thus be estimated with greater confidence in most present surveys than that from other malignancies.

315. The risk rates for stomach, liver and large intestine are less reliably determined, but appear to be substantially lower, and are probably in the region of (10-15) 10^{-6} rad^{-1} for fatal cancers. For the brain, quantitative information is scanty, but the rate for all tumours, which may prove fatal in this situation, may be similar. The salivary glands appear to have an induction rate in about this range also, but the risk rate for fatal cancers is likely to be lower.

316. For bone, oesophagus, small intestine, urinary bladder, pancreas, rectum and the lymphatic tissues, risks of cancer induction are identifiable but appear to be lower again, with values probably in the region of (2-5) 10^{-6} rad^{-1}. The risk for the mucosa of cranial sinuses appears to be similar. No good estimate is available for skin cancer induction, but the induction of fatal cancers of skin appears also to be low. All estimates quoted in these paragraphs (312 to 316) are "rounded" values which are broadly consistent with figures obtainable from different sources, but reference should be made to the paragraphs of the annex which deal with the various tissues for reviews of the different bases for risk estimation and the reservations or limitations which apply to each.

317. Evidence is given in paragraph 247 which suggests that the total of all fatal malignancies which may ultimately result from a given uniform whole-body exposure, may be in the region of 4-6 times that for leukaemia alone. The average rates quoted in paragraphs 312-317 are necessarily tentative, but do not appear inconsistent with this possibility. Thus, the total rate of all fatal solid cancers for the various tissues or organs for which some estimate has been made, amounts to about 200 10^{-6} rad^{-1} for moderately high doses (e.g. of a hundred to a few hundred rads of low-LET radiation). If these tissues have been identified because they are the main contributors to the carcinogenic effects of radiation, and if leukaemia is induced with a rate of 50 10^{-6} rad^{-1} at these dose levels, the final ratio of all total malignancies to leukaemias could thus be in the region of 6.

318. It is to be expected that low-LET radiation is likely to be less carcinogenic per unit absorbed dose at doses of a few rads than at levels of one or a few hundred rads. For dose levels at which a leukaemia induction rate of (15-25) 10^{-6} rad^{-1} may apply (see paragraph 96), a ratio of 4-6 between the frequency of *other* induced fatal malignancies and that for leukaemia would imply a total for *all* fatal induced malignancies, including leukaemia, of (5-7) times (15-25) 10^{-6} rad^{-1}, suggesting a value of about 100 10^{-6} rad^{-1} at such dose levels. It must be emphasized again, however, that such a value is derived essentially from mortalities induced at doses in excess of 100 rad. The value appropriate to the much lower dose levels involved in occupational exposure, and even more so in environmental exposures to radiation, may well be substantially less: and this reservation applies also to values quoted for individual organs or tissues. Moreover, these values, although often consistent with several different sources of evidence, are only very approximately determined, and indicate the need for further investigation of many points. They do, however, form some basis for assessing the possible significance of occupational exposure and for planning of protection measures.

319. It is likely that malignancies may be induced in the foetus by exposure *in utero* at average absorbed doses in the range of 0.2-20 rad from diagnostic x rays (para. 308). The induction rate of fatal malignancies per unit absorbed dose is difficult to determine with any confidence, but is estimated as being in the region of (200-250) 10^{-6} rad^{-1}.

B. INDICATIONS FOR FUTURE WORK

320. Quite clearly, however, much further information is needed before the carcinogenic risks of radiation can be estimated with accuracy and confidence, particularly at low doses. The Committee wishes to emphasize the importance of further investigations, particularly in four areas:

(a) The continuation of surveys of cancer induction following radiation exposure, for long periods of time—ideally throughout the lifetimes of those initially exposed;

(b) Further study of the basis for assessing risk from low-LET radiation at various dose levels, from that resulting from high-LET radiation;

(c) Continued examinations of the effects upon the risk of malignancy, of the uniformity of radiation exposure, both within a tissue of which the cells all have a similar sensitivity to tumour induction, and within organs in which the malignancy may result only from irradiation of certain types of cell;

(d) Further investigation of the proper basis for inferring risk rates at low doses from those observed following high doses, and in assessing the influence of dose rate.

These fields of investigation are discussed in the following paragraphs.

321. The need for prolonged continuation of epidemiological studies is obvious, since it cannot otherwise be known what types or frequencies of cancer may occur at several decades after exposure, or what cancers may develop when those who were exposed in childhood reach an age at which hormonal or other influences facilitate the expression of cancers induced many years previously (see Annex I, paragraph 68). These considerations apply very strongly to the extremely important observations in Hiroshima and Nagasaki, of which the prolonged continuation is regarded by the Committee as being of the greatest value. The same applies also to the studies of uranium miners and to those exposed in childhood or in adult life to local radiotherapy for

benign conditions. Further possible studies of irradiated patients are discussed in Annex F with review of the dosimetric information available (para. 138) or needed (para. 110) in evaluating the carcinogenic effects of radiation on other organs.

322. There is an urgent need for establishing a reliable basis for inferring the risk from a given absorbed dose of low-LET radiation from that resulting from high-LET radiation. Most occupational and environmental exposure is to radiation of low LET. However, four very important sources of human epidemiological evidence yield risk estimates only for, or largely in terms of, high-LET radiation, namely, following the irradiation of bone cells with ^{224}Ra and ^{226}Ra, of lung tissues of uranium miners with radon daughters, of liver cells with thorium, and particularly of the whole body in the populations of Hiroshima who were exposed to absorbed doses from neutrons of up to a hundred or more rads. Investigations in animals have compared the frequencies with which mutations, chromosomal aberrations and cell-killing effects are induced by high- and low-LET radiations at various dose levels. It appears most important that similar comparisons should be made between the carcinogenic effects of such radiations at different dose levels, and should extend over various animal species (see Annex I, paragraphs 13 and 339) and types of tumour, so that the RBE for carcinogenesis, and any variations of it with dose, should be explored on as wide a basis as is practicable.

323. It would be valuable also if available human data could be examined for any evidence as to the RBE for any forms of human carcinogenesis, for example, by the use of epidemiological surveys yielding better values for sarcoma induction in bone following external radiotherapy, or by a more sophisticated intercomparison of the leukaemia induction rates in Hiroshima and Nagasaki than has been possible in the present report.

324. The identification of the cell types at risk within various organs and of the relative importance of homogeneous or non-homogeneous irradiation of a given tissue are essential to an understanding of the process and of the frequency of tumour induction and to the estimation of the relevant dose for risk evaluation (see Annex I, paragraph 301). The approximate consistency of leukaemia risk estimates derived from irradiation of the whole marrow or of only a fraction of the marrow, suggests that a given integral dose of moderate size may be about equally effective whether distributed uniformly or not. When smaller fractions of a tissue are exposed to much higher local doses, the effects are likely to depend on the form of the dose-effect relationship at high doses and the way in which the yield of tumours falls when local doses are very high. The problem has been closely examined on a theoretical basis (86) but further experimental examinations are needed.

325. The direct determination of the risk to man from exposure of the whole body or of particular body tissues to low doses presents considerable difficulties, but the Committee wishes to emphasize the importance of any practicable studies that would be likely to yield statistically reliable information on this question. Large irradiated populations need to be studied, however, if a small increase in a common form of cancer is to be distinguished from the natural incidence of the cancer in the control population. The raised incidence of thyroid cancer following an estimated dose of 6.5 rad to the gland (para. 122) resulted from a study of the records of about 11 000 irradiated children and about 16 000 controls. The increase in childhood cancers after irradiation *in utero* at a probable mean dose of only a few rads entailed identification of whether x-ray examinations had occurred *in utero* on 7500 children who died of malignancies, in Stewart's survey (para. 303).

326. Extended studies of malignancies in occupationally exposed workers would be informative and valuable, if exposures to both external and internal radiation were adequately known, if an appropriate control population was studied, and if the numbers observed—and the time of observation—were sufficient. It can be estimated that the number of deaths from "spontaneous" cancer occurring, for example, in 30 years in a male population of 100 000 of age 18-65 (distributed by age as in the general population) would be 11 200 (as based on mortality rates in the United Kingdom of Great Britain and Northern Ireland). In a group of this size, therefore, and with a sufficient control group, cancer induction by radiation would only be detectable (at the 2-SD levels) if it caused 212 additional deaths within this period, corresponding to an induction rate of over $70\ 10^{-6}\ y^{-1}$ from the doses received by this population. To evaluate the excess rate with any accuracy would require 1.5-2 times this rate, unless unusual forms of cancer were detected. Unless the present estimates of total cancer induction are substantially in error, therefore, it would require studies covering some millions of person-years of workers exposed at annual average whole-body doses of over 1 rad, to evaluate directly the risk of such doses. Equal or smaller surveys might, of course, still be valuable in excluding higher risks than have been estimated, or unexpected forms of malignancy due to undetected local tissue irradiation.

327. In surveys of patients who have had diagnostic examinations with radionuclides involving moderate or low tissue-absorbed doses, the interpretation of epidemiological surveys for the induction of malignancies may involve two problems in particular. In the first place, it will be difficult to know—without suitable control series—whether the patients' diseases may not be associated naturally with an excess incidence of certain types of malignancy. Secondly, it may be difficult to be sure that the radionuclide test itself was not occasionally done to investigate a condition which was in fact due to a developing malignancy. For thyroid scans, for example, this may be particularly difficult, since thyroid cancers may cause modularity or enlargement of the gland which, in the absence of operation, may only become diagnosable as malignant many years later. Any survey of the sequels of diagnostic radionuclide tests should only be undertaken if it is clear that such difficulties will not necessarily make the results useless when they have finally been obtained.

328. The potential importance of examining malignancy rates in populations living in areas of high natural background radiation has frequently been emphasized,

provided that adequate medical records were obtainable, and that parallel studies could be made in a comparison area differing only in being exposed to lower background radiation. However, when the raised background radiation is due to increased external radiation, populations hitherto identified have been of such a size, in relation to the elevation of background radiation, as to require a very prolonged observation with efficient ascertainment of causes of death to detect or evaluate an increase in total cancer mortality above that to be expected from natural causes in a comparison population.

329. It has been estimated (117) that an increased cancer mortality is likely to be detectable in a considerably shorter time if studied on the basis of deaths of those aged less than a certain optimum age, which is likely to vary with the population studied, than if based on deaths at all ages, when the rising natural cancer mortality at higher ages is likely to make the radiation-induced mortality harder to detect. (A similar argument may apply to surveys of occupationally irradiated groups.) Problems of ascertainment, however, continue to be the major difficulty in existing high-background areas with adequate populations, and it may be that studies on larger populations exposed to only moderate elevations of background radiation might be more informative if good records of death rates from malignant diseases were already available and had previously been maintained in these areas. (For given rates of natural cancer incidence and of cancer induction per unit dose, the duration of survey required to detect a radiation-induced increase in rate should vary inversely with the size of exposed population and also inversely with the square of the elevation of background radiation rate as compared with that of the control population.)

330. Populations are also exposed to raised radiation levels in certain areas in which various dietary constituents are unusually radioactive or when living at altitudes at which increased cosmic radiation causes elevation of the external radiation background. It seems unlikely that either situation gives opportunities for useful epidemiological studies. With increased internal radiation from dietary radioactivity, the known populations are small and dosimetric evaluations might be difficult to make on a reliable basis, even for the organs that might be selectively irradiated. For populations living at high altitudes, it would probably be difficult to identify control populations with the same cultural, medical and dietary practices.

331. Some guidance as to the relative risk of high and low exposures may also be obtainable from any practicable analyses of the form of the dose-effect relationship for cancer induction. Particular importance attaches, therefore, to any studies of human carcinogenesis in which that is possible, since it will be seen that in much of the work reviewed in this Annex, the risks determined at lower doses are evaluated too imprecisely for the likely values at very low dose to be estimated with confidence.

332. It remains of considerable importance, therefore, that the likely form of the dose-effect relationships for a number of different types of radiation carcinogenesis should be closely studied in experimental animals, and preferably in a range of species (see Annex I, paragraphs 13 and 339), so that any quantitative generalization that might apply to different species might be recognized (as appears to hold very approximately for the induction of chromosomal aberrations (20)). In particular, if the form of such dose-effect relationships could be reliably shown to depend mainly on terms in dose and $(\text{dose})^2$, with modification at high doses from cell killing (as discussed in paragraph 35), and if the coefficient of the linear and quadratic terms were determined for a number of different types of tumour in different species, some indication might be obtained of the amount by which the risk per unit absorbed dose at moderately high doses is likely to exceed that at very low doses for carcinogenesis in general.

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ANNEX H

Genetic effects of radiation

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Introduction

1. The 1972 report of the Committee (589) presented a comprehensive review of the genetic effects of ionizing radiation. The present report will be devoted to (a) an updating of the 1972 report, especially those parts that require significant revision in the light of information that has accumulated during the last few years, with particular attention being paid to those results that bear on the problem of the evaluation of genetic radiation hazards in man, and (b) a comparison of the main conclusions reached by the Committee in 1972 with those of the Advisory Committee on the Biological Effects of Ionizing Radiation (BEIR) of the National Academy of Sciences of the United States of America (34).

I. RELEVANT HUMAN DATA

A. THE PREVALENCE OF NATURALLY OCCURRING HEREDITARY DEFECTS AND DISEASES IN HUMAN POPULATIONS

1. The results of the British Columbia Survey and comparison with other results

2. Trimble and Doughty (576) have published the results of a major study whose primary objective was to determine the frequency of live-born individuals affected by hereditary or partially hereditary defects and diseases in a large, geographically defined population, namely that in the Canadian province of British Columbia, with a current population in excess of two million people. Since these results have been obtained and interpreted using information on the inheritance of specific traits that has been gained during the last fifteen years or so, and since knowledge of the amount of hereditary diseases in human populations is crucial to an evaluation of genetic radiation hazards in man using the doubling-dose method, they will be discussed in some detail in the following paragraphs.

3. The data used for this study were derived from the records of the British Columbia Registry for Handicapped Children and Adults and pertain to a period of 21 years (1952-1972). These include cases actually registered with the Registry as well as those ascertained through the province-wide Surveillance System of Congenital Anomalies, both systems having multiple sources of ascertainment. Of the total case-load of 48 212 individuals recorded with the Registry by the end of 1972, only about 44 per cent (21 290) were born in the province during the period 1952-1972. In addition, 9313 children also born in the province during the period 1964-1972 were ascertained through the Congenital Anomalies Surveillance System. The data relate to this total of 30 603 affected children among 756 304 live births. Adequate precautions were taken to avoid duplicate entries from multiple sources of ascertainment. The details of the different kinds of diseases or disorders included in the analysis are given in tables 1 to 8. Diseases of unknown aetiology and environmentally caused disorders (representing a total of 4949 cases out of 30 603) are not listed in these tables.

4. An examination of the frequencies of children with one or another kind of genetic or partially genetic disease in the successive annual birth cohorts showed that, in general, these remained relatively constant up to the year 1963 (2.5-3.8 per cent), increased from 1964 to 1968 (5.1-6.0 per cent) but decreased in recent years (to 2.6 per cent in 1972 for example). The higher figures from 1964 onwards are due to individuals ascertained through the Surveillance System, which contains information only for children born since 1964. The decline in the more recent cohorts is only apparent, since there is a tendency for the affected children born in later years not to be registered until they reach school age. To arrive at the best estimates of the frequencies of single gene, chromosomal and multifactorial diseases, the authors used the data for the period 1964-1966; for congenital malformations, they used those from 1967-1969. The reason was that, for these birth years, there appeared to be nearly complete registration of conditions that manifest themselves during childhood or youth. The total thus estimated is about 6 per 100 live-born for all registered conditions, regardless of the particular aetiology of a condition (0.18 per cent, single gene diseases; 0.16 per cent, chromosomal anomalies; 3.58 per cent, congenital anomalies; 1.58 per cent, other multifactorial diseases; and 0.60 per cent, diseases of unknown aetiology).

5. To allow for biases due to delay in disease onset, migration and incompleteness of ascertainment, suitable correction factors were used to get "adjusted estimates" from "minimal estimates" given above and both these are presented in table 9 together with the earlier ones of Stevenson (566) for Northern Ireland, a division of the United Kingdom of Great Britain and Northern Ireland, which were revised subsequently by UNSCEAR (586, 587). Examination of table 9 will show that there are several differences between the estimated incidence rates in British Columbia and in Northern Ireland: (a) the total frequency of serious diseases or handicaps believed to be genetic is about 9 per cent in British Columbia as compared with about 6 per cent in Northern Ireland; (b) the incidence of diseases due to single dominant genes is lower by a factor of more than 10 in the present study; (c) the frequencies of single-gene autosomal recessives and of chromosomal anomalies are also lower (by a factor of 2) in British Columbia; and (d) the incidence of diseases that fall under the categories of congenital malformations and other multifactorial diseases is higher by a factor of more than 2 in the present work (9.0 per cent compared with 4.0 per cent).[1]

6. Nearly all (97 per cent) of the chromosomal anomalies recorded in the British Columbia Survey are due to Down's syndrome, whereas in the UNSCEAR estimates, other chromosomal anomalies were also included (see footnote c to table 9). The frequency of cases with Down's syndrome in British Columbia is roughly the same as that reported in the UNSCEAR reports. The low estimate of the total frequency of registered chromosomal anomalies (0.20 per cent versus 0.42 per cent) indicates that some of the individuals with other chromosomal disorders such as Klinefelter's

[1] The 9.0 per cent is from column 4 (4.28 + 4.73 = 9.01), and the 4.0 per cent is from column 2 (2.50 + 1.50 = 4.00)

or Turner's syndrome were not brought to the attention of the Registry, presumably because they were not regarded as handicapped during childhood or had the aetiology of their disorders incorrectly classified as not due to chromosomal aberrations. Many cases of sex-chromosomal abnormalities and structural anomalies of the autosomes would have been classified as congenital malformations or as diseases of unknown aetiology because the correct cause of the defect would not be readily recognized in the absence of routine cytogenetic analyses. While the precise extent of underestimation of these cases is difficult to determine, the authors surmise that accounting for these individuals could increase the estimate of the total frequency of chromosomal anomalies by as much as threefold (i.e., from 0.2 per cent to 0.6 per cent). The recent summary estimates on the incidence of chromosomal anomalies in new-born babies (table 11) in fact give a total frequency of 0.6 per cent.

7. The major discrepancies between the present data and the earlier ones based on the Northern Ireland survey relate to the very low incidence of diseases presumed to be caused by regular dominants (0.08 per cent compared with 0.95 per cent) and in the rather high incidence of conditions that fall under the categories of congenital anomalies and multifactorial diseases (9.0 per cent compared with 4.0 per cent). The discrepancy for regular dominants is in part due to a considerable underestimate of the incidence of dominant disorders with onset in adult life in the British Columbia survey, and in part, to the inclusion in the Northern Ireland survey of conditions which would not now be regarded as having a simple dominant mode of inheritance. This discrepancy is of major concern since regularly inherited dominant (and X-linked) conditions are expressed in the immediate descendants of exposed individuals and are expected to increase in direct proportion to an increase in mutation rate. They are therefore an important component of the genetic hazard from radiation exposure.

8. The 12 most frequent disorders in Stevenson's list of dominant diseases account for about 75 per cent of all his cases of dominants. A review of the inheritance of these 12 conditions[2] has shown that at least 7 of them would not now be regarded as being inherited as simple dominant disorders (360). This has been illustrated by Newcombe (360) for hydrocephaly, which accounts for one fifth of all the cases in Stevenson's dominant category. This condition is now known to be heterogeneous and the family patterns observed exclude simple dominant (or even simple recessive) inheritance in any substantial proportion of cases.

9. The British Columbia survey relates largely to diseases with onset in childhood and is based on a follow-up of individuals from birth to ages 1-21 years, and Sutton (555) has expressed the view that the study of Trimble and Doughty "clearly underestimates diseases of late onset such as Huntington's chorea". In the British Columbia survey, only 2 cases of Huntington's chorea were found, giving an incidence of 2.6 per million. However, *ad hoc* surveys such as that of Shokeir (534) indicate a prevalence in Saskatchevan and Manitoba of 8.7 per 100 000 which (since patients have the overt disease for only about 15 years) corresponds to a birth frequency of heterozygotes of about 1 in 2000.

10. Similar underestimates are likely to exist in the British Columbia data for conditions such as neurofibromatosis, the adult type of polycystic disease of the kidney, multiple polyposis of the colon and monogenic hypercholesterolaemia. The same limitations apply to Edwards' (145) low estimates of the incidence of dominant disease. Sutton (555) is of the opinion that "it would seem wise to use the figure of 1 per cent dominant disorders until additional reliable data indicate this not to be correct".

11. *Ad hoc* surveys of the prevalence of individual dominant conditions by observers skilled in the diagnosis of particular disorders and using all available means of ascertainment of cases, such as those quoted by Vogel and Rathenberg (599) in estimating human mutation rates and listed in table 10, with the addition of more recently recognized dominant disorders such as monogenic hypercholesterolaemia (82a) suggest that the total birth frequency of such disorders may well be 1 per cent. The total figure of 1 per cent dominants used in the 1972 report may therefore be retained, though the individual conditions contributing to it have been reappraised.

12. X-linked and autosomal recessive conditions are usually more severe and already expressed in childhood and therefore, the estimates of their incidence are more straightforward. Edwards' (145) estimates of 0.05 per cent for X-linked and 0.25 per cent for autosomal recessive conditions would appear to agree well with estimates from *ad hoc* prevalence studies (82a). However, some of the more common autosomal recessive disorders are probably maintained by heterozygous advantage and a figure of 0.1 per cent is a more realistic estimate for the incidence that is maintained by mutation.

13. Turning now to the incidence of diseases that falls under the category of congenital anomalies, multifactorial and irregularly inherited diseases,[3] as was

[2] Cataracts (senile and pre-senile), hydrocephaly (internal obstructive), alopecia areata, nystagmus (familial idiopathic), cystic disease of lungs, choroidal sclerosis, multiple exostoses, neurofibromatosis, colobomata, ataxia (dominant hereditary including Friedrich's), porphyria (dominant detectable) and cataracts (congenital).

[3] In contrast to simple dominant diseases where affected carriers transmit the disorder to half of their offspring on the average, the dominants of incomplete penetrance constitute mutationally-maintained conditions whose inheritance is not yet fully understood and which at present, may be incorrectly classified as disorders with a multifactorial aetiology. Incomplete penetrance may be due to environmental factors or due to genetic ones and in the latter case, the category of dominants of incomplete penetrance merges with the multifactorial category. It is difficult at present to estimate the birth frequency of these diseases due to dominant genes of incomplete penetrance or to give unequivocal examples. They may include some cases of common congenital malformations and other common disorders of late onset. However, the great majority of cases of common congenital malformations and constitutional and degenerative diseases are thought to be truly multifactorial in origin and are characterized by high frequency, a non-dominant pattern of inheritance but a familial pattern of incidence in twins, sibs, cousins and so forth that is indicative of multilocal transmission.

mentioned earlier, it is higher by a factor of 2 in British Colombia relative to Northern Ireland (9.0 per cent compared with 4.0 per cent). These diseases constitute a very substantial proportion of human disorders, but there are great uncertainties concerning the exact mechanisms involved in their aetiology. It is not really possible to make any realistic quantitative apportionment of their causation between genetic and environmental factors, both of which play varying roles. The 9 per cent of Trimble and Doughty may include an unknown proportion of incorrectly classified chromosomal anomalies, monogenic disorders and diseases of largely environmental aetiology. It is therefore likely to be somewhat of an overestimate. On the other hand, underestimations are likely to exist for constitutional disorders of adult onset, for example, schizophrenia or death in the fifth decade from coronary heart disease.

14. Insofar as this major group of disorders is genetically determined, the family pattern they show suggests that the genetic component is usually multilocal, i.e., depending on genetic variation in at least several gene loci (82b, 82c). Their high frequency, e.g., 1 in 250 to 1 in 2000 in different human populations for spina bifida cystica, 1 in 1000 for the commonest congenital heart defect (ventricular septal defect), and 1 in 100 for schizophrenia, indicates that selective mechanisms are responsible for their maintenance and that they are not mutation-dependent. Newcombe (361) has recently stressed this point.

15. On the other hand, it is known that there are relatively rare monogenic disorders already recognizable among this group of disorders, for example the dominant conditions cleft lip and mucus pits of the lower lip (among the large group of multifactorially determined facial cleft malformations). These are readily assigned to the dominant category. It is likely, however, that there are further unrecognized rare regular dominant and irregularly dominant conditions in this group which would be mutationally maintained. The size of this mutationally-maintained fraction is unknown. BEIR (34) conservatively assumed that this component[4] is not likely to be more than 50 per cent or less than 5 per cent. The upper limit of 50 per cent is perhaps implausibly high and a more realistic figure would be around 10 per cent. In this report, for purposes of hazard evaluation, we shall use the figure of 9 per cent for the incidence of the class of congenital, multifactorial and irregularly inherited diseases (based on the British Columbia data) and assume that the mutational component[4] is 5 per cent (best average estimate) (82).

2. Summary and conclusions

16. The rates of spontaneous incidence of different kinds of genetic disease in man available from the survey carried out in British Columbia represent a significant addition to our knowledge on the load of genetic ailments carried by the human population.

17. In this survey, the total frequency of these diseases has been estimated to be 9.44 per cent and can be broken down into 0.12 per cent autosomal dominant and sex-linked diseases, 0.11 per cent recessive and 0.20 per cent chromosomal ones, 4.28 per cent congenital malformations and 4.73 per cent other multifactorial diseases.

18. Discrepancies exist between these rates and those obtained earlier by Stevenson (which, with some revisions, are the ones that have thus far been used in hazard evaluations), particularly with respect to the incidence of dominant diseases and those included under the category of congenital malformations, multifactorial and irregularly inherited diseases. For the former, the present estimate is lower by about an order of magnitude (0.12 per cent compared with 1.0 per cent) and for the latter, higher by a factor of 2 (4.0 per cent compared with 9.0 per cent). In addition, the rate of incidence of chromosomal abnormalities in British Columbia is also lower by a factor of 3 relative to recent results of new-born surveys (0.20 per cent compared with 0.60 per cent).

19. The Committee reappraised the above figures, taking into account, among other things, the results from different *ad hoc* surveys for specific dominant conditions, those from new-born surveys for chromosomal anomalies and the uncertainties involved in the aetiology of diseases that fall under the category of congenital malformations, multifactorial diseases and irregularly inherited conditions. The following figures that were arrived at will be used in the context of hazard evaluations: 1.0 per cent dominant and X-linked diseases, 0.1 per cent recessive diseases, 0.4 per cent chromosomal diseases and 9.0 per cent congenital malformations, multifactorial and irregularly inherited conditions.

20. The magnitude of the mutational component for the last mentioned category of diseases is thought to be not more than 10 per cent (upper limit) in contrast to the upper limit figure of 50 per cent used by BEIR; for the purpose of calculations, the Committee will use a figure of 5 per cent as the best average estimate.

B. NUMERICAL AND STRUCTURAL CHROMOSOME ABNORMALITIES IN NEW-BORN INFANTS

1. Spontaneous rates of incidence

21. In its 1972 report, the Committee presented the results of surveys carried out in different parts of the world on the chromosomal constitution of live-born infants; the data available at that time showed that out of 21 996 babies, 114 (0.52 per cent) had an abnormal chromosome constitution. Additional data obtained since then in different laboratories (summarized by Jacobs *et al.* (250), Hamerton *et al.* (212), and Nielsen and Sillesen (363) and including the more recent work of Lin *et al.* (289) bring the total number of babies examined to 55 679, with 336 of them (0.60 per cent) having abnormal karyotypes. All these karyotypes (except those in the work of Lin *et al.*) were examined

[4] The mutational component of a disease is the proportion of its incidence that is directly proportional to the mutation rate.

with conventional techniques. The kinds and frequencies of the different abnormalities recorded in these surveys are given in table 11.

22. The data summarized in table 11 permit the following conclusions: (a) the total frequency varies from 0.47 per cent to 0.83 per cent in the different surveys; the overall rates of incidence (based on pooled results) are 0.22 per cent sex-chromosome anomalies, 0.14 per cent autosomal trisomies, 0.19 per cent euploid structural rearrangements, and 0.05 per cent aneuploid structural rearrangements (including supernumerary chromosomes);[5] (b) the frequencies of 47,XYY males range from 0 in Moscow to 0.03-0.05 per cent in Boston, Winnipeg and Århus, 0.13-0.14 per cent in Edinburgh and New Haven, to a high of 0.37 per cent in Ontario; (c) variations in the incidence rates of 47,XXY males is less (ranging from 0.07 per cent in Boston to 0.18 per cent in New Haven), and in general the rates are comparable; (d) the overall incidence of sex-chromosome anomalies in males is 0.26 per cent (93/34 872) and in females, 0.14 per cent (29/20 807); (e) the frequency of 45,X females is very low, being only 0.01 per cent (2/20 807); nearly all the other babies listed under "Other" (column 10) were mosaics, suggesting that the vast majority of XO conceptions do not survive to term and those which do are indeed mosaics; (f) the frequency of autosomal trisomies (trisomy-21; listed under +G) is 0.12 per cent (compare this frequency with that recorded in the British Columbia survey, 0.19 per cent, table 9); (g) the incidence rates of euploid structural rearrangements are reasonably consistent for six of the surveys (Edinburgh, Winnipeg, Hamilton, Boston, New Haven and Moscow: 0.14-0.21 per cent), while in Århus, the frequency is high (0.30 per cent) and in Ontario, low (0.05 per cent); the results also demonstrate that the frequency of Robertsonian translocations (D/D and D/G types) and that of detected balanced reciprocal translocations are roughly the same; and (h) aneuploid structural rearrangements are relatively uncommon, only 30 being observed in the whole sample.

2. Mutation rates

23. Jacobs *et al.* (250) used the data pertaining to 43 558 babies to estimate the "rates of mutation" for the different kinds of chromosomal abnormalities. For numerical errors of chromosomes which result in live-born children, this was $14.0\ 10^{-4}$ per gamete per generation (mosaic individuals and those with 46,X inv (Y) were excluded). The estimate based on 55 679 babies (table 11) is nearly the same, being $14.2\ 10^{-4}$ per gamete per generation (sex-chromosome anomalies: $7.5\ 10^{-4}$ per gamete per generation; autosomal anomalies: $6.7\ 10^{-4}$ per gamete per generation; mosaics and Y chromosome inversions likewise excluded).

24. For structural abnormalities of the autosomes, the estimates of Jacobs *et al.* were based on the incidence in the total sample of 43 558 and an analysis of the proportion which was non-familial (and thus new mutants) in a sample of 56 babies found to carry non-mosaic structural rearrangements; they found that 10 out of 50 euploid babies (20 per cent) and 2 out of 6 aneuploid ones (33 per cent) were new mutants. Multiplying the incidence rate of 0.19 per cent (euploid) by 0.2 and dividing by 2 (to correct for the possibility that the mutation could have arisen in either sex), the authors estimated that the rate for all euploid structural rearrangements (Robertsonian translocations, reciprocal translocations and inversions) and $1.9\ 10^{-4}$ per gamete per generation; for reciprocal translocations alone, the figure was $1.33\ 10^{-4}$ per gamete per generation (36/43 558 multiplied by 0.33 (proportion of new mutants: 8/24) and divided by 2). For aneuploid structural abnormalities (translocations, inversions and deletions), the rate was $0.30\ 10^{-4}$ per gamete per generation (8/43 558 multiplied by 0.33 and divided by 2).

25. Under the assumption that the proportions of new mutants found by Jacobs *et al.* are applicable to the present total sample of 55 679 babies, the following rates can be estimated using calculation procedures as above (para. 24): all euploid structural rearrangements, $0.0019 \times 0.2 \times 0.5 = 1.9\ 10^{-4}$ per gamete per generation; reciprocal translocations alone, $0.00086 \times 0.33 \times 0.5 = 1.4\ 10^{-4}$ per gamete per generation; aneuploid structural abnormalities, $0.00027 \times 0.33 \times 0.5 = 0.45\ 10^{-4}$ per gamete per generation. The above estimates are roughly similar to those made by Jacobs (249) from less extensive neo-natal data and to those of Jacobs, Frackiewicz and Law (249) who combined both neo-natal and post-natal data.

26. Jacobs *et al.* (247) have pointed out that the mutation rates for autosomal rearrangements must be underestimates of the true rates for at least two reasons: (a) only a fraction of all chromosome rearrangements in man is detectable in somatic cells by conventional staining techniques. Of the structural aberrations considered here, only Robertsonian translocations allow a detection rate approaching 100 per cent; and (b) many aberrations may be selected against before they give rise to live births; such selection is presumably almost completely restricted to unbalanced rearrangements. On the basis of unpublished results of Buckton[6] with irradiated human lymphocytes, Jacobs *et al.* (247) concluded that approximately 75 per cent of symmetrical exchanges (reciprocal translocations) may escape detection. However, human cytogeneticists who have used the new banding techniques (the latter, among other things, permit a precise identification of chromosomes or chromosome parts involved in translocations) are of the opinion that the efficiency of the new banding techniques with respect to the detection of reciprocal translocations is only slightly higher (by 10-20 per cent) than the conventional staining techniques; this means that the rate of $1.4\ 10^{-4}$ per gamete per generation estimated for reciprocal translocations is not likely to be strikingly lower than the true rate. Since there remains the possibility that, even with the banding techniques, small equal symmetrical exchanges may

[5] A person was considered to have a supernumerary chromosome if he had 47 chromosomes, 46 of which were apparently normal, the additional chromosome being equal to or smaller than a member of Group G and clearly different in morphology from a G-group chromosome (250).

[6] The paper has recently been published (66).

escape detection, it is perhaps wise at present to multiply the rate mentioned above by 2 to get an estimate of the probable true rate, i.e., we shall assume that the spontaneous rate of origin of reciprocal translocations in man is $2.8\,10^{-4}$ per gamete per generation.

C. CHROMOSOMAL ANOMALIES IN SPONTANEOUS ABORTIONS

27. The incidence of chromosomal anomalies in spontaneous abortions in man has been extensively reviewed by Carr (78, 79) and Boué and Boué (46) and has been considered to some extent in the Committee's earlier reports (587, 589). It is well established that chromosomal anomalies are frequent among spontaneous abortions with an incidence rate that is much higher than in live-born infants. The total frequency of these anomalies in the major abortion studies varies from 8 per cent in that of Stenchever *et al.* (565) to 64 per cent in that of Szulman (559); the wide discrepancies are most probably due to the operation of a variety of factors, such as geographical variation, maternal age, prevalence of unsuspected induced abortions in the population, variations in hospital admission practices and especially the procedure and scope (selected *versus* unselected) of the collection of abortuses. Boué and Boué (46) (and several others) have found that the phenotype and gestational age of the conceptus are both related to the incidence of chromosomal anomalies: in their large-scale study, they recorded one or another kind of chromosome abnormality in 66 per cent of the abortuses arrested in their development before 8 weeks of gestation, this falling to 23 per cent of zygotes with 8-12 weeks of development. (In 1097 out of 1205 observations, the developmental arrest occurred before the eighth week and these represent about 90 per cent of all abortions; developmental arrests before the third week are rare, since in these cases the pregnancy might be unrecognized and such specimens are seldom received for examination.)

28. Most of the chromosomal anomalies which have been described among abortuses are numerical such as monosomy-X, autosomal trisomy, triploidy and tetraploidy. Boué and Boué (45, 46) recently summarized the results of their continuing investigations and compared them with those obtained by some other workers whose sample sizes were adequate enough to permit some general inferences. These are given in table 12 in addition to the data of Kajii *et al.* (253) and of Creasy *et al.* (127) not covered in the above paper. Since the data of Boué and Boué are the most extensive, they can be used to establish a rank order of incidence of the different abnormalities to inquire the extent to which these results agree with those of others and to gain an insight into the kinds of aberrations that are more or less frequent in abortuses in contrast to live-borns. As will be evident from an inspection of table 13, the agreement between these results is good, with trisomy constituting the most predominant class of abnormalities (~50 per cent), followed by monosomy-X, triploidy, tetraploidy and others.

29. In trisomic abortuses, the extra chromosome is almost always an autosome (in contrast to monosomy in which the missing chromosome is a sex chromosome). Trisomies of all autosomal chromosome pairs are found, but their relative incidences are different, trisomy for C, D, E, and G being more, and those for A, B and F less, frequent (table 14). All the three possible kinds of triploidy (69,XXX, 69,XXY and 69,XYY) are seen although again their relative frequencies appear different (XXY > XXX > XYY) (46). The small number of triploid abortuses with the 69,XYY constitution does not necessarily demonstrate the rarity of occurrence of this class, since a similar result can be obtained if these karyotypes lead to very early developmental arrest. The virtual absence of autosomal monosomy and the rather low frequency of some kinds of trisomy (A, B and F) might likewise be due to their very early developmental arrest. This view is supported by the experimental work of Gropp (203) and of Ford and Evans (169), who studied the time of action of the lethal effects of zygotic aneuploidy in F_1 hybrids between the tobacco mouse and the laboratory mouse. It was found that autosomal zygotes could be observed only before implantation; the trisomic embryos however, died during the post-implantation period with a considerable reduction in numbers between the earlier gestation period (8-11 days) and the later period (12-15 days) and none was observed at birth.

30. An analysis of the relationship of maternal age and the different types of chromosomal anomalies (table 15) shows that the mean maternal age is higher for lethal trisomies relative to other abnormalities as well as to abortuses with normal karyotype. Close inspection of table 15 will reveal that it is primarily for the trisomies involving acrocentric chromosomes (D and G groups) that the influence of maternal age is marked; in lethal G-trisomies, the curve of maternal age distribution (45) shows bimodality, with 60 per cent of the observations in the age-dependent group, a pattern very similar to that noted by Penrose and Smith (406) for children with Down's syndrome. This suggests that whether a zygote with a trisomy G will lead to a spontaneous abortion or a delivery at term may not depend on the age of the mother.

31. It is instructive to compare the results from newborn surveys with those from the abortion studies (tables 11, 13 and 14). It will be evident that monosomy-X is one of the most frequently encountered class of abnormalities in spontaneous abortions whereas it is very rare in new-borns. About 40 per cent of all spontaneous abortions with chromosome anomalies (and about 80 per cent of all trisomy) are due to trisomy for D, E and G group chromosomes; in the new-born population, trisomy for these chromosomes accounts for 0.14 per cent of all new-born children (or about 23 per cent of the abnormalities recorded in these). Structural anomalies of chromosomes and mosaics constitute about 5 per cent of all abnormalities scored in the abortus material, whereas in new-borns, about 40 per cent of all abnormalities scored are structural and involve the autosomes (both euploid and aneuploid structural aberrations), 0.24 per cent of the children having structural abnormalities.

D. PARENTAL X IRRADIATION AND SPONTANEOUS ABORTIONS

32. Alberman *et al.* (5) made a comparison of the histories of medical irradiation received by parents of spontaneous abortuses of abnormal karyotypes with corresponding histories in cases of abortions of normal karyotype and with those in parents of live births. The overall finding was that the mothers of chromosomally abnormal foetuses had received the largest mean gonadal dose of irradiation for medical reasons compared with the other spontaneous abortions and the live-birth controls. As in their Down's syndrome study (6) the radiation doses tended to be rather small and the effects of radiation appearing to be cumulative and, seemingly, often maternal age-dependent. Irradiation appeared to be an especially important factor in the case of triploid abortuses: the mean gonadal dose of mothers of triploids (about 0.74 rad) exceeded that received by mothers of those with autosomal trisomy of one chromosome including trisomy of the G group (0.30 rad) or of the 45,X abortuses (0.18 rad). The authors stress the point that most of the chromosomally abnormal foetuses are not viable and are lost early in pregnancy.

E. PARENTAL X IRRADIATION AND DOWN'S SYNDROME

33. Even though several retrospective and prospective studies have been conducted to find out whether parental irradiation may increase the risk of producing Down's syndrome (trisomy for chromosome 21) in the progeny, the answer to the question remains equivocal. For instance, the retrospective studies of Uchida and Curtis (581), Sigler *et al.* (537) and Cohen and Lilienfield (115) have been interpreted as showing an association between maternal irradiation and Down's syndrome. The investigation of Alberman *et al.* (6) showed that the mothers of those with Down's syndrome had had more total x-ray examinations, both in number and in dose, before the conceptions (relative to those "control mothers") of children with a variety of other serious congenital handicaps which are not thought to be in any way associated with parental irradiation; the overall difference did not reach a significant level. However, when the mean doses for the different maternal age groups and conception histories were compared (i.e., radiation doses received less than 6 years before, 6-10 years before and more than 10 years before the conceptions), (a) the variation with age was more marked in the mothers of the Down's syndrome group (than in the control) and (b) the effect was greatest in the subgroup where x-ray exposures were administered more than 10 years before the conceptions.

34. In contrast, the retrospective studies of other investigators (83, 305, 324) failed to provide any evidence for an association between maternal irradiation and Down's syndrome in the progeny, but these reports were based on small numbers of cases.

35. The prospective studies of Schull and Neel (563) of children born to mothers exposed to the A-bomb radiation at Hiroshima likewise showed no association, but the doses involved were of a different order of magnitude from those used for medical purposes. The study of Stevenson *et al.* (567) also failed to support the hypothesis that x-ray diagnostic procedures before conception increase the frequency of Down's syndrome in children subsequently born. However, the prospective study of Uchida *et al.* (583) indicated that a significantly greater number of trisomic children were born after maternal radiation exposure.

36. In a recent paper, Kochupillai *et al.* (260), claimed that the incidence of Down's syndrome in the population living in an area of high background radioactivity in coastal Kerala in southern India was significantly higher relative to a control population and to the rates recorded in similar surveys by other investigators elsewhere in the world. The exposure risk in the study population was estimated as 1.5-3 rad per year (control, 0.1 rad per year) and the frequency of Down's syndrome observed was 12 in 12 918, giving a rate of 1 in 1076 (or 0.93 per 1000). No Down's syndrome cases were detected in the control (5938 individuals screened). In terms of maternal age, the distribution of Down's syndrome cases in the study population was as follows: 1 in 862 (age range 20-29), 1 in 81 (age range 30-39) and 1 in 266 (age range 40-49).

37. Sundaram (548) re-examined the data presented by Kochupillai *et al.*, and concluded that the author's claim could not be substantiated for the following main reasons: (a) only about 11 per cent of the females included in their study receive radiation doses in the range 1.1-2 rad per year, and 2.8 per cent receive exposures higher than 2 rad per year. This type of dosimetric profile is due to the non-homogeneous distribution of monazite-containing beach sands; (b) the age structure of the Kerala study population is quite different from those of others with which the data are compared, i.e., while in most surveys, only about 4 per cent of all births is contributed by females in the age group 40 years and older, in the Kerala survey, this figure is around 20 per cent and this age group is known to have the highest risk for children born with Down's syndrome; (c) when the data are re-calculated to estimate the incidence at birth and at the time of study (taking into account the family size, the number of females in each age group and the infant mortality rate), one arrives at 9-10 cases for the population sample studied, and the observed 12 cases therefore do not show any significant difference; (d) the observation of Kochupillai *et al.* that the risk in the maternal age group 40-49 is only one third of that in the age group 30-39 is puzzling and at variance with what is so far known about the relationship between maternal age and the incidence of Down's syndrome.

F. MORTALITY IN THE CHILDREN OF THE A-BOMB SURVIVORS IN HIROSHIMA AND NAGASAKI

38. Neel *et al.* (359) and Kato (254) have published the results of a continuing study of mortality rates among children born to survivors of the atomic bombings of Hiroshima and Nagasaki which updated those presented in an earlier report (255). Although the actual numbers of deaths since the previous review was

small, the present report was prompted more by the fact that significant revision of the dose estimates had become available.

39. The mortality experience pertains to (a) 18 946 children born live to parents both of whom were proximally exposed (i.e., either one or both parents less than 2000 m from the hypocentre and receiving jointly an estimated dose equivalent of 117 rem);[7] (b) 16 516 children born to distally exposed parents (i.e., neither parent less than 2000 m, but either or both less than 2500 m, from the hypocentre and receiving essentially no radiation) and (c) 17 263 children born to parents not in Hiroshima or Nagasaki at the time of the bombing. The average interval between birth and verification of death or survival was 17 years. Analysis of the data has shown that no significant effects of parental exposure on childhood mortality can be demonstrated.[8] However, the data permit an estimate of the lower limit of doubling dose[9] (for the type of damage[8] resulting in death during the first 17 years of life among live-born children conceived 0-13 years after parental exposure), and this is equal to a gamma-ray dose of 46 rad for fathers and 125 rad for mothers.[10] Neel *et al.* suggest that, on the basis of mouse data, the gametic doubling dose for chronic low-level radiation would be expected to be 3-4 times the value of 46 rad for males (i.e., at least 138 rad) and over 1000 rad for females.

G. CYTOGENETIC SURVEY OF THE OFFSPRING OF THE A-BOMB SURVIVORS IN HIROSHIMA AND NAGASAKI

40. A continuing survey of the offspring of the survivors of Hiroshima and Nagasaki bombings for structural and numerical anomalies of the chromosomes is in progress. The latest report published by Awa (15) shows that among 2885 children of A-bomb survivors[11] (1386 males and 1499 females), a total of 18 individuals (0.62 per cent) with chromosome abnormalities have been found (3 XXY, 3 XYY, 2 XXX and one X/XXX mosaic, together 0.31 per cent; 9 structural abnormalities, including 3 t(Dq Dq), 1 t(Dq Gq) and 5 balanced autosomal translocations, together 0.31 per cent). In the matched control[11] of 1090 subjects (510 males and 580 females), 3 individuals with chromosomal anomalies have been found (1 XXY and 2 balanced reciprocal translocations). Awa has pointed out that although the prevalence of sex-chromosome aneuploidy in the children of exposed parents is higher than in the controls (0.31 per cent compared with 0.09 per cent), the difference is not significant.

41. The above incidence rates can be compared with those obtained in surveys of new-born infants (paras. 21-22 and table 11):

	Hiroshima and Nagasaki data controls 1 090 subjects		*Children of exposed parents 2 885 subjects*		*Surveys of new-born infants 55 679 subjects*	
Anomaly	*Number*	*Percentage*	*Number*	*Percentage*	*Number*	*Percentage*
Sex-chromosome	1	0.09	9	0.31	122	0.22
Numerical autosome	–	–	–	–	76	0.14
Structural autosome	2	0.18	9	0.31	137	0.24
All	3	0.28	18	0.62	336	0.60

It can be seen that the frequencies in new-born surveys are similar to those in the children of exposed parents from Hiroshima and Nagasaki and that there are no significant differences. The control frequencies in the Hiroshima and Nagasaki data however are lower than in the other groups, but the differences are not significant.

H. SPONTANEOUS NON-DISJUNCTION IN THE HUMAN MALE

42. One of the important recent developments in mammalian cytogenetics has been the introduction of differential staining techniques that have permitted the identification of specific chromosomes in interphase nuclei. Thus, quinacrine staining of interphase cells has shown that the human Y chromosome can be visualized as an intensely fluorescent dot (404) and that it can be seen throughout the male germ-cell series (403) including the spermatozoa (26). New techniques have now been developed for differential staining of chromosomes 1 and 9 (37, 189, 401, 402). It has become clear that the specific staining reactions are confined to regions of constitutive heterochromatin composed of highly repetitive nucleotide sequences of DNA with varying base ratios dependent upon the chromosome concerned (251). The general category of differential staining involved here has been designated as C-banding.

43. These technical developments have been found useful to identify and measure the frequency of aneuploid spermatozoa (aneuploid with respect to chromosomes Y, 1 and 9) in ejaculates. Initial estimates for Y chromosome, i.e., for those spermatozoa containing two Y bodies (and not one) were 1.3 per cent

[7] The unit used in the paper of Neel *et al.* is the rem and was obtained by summing the dose equivalents of the gamma and neutron components of the irradiation and assuming that the quality factor for neutrons is 5.

[8] It is assumed that the childhood mortality as measured here is due to different kinds of genetic damage (point mutations, small deletions, unbalanced translocation and non-disjunction).

[9] The 97.5% lower confidence limit. The data exclude a doubling dose equivalent lower than 46 rem for males and 125 rem for females.

[10] The doubling dose is calculated from the relationship $d = xy/z$, where d is the doubling dose, x is the mortality due to spontaneous mutation in the preceding generation (included both gene and chromosome mutations), y is the contribution of a given sex to the mortality, assumed to be 0.5 for each sex, and z = the maximum slope of the dose-effect curve (calculated in a stepwise regression analysis) which can not be excluded by present data at the 5% confidence level. The numerical values used in the above equation are, for males, $x = 0.005$, $y = 0.5$ and $z = 0.000054$, and for females, $x = 0.005$, $y = 0.5$ and $z = 0.00002$.

[11] Subjects in the exposed group were those whose parents (either one or both) were exposed to a dose of more than 1 rad; the parents of the controls were either not exposed or received less than 1 rad.

(37) and 2 per cent (403). A later study (401) confirmed these frequencies for the Y chromosome and also suggested a similar frequency for chromosome 9. It should be pointed out here that the above frequencies refer only to those of hyperhaploid spermatozoa; if the reciprocal class of hypohaploids occurs at the same rates, the calculated figures have to be doubled. The implication of these findings is that, if non-disjunction of other chromosomes occurs at about the same rates, the proportion of aneuploid spermatozoa will be considerable and will lead to the production of many trisomic embryos, most of which will be spontaneously aborted.

44. The above data of Pearson and Bobrow (403), Bobrow *et al.* (37) and Pawlowitzki and Pearson (401) have been criticized on a number of points (141) as follows: (a) single Y chromosomes are known to have a bifid structure in a proportion of interphase cells and that extra dots in spermatozoa could be explained by single Y chromosomes being bifid; (b) the extra dots might represent adventitious spots either through staining artefacts or by areas on other chromosomes staining up with the same reaction; (c) such a high frequency of YY spermatozoa is not reflected in the number of XYY individuals found either in live-born or abortion series, and, since there is no evidence of aneuploid gametic selection in mice, there is likely to be little or no selection in man which could account for the differences found in the frequency of YY spermatozoa and XYY individuals.

45. In a subsequent paper, Pearson *et al.* (405) obtained results that confirmed their earlier ones and were compatible with their expectations (rates of "non-disjunction" for chromosomes 1, 9 and Y being respectively 3.5, 5 and 2 per cent), but have not been able to rule out the criticisms mentioned above. It is perhaps worth remembering that the specific staining reactions used in these studies are confined to regions of constitutive heterochromatin and that chromosomes 1, 9, Y (and 16) have well defined and prominent blocks of these at the centromeric region (except in the Y where it is localized in the distal portion of the long arm) (14). To what extent heterochromatin *per se* may play a role in non-disjunction and whether one can generalize from the behaviour of those chromosomes with large blocks of heterochromatin to others which do not have these, are questions that have to be satisfactorily answered before the results discussed above can be used in the context of estimating total non-disjunction frequencies (for all chromosomes).

I. MITOTIC NON-DISJUNCTION IN LYMPHOCYTES OF YOUNG ADULTS

46. Uchida *et al.* (584) conducted experiments to see whether low-dose irradiation of human lymphocytes would lead to non-disjunction of chromosomes. It was realized that a positive finding in a study of this type does not necessarily imply that these results can be extrapolated to meiotic segregational errors; rather, it was thought that such a finding may indicate the usefulness of somatic cell systems as models for the study of meiotic non-disjunction.

47. Peripheral blood from 28 subjects aged 19-29 years was used for lymphocyte cultures; 7 of these were fathers and 7 were mothers of children with trisomy-21; the remaining 14 were age- and sex-matched controls with no known history of Down's syndrome among close relatives. After irradiation (50 R of ^{137}Cs gamma rays at 29 R/min), the irradiation and control samples were appropriately processed for chromosome studies. (After 69 h in culture, colcemid was added; harvesting was at 72 h. The latter time period was used to recover cells containing non-disjunctional products in preference to chromosome breakage products.)

48. The results were: (a) the total frequency of hypermodal cells in the irradiated sample was 0.1 per cent (29/28 000), which was higher than that in the controls (0.025 per cent); (b) in the unirradiated lymphocytes exposed to irradiated serum, there was also an increase in the frequency of hypermodal cells (28/28 000); (c) more hyperdiploid cells were found in the irradiated samples from control males than from fathers of progeny with trisomy-21; 2 of the control males had a total of 12 hyperdiploid cells, suggesting an increased susceptibility to non-disjunction; (d) of the total of 57 hyperdiploid cells, 1 was tetrasomic for chromosome 21, 1 had double trisomy and 1, triple trisomy. The extra chromosome could be accurately identified in 38 cases; there appeared to be a non-random non-disjunction of chromosomes, this being higher for the G-group chromosomes (10 cases) and for the X (C-group, 11 cases). All identifiable G-group chromosomes were No. 21. These results therefore suggest that the X and chromosome 21 may be particularly susceptible to somatic non-disjunction.

J. SUMMARY AND CONCLUSIONS

49. Since the publication of the 1972 report, additional data have become available on the incidence of chromosomal anomalies in new-born babies. All these results considered together show that the total incidence is 0.60 per cent of which roughly one third (0.22 per cent) attributed to sex-chromosome anomalies, one quarter (0.14 per cent) to autosomal numerical anomalies, one third (0.19 per cent) to autosomal euploid structural anomalies and one twelfth (0.05 per cent) to autosomal aneuploid structural anomalies.

50. The total frequency of chromosome anomalies recorded in the children of the A-bomb survivors of Hiroshima and Nagasaki (0.62 per cent) is very similar to that found in new-born surveys (0.60 per cent) although, in the control group for the former, this figure is only 0.28 per cent. The differences however, are not significant.

51. On the basis of the total data from new-born surveys and the family history of some of the abnormalities studied, spontaneous mutation rates can be estimated. These are $14.2\ 10^{-4}$ per gamete per generation for all numerical errors of chromosomes which result in live-born children, $7.5\ 10^{-4}$ for sex-chromosome anomalies alone and $6.7\ 10^{-4}$ for autosomal numerical anomalies. The corresponding figures for all euploid structural rearrangements of the

autosomes is $1.9\,10^{-4}$ and for balanced autosomal reciprocal translocations alone, $1.40\,10^{-4}$. Considering the fact that the efficiency with which the latter type of aberration can be scored in somatic cells may be lower than 100 per cent, it is thought that the true rate may be $2.80\,10^{-4}$ per gamete per generation, for those gametes which give rise to live-born children.

52. Chromosome anomalies are frequent among spontaneous abortions, with an incidence rate that is much higher than in live-born infants and most of the former are numerical anomalies. It has been found that both the phenotype and gestational age of the conceptus are related to the incidence of chromosome anomalies in spontaneous abortions. In over 90 per cent of observations, the developmental arrest occurred before the eighth week of gestation.

53. In spontaneous abortions, trisomy for one or another autosome is the predominant type accounting for about 50 per cent of all the abnormalities, followed by monosomy-X, triploidy, tetraplody and others. In contrast, in new-borns, autosomal trisomies (especially of D, E and G) accounts for only one quarter of all abnormalities. A second difference lies in the high frequency of monosomy-X in spontaneous abortions (about 20 per cent of all anomalies) and its rather low frequency (0.6 per cent of all anomalies) in new-borns. Thirdly, structural anomalies of chromosomes and mosaics account for about 5 per cent of the abnormalities scored in the abortus material, whereas in new-borns, more than one third of the abnormalities are of this type.

54. There seems to be an association between maternal radiation history and spontaneous abortions in the sense that in the work reported, mothers of chromosomally abnormal foetuses have received higher mean gonadal doses relative to comparable controls.

55. The results of both retrospective and prospective studies on the relationship between maternal irradiation and the incidence of Down's syndrome are conflicting. Recent work in India showing that the frequency of Down's syndrome in a population living in an area of high natural background radioactivity is significantly higher than in controls and than those recorded elsewhere has not stood the test of a critical re-examination which took into account the family size, the number of females in each age group and the mortality rate.

56. Recent results of a continuing study of mortality rates among children born to the A-bomb survivors of Hiroshima and Nagasaki show that no significant effects of parental exposure can be demonstrated. However, the data permit the estimation of doubling doses, lower than which can be excluded. These are 46 rad for males and 125 rad for females under the radiation conditions during the bombings. For chronic low-level exposures, based on mouse data, it has been estimated that the gametic doubling dose for males is about 138 rad and for females, over 1000 rad.

57. Techniques are now available for specifically staining human chromosomes Y, 1 and 9 and studying non-disjunction in sperm samples. However, no radiation studies have thus far been reported.

58. Data have become available which show that non-disjunction can be induced by irradiation of human lymphocytes and that the X chromosome and chromosome 21 may be particularly susceptible to somatic non-disjunction.

II. EFFECTS IN EXPERIMENTAL MAMMALS

A. DOMINANT LETHALS

1. Introduction

59. The 1972 report of the Committee considered in some detail the induction of dominant lethals in mice and in other experimental mammals. In most of the experiments reviewed in the report, dominant lethality had been measured by the pre-natal method, i.e., by examination of the uterine contents of females at suitable stages of pregnancy, counting the numbers of corpora lutea, living and dead implanted embryos and assessing the amount of mortality occurring before and after implantation.

2. Dominant lethals in male mice

60. Although no substantially new information has accumulated since the publication of the 1972 report, at least as far as male mammals are concerned, the paper of Searle and Beechey (510a) has helped to throw light on the best choice of an index dominant lethality where the mutagenic treatment also induces germ-cell killing.

61. The reasoning of Searle and Beechey is based on their study involving exposure of adult male mice to 200 rad of acute x irradiation and mating them at intervals to females over the next 9 weeks. Testis weights fell to 44 per cent of normal during the 5th week and were still subnormal when observations were terminated in the 10th week. Epididymal sperm counts fell in the 4th week (after a peak in the 3rd) and were very low in the 6th and 7th weeks, though still above zero. This reduction was correlated with high frequencies of pre-implantation loss in females mated to these males and dissected on the 12th day of gestation (table 16). Examination of eggs 1-2 days after ovulation showed that there was a sharp decrease (from the normal level of almost 100 per cent) in the fertilization index; it was therefore concluded that much of the pre-implantation loss really stemmed from non-fertilization rather than zygotic death.

62. It has long been suggested that, if a particular mutagen causes intense cell killing with resultant spermatozoal depletion, then what appears to be pre-implantation death may really be the expression of a lowered fertilization rate (29, 451, 560). The work of Searle and Beechey provides experimental proof for that assertion, and they propose that, in these circumstances, an index of dominant lethality based on post-implantation survival should be used (e.g., the ratio live

embryos/total implants) rather than the ratio live embryos/corpora lutea or the number of live embryos per pregnant female. They show that use of the last two indices can sometimes lead to a very substantial overestimate of the true rate of dominant lethality. However, the index of post-implantation mortality underestimates the dominant lethal frequencies in spermatozoa and spermatids. Therefore, for a precise determination of the dominant lethal frequency, it is necessary to establish the fertilization rate of the ova.

63. In experiments designed mainly to study the induction of translocations in mouse spermatozoa, Searle *et al.* (520) estimated the amount of dominant lethality from the rate of decrease of mean litter size with increasing dose. It was found that the relationship between mean litter size and dose was roughly exponential and gave a satisfactory fit to the equation $y_D = y_0 e^{-kD}$, where y_D is the litter size at dose D, y_0 is the litter size in controls and k is the rate of induction of dominant lethals. The estimated value of y_0 was 9.44 ± 0.35 and that of k was $(1.28 \pm 0.07)\ 10^{-3}$ rad^{-1}. The authors stress that the rate of dominant lethals as estimated above can only be approximate, based as it is on new-born litters.

64. Léonard *et al.* (285) studied the genetic radiosensitivity of different mouse strains (RF, BALB/c, C3H, CBA, CO13, AKR/T1Ald, C57BL and AKR) using the rate of induction of dominant lethals in spermatozoa as the criterion (germ cells were sampled during the first week of mating after irradiation). An x-ray exposure of 400 R was used and both pre- and post-implantation mortality were scored. The results showed that (a) the frequency of fertile matings in most of the strains was slightly lowered by the radiation exposure; in the RF and CO13 strains, this was enhanced and significantly so in the latter; (b) there were no significant differences between the numbers of corpora lutea in the control and irradiated series of each strain; (c) the magnitude of radiation-induced pre-implantation losses varied widely in the different strains from a low 13.4 per cent in the BALB/c strain to a high 52.7 per cent in the AKR/T1Ald strain; likewise, the amount of post-implantation losses also varied from 13.3 per cent in the AKR/T1Ald to 39.3 per cent in the BALB/c; and (d) the total amount of dominant lethality (both pre- and post-implantation losses) estimated from the expression $100 \log_e (1-P)^{-1}$ where

$$P = 1 - \frac{\text{Number of live embryos/ number of corpora lutea in the irradiated series}}{\text{Number of live embryos/ number of corpora lutea in the controls}}$$

also varied from about 13 in the RF strain to 43.5 in the C57BL strain. In most of the strains, the increased pre-natal loss is the result of an increase in both pre- and post-implantation death. A comparison of these data with those available for rats, guinea-pigs and rabbits (most of the latter were reviewed in the 1972 report: see paragraphs 22-23, Annex E (1)) would indicate that the variation between different strains of mice with respect to radiation-induced dominant lethals is as large as that between the mouse and the other species.

3. Dominant lethals in female mice

65. The 1972 report of the Committee considered the early data of L. B. Russell and W. L. Russell (458) and those of Edwards and Searle (146) on the sensitivity of mouse oocytes to dominant lethal damage. In addition, the results of Lyon and Smith (313) in guinea-pigs and golden hamsters were dealt with. It was concluded that, as after irradiation of males, most of the induced embryonic death occurs after implantation. Recently, Searle and Beechey (513) have published some data on the induction of dominant lethality in mouse females after x and neutron irradiation. In the x-ray series, mature females received acute x-ray doses of 100-400 rad and were mated to males either 1 day after irradiation or 2 weeks later with daily examination for vaginal plugs; in the neutron series, the females were irradiated with doses of 50-200 rad of fission (0.7-MeV) neutrons and were mated 1 day later. Pregnant females were killed on or around the 14th day of gestation for examination of the uterine contents. Appropriate controls were maintained. In contemporaneous experiments, meiotic preparations of oocytes were made to assess the amount of cytological damage.

66. The x-ray data are given in table 17. It can be seen that the survival of implanted embryos to the time of examination in late pregnancy (as measured by the live embryo/total implant ratio) declines with increasing radiation dose. Unexpectedly, this decline is much more rapid when these embryos were conceived in the 3rd week after irradiation. The increasing dominant lethality correlated well with the amount of chromosomal damage found in the meiotic preparations of the oocytes. The dose-effect relationship for post-implantation dominant lethality is roughly linear in both the 1st- and 3rd-week groups, but in the latter, its level is twice as high over the 200-400 rad range. In the 3rd week the amount of post-implantation loss rose considerably at higher doses, this rise being associated with increasing non-fertilization of ova. Therefore, the live embryo/corpus luteum ratio is not a satisfactory index of total dominant lethality for the 3rd-week group (133). In the 1st-week group, the dominant lethality seemed to reach a plateau at about 200 rad.

67. In the fission-neutron experiments, post-implantation dominant lethality is negligible at 50 and 100 rad but high at higher doses (table 18). For total dominant lethality, the dose-effect relationship seems curvilinear.

68. Since the females exposed to neutrons were mated 1 day after irradiation, Searle and Beechey compared their neutron results with those of the 1st-week x-ray data to estimate the efficiency of neutrons relative to x rays in inducing dominant lethals. Because of the lack of clear-cut dose response in the post-implantation mortality data with neutrons, they do not lend themselves to a ready calculation of the RBE; likewise the "total dominant lethality" data with x rays also do not permit an easy comparison with neutron results. The finding that at a dose of 100 rad (neutrons or x rays) the total dominant lethal frequencies are roughly the same may suggest that at low doses the RBE may be about 1, but more data are needed to verify this suggestion.

4. Species differences

69. In the 1972 report, the work of Lyon (307) comparing the x-ray induction of dominant lethals in post-meiotic male germ-cell stages of the mouse, guinea-pig, golden hamster and rabbit (scored by the pre-natal method) were discussed. The x-ray doses used were: 100 and 500 rad (mouse), 500 rad (guinea-pig and rabbit) and 100-300 rad (golden hamster). It was found that (a) the pattern of relative sensitivity of the germ cells in mouse, guinea-pig and rabbit was similar, with spermatids being more sensitive than mature spermatozoa; in hamsters, spermatids and mature spermatozoa were about equally sensitive to dominant lethal induction; (b) in the guinea-pig and rabbit, the frequency of dominant lethals at 500 rad were lower than in the mouse; after 200 rad to hamsters, the yield of dominant lethals in mature spermatozoa was nearly as high as after 500 rad to the mouse; for weeks 2-4, however, the yield in hamsters after 200 rad was considerably lower than in mice; (c) in the mouse, guinea-pig and hamster, a large proportion of deaths occurred after implantation, whereas in the rabbit, they occurred before implantation.

70. In experiments aimed at studying the x-ray induction of heritable translocations in post-meiotic male germ cells of guinea-pigs, rabbits and golden hamsters, Cox and Lyon (122) have collected data on litter-size reduction (a rough index of dominant lethality) which corroborate the earlier results of Lyon (307) discussed above, in terms of pattern of relative sensitivity of the different germ-cell stages and the amount of damage observed in the successive "mating weeks" after irradiation (1-4 in hamsters and rabbits and 1-5 in guinea-pigs). The x-ray doses used in the present study were: 200 and 600 rad (hamster), 600 rad (guinea-pig, rabbit). The results demonstrate that (a) in all the species studied, irradiation of post-meiotic cells result in reduction in litter size; (b) after 600 rad, the pattern of litter-size reduction and the pattern of sterility for the matings in the successive weeks are similar for golden hamster, guinea-pig and rabbit; for matings utilizing irradiated spermatocytes, i.e., week 4 for the hamster and possibly week 5 for the guinea-pig, a high incidence of infertility is not accompanied by a high reduction in litter size, suggesting that the latter infertility is only partly due to the induction of dominant lethals; such infertility could also stem from reduced fertilizations; (c) in the hamster, the dominant lethal yields (as measured by litter-size reduction) in weeks 1-4 after 200 rad and in week 1 after 600 rad are similar to those of the mouse, but the yields for both these species are above those obtained for the rabbit and guinea-pig; (d) it can be concluded that the golden hamster is more sensitive than both the rabbit and the guinea-pig for the induction of dominant lethals by x rays in post-meiotic male germ cells.

71. Cox and Lyon (121) have completed a comparative study of x-ray-induced dominant lethality in guinea-pig and golden hamster females. The choice of these two species was dictated in part, by the following considerations: (a) in all female mammals, the bulk of the oocytes are in small follicles (primordial follicles), and the response of these stages more accurately reflects the reproductive performance of the irradiated females; in the guinea-pig, the immature oocytes in primordial follicles are more resistant than those of the mouse with respect to cell killing by irradiation, although more sensitive than those of human oocytes (guinea-pig, LD_{50} = 500 R; man, $LD_{50} \cong$ 2000 R (25, 376)); (b) in contrast, the oocytes in the maturing follicles in the guinea-pig are more sensitive than those of the mouse: an exposure of 200 R virtually destroys the larger follicles in the guinea pig whereas this does not happen in the mouse; (c) on the evidence available (408) the golden hamster appears to be intermediate in sensitivity between the mouse and guinea-pig; (d) it thus appears that there is no relationship between the nuclear stage of the "arrested" oocyte, cell killing, and dominant lethal induction; for the dictyate oocyte of mouse and hamster is sensitive, and the condensed diplotene oocyte of the guinea-pig is resistant, to cell killing, yet all three show a low frequency of dominant lethality; (e) in the mouse, dominant lethal yields are higher in the oocytes sampled in the third post-irradiation week than in the first (513), and it would be instructive to inquire whether the pattern observed in guinea-pigs and golden hamsters resembles that of the mouse and whether any correlation between sensitivity to killing and genetic radiosensitivity can be made.

72. Guinea-pigs aged 3-5 months and golden hamsters aged 2.5-3.5 months were irradiated during middle dioestrus (day 6-12 of the 17-day cycle in the guinea-pig and day 2 and 3 of the 4-day cycle in the golden hamster) with 100, 200 and 400 rad of x irradiation at a high dose rate. Three post-irradiation matings were employed for the guinea-pig 1st oestrus, 2nd oestrus and 3 months) and this number was 4 in the golden hamster (1st oestrus, 2nd oestrus, 1 month and 4 months). In addition, the effect of maternal age on dominant lethal yield in the golden hamster was determined in parallel experiments involving irradiation of animals 9-11 months old and the study of dominant lethality at the 1st oestrus mating after irradiation. The pregnant females were killed at appropriate times after matings (3-4 weeks for the guinea-pigs and 10-12 days for hamsters) and the amount of dominant lethality was ascertained by the pre-natal method.

73. Table 19 shows that irradiation did not cause any sterility in the guinea-pig, except at the 1st-oestrus matings (after 400 rad) suggesting that at this dose the mature oocytes are more sensitive than the immature (3-month matings) to killing by radiation. In the golden hamster, there is a marked effect: a large number of females irradiated with 400 rad and mated 3 months after exposure were sterile (10 out of 13) and had ovaries that were approximately one third of the normal size. Histological sections of these ovaries revealed no corpora lutea or oocytes, suggesting that the sterility was due to killing by the radiation of all oocytes which were in either primary or growing follicles at the time of treatment. Sterility in one month matings after 400 rad may have similar causes although histological evidence on this was not obtained. All the other groups of females, both control and irradiated, showed a small amount of infertility and this might have been, in part, due to the seasonal breeding habit of this species. These results thus indicate that the less mature oocytes, i.e., 1- and 3-month matings are more sensitive to killing than are the mature oocytes.

74. The data given in table 19 also show that irradiation of mature oocytes of the guinea-pig with 400 rad lead to superovulation, i.e., a 30 per cent increase in the number of corpora lutea per female. Although this difference was not statistically significant, the amount of increase was very similar to that seen when mature oocytes of the mouse were treated with the same dose of x rays (455). No superovulatory effects could be seen for the 2nd-oestrus and/or the 3-month matings. In hamsters, irradiation with 400 rad produced a significant increase in the number of corpora lutea per female for the 2nd-oestrus but not for the 1st-oestrus matings.

75. The details of the intra-uterine mortality for both species are presented in table 20. It can be seen that in the guinea-pig, in general, the incidence of dominant lethals increases with dose and that the yields for mature oocytes were above those for the immature oocytes at each level. In the golden hamster, the situation is nearly the same.

76. An examination of the components of dominant lethality will show that, in the guinea-pig, both components increased with dose for the 1st-oestrus matings; for the 1st- and 2nd-oestrus matings, pre-implantation death exceeded port-implantation mortality in contrast to the 3-month matings, where the magnitude of both of these mortalities was relatively low. In the golden hamster, mortality before and after implantation increased with dose for the 1st- and 2nd-oestrus matings and in general, the amount of death before implantation was somewhat higher than that after implantation. In both species, some of the pre-implantation death could have been due to the shedding of dead or dying ova, rather than to true zygotic death.

77. The experiments on the effects of maternal age on dominant lethality in the 1st-oestrus matings in the golden hamster showed that the yields of dominant lethals were higher from older females than from young females at 100 and 400 rad levels, but not at 200 rad; however, the differences were not significant.

78. Statistical comparison of the dose-effect relationships for dominant lethals in both species showed that these were consistent with linearity with no significant differences between the slopes (model: $M = M_0 + bD$; $b_{\text{guinea-pig}} = (1.19 \pm 0.25)\,10^{-3}$ and $b_{\text{golden hamster}} = (1.59 \pm 0.18)\,10^{-3}$ (M is the mortality, M_0, the control mortality)). Although statistically a difference between the two species cannot be demonstrated, examination of the raw data suggests that the mature oocytes of the golden hamster may be slightly more sensitive to dominant lethal induction than those of the guinea-pig; in addition, the higher dominant lethal yields for the 2nd-oestrus matings in the golden hamster are indicative of a similar situation.

79. As may be recalled, in the mouse, the work of Searle and Beechey (513) demonstrated that the yields of dominant lethals for the 3rd week were generally higher than those for the 1st week; this pattern is in contrast to that seen in the two species studied by Cox and Lyon (121), where the yields for the 2nd-oestrus matings were in general lower than those for the 1st-oestrus matings. A second difference between the mouse and the other two species is that, in the 1st-week matings of the former, the total frequency of dominant lethals seemed to reach a plateau at about 200 rad, whereas in the latter, the data were consistent with a linear increase with dose. Since the x-ray data for post-implantation mortality in the mouse did not deviate from a linear relationship with dose, Cox and Lyon compared the slopes of the regression (on a linear model for this component) for the three species. The values of the slopes were (in units of 10^{-4} rad^{-1}):

Guinea-pig	3.88 ± 1.18
Golden hamster	6.19 ± 1.18
Mouse	3.57 ± 0.69

80. Thus, although the rate per unit dose for mature oocytes of the golden hamster appears to be higher than that of the other two species, this difference does not reach statistical significance. However, the authors point out that when total dominant lethality in mature oocytes of the three species is compared, the yield in the mouse after 400 rad is significantly below that of the other two species. All these data considered together suggest that the order of species in terms of decreasing sensitivity of the pre-ovulatory oocytes to dominant lethal induction by x rays is: golden hamster, guinea-pig, mouse.

81. For dominant lethal induction in post-meiotic male germ-cell stages (as measured by litter-size reduction), the golden hamster and the mouse appear to have the same sensitivity (in week 1-4 after 200 rad and in week 1 after 600 rad). Likewise, the rabbit and the guinea-pig have similar sensitivities (after 600 rad, week 1-4). The magnitude of litter-size reduction however, is higher in the first two species than in the rabbit and guinea-pig.

5. Summary and conclusions

82. Under conditions where irradiation (or other mutagen treatment) causes germ-cell killing with resultant spermatozoal depletion, the ratio of dead implants to total implants is a better index of dominant lethality than that based on the ratio of dead implants to corpora lutea or the number of dead embryos per pregnant female.

83. There are striking differences between different strains of mice in the amount of x-ray-induced dominant lethality (spermatozoal irradiation), which are as large as those between the mouse and other laboratory mammals studied in this respect.

84. X irradiation of female mice leads to a reduction in the mean number of implants per female (while the number of corpora lutea remain high) and in the ratio of live embryos to total implants; this reduction is more marked in conceptions occurring in the 3rd week than in the 1st week after irradiation; in contrast, in golden hamsters and guinea pigs, the yields of dominant lethals for 2nd-oestrus matings are lower than those for 1st-oestrus matings.

85. X irradiation of female mice (100-400 rad) leads to an increase in post-implantation mortality in conceptions occurring during the 1st and 3rd weeks after

irradiation. The dose-effect relationships are roughly linear, but in the 3rd-week group, the level of mortality is about twice as high as in the 1st-week group. The total dominant lethality (pre- and post-implantation) in the 1st-week group seems to reach a plateau at about 200 rad.

86. In guinea-pigs and golden hamsters, the dose-effect relationships for both post-implantation and total dominant lethality are consistent with linearity. For the induction of post-implantation mortality in pre-ovulatory oocytes, the order of the three species in terms of decreasing sensitivity is: golden hamster, guinea-pig, mouse.

87. For the induction of dominant lethals in post-meiotic male germ-cell stages, the mouse and golden hamster are more sensitive than rabbit and guinea-pig.

88. At a dose of 100 rad, fission neutrons (0.7 MeV) appear to have the same effectiveness as x rays in inducing dominant lethals in female mice.

B. TRANSLOCATIONS

89. Ever since the air-drying technique for making meiotic preparations of mammalian testes was developed by Evans, Breckon and Ford (162), the cytogenetic study of translocations in mammals, especially of those induced by irradiation, has been growing explosively. During the period 1964-1972, a large number of papers were published dealing with dose-effect relationships, dose-rate and dose-fractionation effects, effectiveness of radiations of different quality, the types of translocations and their effects on fertility etc. These were extensively reviewed in the 1972 report of the Committee. The general findings are summarized in the paragraphs that follow (unless otherwise stated, the comments refer to studies with the mouse):

90. Translocations can be induced by ionizing radiation in all stages of spermatogenesis in adults, in embryos *in utero* and in late oocytes. Radiation-induced translocations during spermatogenesis have also been observed in adult male rabbits, guinea-pigs and golden hamsters.

91. The pattern of radiosensitivity as it emerges from the cytological studies closely parallels that from genetic studies in demonstrating that post-meiotic male germ cells are more radiosensitive with regard to translocation induction than premeiotic cells; among the post-meiotic stages, spermatids are by far the most sensitive.

92. In spermatogonia, translocation induction by x and fast-neutron irradiation at high dose rates is consistent with a linear kinetics (up to 600-700 rad with x rays and up to 100 rad with neutrons), after which the yield falls off drastically, giving an overall humped curve; the results with gamma irradiation at high dose rates showed that the dose-effect relationship was concave in the range 56-402 R (suggesting the contribution of a quadratic component to the observed yield), although when the data were analysed as a whole (56-816 R) the relationship did not significantly depart from linearity. All these features are very probably the result of secondary distortions of the primary dose-effect relationship, which may well have a more marked square-law component.

93. In rabbit and guinea-pig spermatogonia, the overall dose-response curve after acute x irradiation is also humped (as in mice), but the peak incidence occurs at 200-300 rad.

94. The yield of translocations obtained from spermatogonia is reduced after x and gamma irradiation at low dose rates, the effect being more pronounced with gamma rays; at high doses, protracted neutron irradiation is more effective than acute irradiation whereas the reverse is true at low doses; the effects of fractionation are dependent on total doses and fractionation procedures. Especially important is the observation that the fractionation of a total dose of 300 rad of x rays into several small fractions of 10 or 5 rad each leads to a significant reduction in translocation yields, as compared with the effects of a single dose.

95. Some translocations induced in spermatogonia can successfully pass through the remaining stages of spermatogenesis and can contribute to zygotic populations; all the dominant lethality observed after spermatogonial irradiation can be accounted for by the segregation of unbalanced haploid genomes from spermatocytes with translocation multivalents.

96. A marked discrepancy was found between the frequencies of translocations diagnosed cytologically (in spermatocytes following spermatogonial irradiation) and genetically (in F_1 progeny) in that the observed frequency in the F_1 is only one half that expected on the basis of the frequencies observed in primary spermatocytes; these experiments had been carried out at an exposure level of 1200 R administered in 2 equal fractions separated by a period of 8 weeks.

97. Certain translocations (autosomal) can be fully viable in the heterozygous state and yet cause male sterility through a failure of spermatogenesis. If such translocations are induced in spermatogonia, they will not be represented in the effective sperm population and consequently will not be expected in the progeny of fathers whose spermatogonia have been exposed to irradiation; this is also true for translocations involving the X chromosome.

1. Dose-effect relationships in mouse spermatogonia

(a) *X and gamma irradiation*

98. Preston and Brewen (419) re-examined the problem of dose-effect relationship using x irradiation at a high dose rate (50-1200 R; 11 exposure levels). There was one important methodological difference between their work and that of other authors: while in most of the earlier investigations, a single sampling time (ranging from about 56 to 120 days, depending on the investigator, following irradiation with different exposures) was employed, Preston and Brewen staggered the

sampling time so that it coincided with the first wave of meiotic activity following recovery of the germinal epithelium. In other words, the time interval between irradiation and killing of the animals (to make preparations of the testes) varied with the exposure.

99. Their results are reproduced in table 21. In the range 0-500 R, the data best fit a model that incorporated both a linear and a quadratic component. The value for these two components are given by the equation

$$Y = 1.08\ 10^{-4}D + 5.00\ 10^{-7}D^2$$

Above 600 R, however, the yield of translocations decreased with increasing exposures, leading to a humped curve over the whole range studied, as has been observed by several workers previously. The authors suggest that in earlier work, the use of a single sampling time might have led to the sampling of different populations of stem cells at different exposures and that these might be responsible for the discrepancies between their results and the earlier ones with respect to the shapes of dose-response curves up to exposures of 600-700 R.

100. It is worth pointing out here that Wennström (605), on the basis of somewhat limited data, had earlier reached the conclusion that, in the dose range 25-400 rad, the dose-effect relationship for the induction of translocations in mouse spermatogonia was supra-linear. At all the dose levels, the interval between irradiation and observation was 2 months. The frequencies of cells with multivalents were (per cent): 0.33 (control), 0.33 (25 rad), 0.66 (50 rad), 2.7 (100 rad), 3.7 (200 rad) and 4.0 (400 rad). The numbers of cells analysed were respectively 1521, 300, 300, 300, 273 and 400. These data appear to suggest that, in the particular strain of mice used by Wennström (albino mice of the NMRI strain), the yield peaks at a rather low dose level. The author did not attempt any mathematical curve-fitting.

101. Pomerantzeva, Ramaiya and Ivanov (415) studied the gamma-ray (^{137}Cs) induction of translocations in mouse spermatogonia at three different exposure rates (710, 0.07 and 0.007 R/min). At the highest exposure rate, the frequencies were (per cent): 3.3 ± 0.7, 5.1 ± 0.7, 4.7 ± 0.8, and 4.2 ± 0.8 per cent at exposure levels of 300, 600, 900 and 1200 R, respectively. At the middle rate, the frequencies were lower, being 2.8 ± 0.5 per cent at 300 R, 3.8 ± 1.4 per cent at 600 R and 1.8 ± 0.7 per cent at 900 R. At the lowest rate, the frequencies were consistent with a linear increase with exposure (300, 600, 900 and 1200 R), the equation of best fit being

$$Y = (0.225 \pm 0.086)\ 10^{-2} + (1.74 \pm 0.21)\ 10^{-5}D$$

where Y is the translocation frequency and D, the exposure. In a subsequent paper, Pomerantzeva, Vilkina and Ivanov (417) demonstrated that when the exposure rate was further reduced to about 0.003 R/min, the response over the range of exposures from 100 to 920 R (5 levels) was nearly the same as that obtained with the lowest rate (0.007 R/min) above.

102. Searle *et al.* (516) analysed the available low dose-rate data obtained with chronic gamma irradiation (^{60}Co or ^{137}Cs) down to 0.003 rad/min (82, 83, 89, 90) (with total doses varying from 100 to 1200 rad) and concluded that (a) the yield fell with decreasing dose rate, with little further decrease in rate of induction below 0.02 rad/min, and (b) it seemed unlikely that the minimal rate would be less than $1.0\ 10^{-5}$ rad^{-1}.

(b) *Neutron irradiation and RBE estimates*

103. Muramatsu *et al.* (354) have reported the results of their studies on RBE of 2-MeV neutrons relative to 250-kVp x irradiation for the induction of reciprocal translocations in mouse spermatogonia. A wide range of doses was used (48-672 rad of x rays, 8 levels; 24-267 rad of neutrons, 8 levels). The dose-response curve for the neutrons was linear up to 94 rad beyond which the yield fell off, giving an overall humped curve, as had been observed earlier with 0.7-MeV neutrons (29). For x irradiation, the picture was essentially the same, except that the peak was at 672 rad. The regression coefficient for the linear part of the neutron curve was $11.4\ 10^{-4}$ and that for the x-ray curve, $2.69\ 10^{-4}$. The RBE for 2-MeV neutrons was estimated as 4.2, the ratio of these values, which is close to that of 3.7 estimated by Searle, Evans and West (518) and that of 4.4 recorded in the work of Pomerantzeva *et al* (414) for 1.5 MeV neutrons.

104. Valentin (596) carried out experiments on translocation induction in mouse spermatogonia with 14.5-MeV neutrons at acute dose levels of 75, 150 and 250 rad (dose rate, 1.7 rad/min). It was found that one mouse in the 150-rad series (out of the 11 used) contributed significantly to the variation between the mice (10 out of 16 affected cells were from this mouse, which in addition carried 2 translocations in one of the cells scored). The frequency of affected cells at doses of 75, 150 and 250 rad were, respectively, 0.7 ± 0.2 per cent, 0.8 ± 0.2 or 0.4 ± 0.1 per cent (depending on whether the aberrant mouse is included or excluded) and 1.6 ± 0.2 per cent. Between 1700 and 2500 cells were scored for each dose point in addition to 4700 cells in controls, where no translocations were found. The author points out that the dose response was consistent with linearity in the range studied, although if the aberrant male is excluded, the data give a better fit to a curvilinear relationship. Since no comparable x-ray data were obtained in her experiments, Valentin has refrained from making any RBE estimate except to point out that, in comparison with the results of Searle, Evans and West (518) with 0.7-MeV neutrons, the 14.5-MeV neutrons used in her study were presumably not as efficient and that the RBE value may be much lower than 3.7.

105. Bajrakova *et al.* (22) examined the effects of irradiation with 4.1-MeV neutrons (from a Pu-Be source) delivered at a low dose rate of about 0.08 rad/h on the induction of translocations in male mice. They found that the dose-effect relationship up to 52 rad (3 levels) was linear with an increase of about $3.3\ 10^{-4}$ translocations per rad, beyond which the curve saturated. The frequencies at the two high doses used were 1.91 ± 0.45 per cent, at 98 rad, and 1.65 ± 0.40 per

cent, at 150 rad. Since no comparable x- or gamma-ray experiments were conducted, the RBE value cannot be estimated. However, in comparison with the results of Pomerantzeva *et al.* (415) with chronic gamma irradiation, 4.1-MeV neutrons (also delivered chronically), appear to have an RBE of about 20.

2. Dose rate

106. It may be recalled that the earlier results of Searle *et al.* (517) discussed in the 1972 report (para. 66) demonstrated that, at the 600-rad level, a lowering of the gamma-irradiation dose rate from 83 rad/min to 0.02 rad/min led to a concomitant lowering of the yields of translocations and that the frequency at 0.02 rad/min was about one ninth of that at the higher rate. The results of Pomerantzeva *et al.* (415, 417) discussed earlier in this report (para. 101) corroborate the above finding and extend the data to more exposures and still lower exposure rates. They show that (a) when the exposure rate is reduced from 710 R/min to 0.007 R/min, the translocation yields are lower by at least an order of magnitude (range of exposures, 300-1200 R); (b) over this range of exposures, the data are consistent with a linear exposure-frequency relationship (see paras. 101, 102); and (c) a further lowering of the exposure rate to 0.003 R/min (range, 100-920 R) does not lead to any additional sizeable reduction in the frequencies over that already observed after irradiation at 0.007 R/min.

107. In more recent experiments, Searle *et al.* (516) demonstrated that when a gamma-ray dose (^{60}Co) of 1128 rad was administered to male mice over a 28-week period (0.004 rad/min) the frequency of translocations per spermatocyte was 1.70 ± 0.4 per cent, corresponding to a rate of induction of $1.40\ 10^{-5}$ rad^{-1}. This rate is quite similar to that of Pomerantzeva *et al.* (415), $1.74 \pm 0.21\ 10^{-5}$ R^{-1}. Relative to the yields after acute x irradiation (163) and after acute gamma irradiation (511), the results of Searle *et al.* (516) at 0.004 rad/min show that the efficiency of these is only about 0.05 and 0.01, respectively.

108. Van Buul and Roos (72) irradiated male mice with 400 R of x rays or gamma rays at exposure rates of 60 R/min and 130 R/min respectively and compared the yields of translocations obtained with those observed after a similar exposure of gamma rays delivered at rates of 1.92 R/min and 0.03 R/min. The data show that the yield after 400 R of acute gamma rays is slightly lower than that after x rays (abnormal cells, 6.6 per cent compared with 8.6 per cent; translocations, 7.0 per cent compared with 9.0 per cent; number of cells scored, 1400 and 1200) but not significantly so. With gamma rays at 1.92 R/min, the yield fell to one half of that observed after acute gamma irradiation (3.0 per cent abnormal cells or 3.2 per cent translocations; 1300 cells scored) and at 0.03 R/min, to 1.9 per cent (1400 cells scored). It is of interest to note that the magnitude of reduction observed here (by a factor of 3.5) is lower than that recorded by Searle *et al.* (517) at a dose level of 600 rad (83 rad/min compared with 0.02 rad/min; 12.1 per cent to 1.4 per cent), where it is by a factor of about 9.

109. In the study of Valentin described earlier (596), the effects of 250 rad of 14.5-MeV neutrons administered at rates of 1.67 rad/min and 0.01 rad/min were compared. The frequency of abnormal cells with either dose rate was nearly the same (1.6 ± 0.2 and 2.2 ± 0.3 per cent with high and low dose rates, respectively), thus showing no demonstrable dose-rate effect at this dose and with the range of dose rates employed.

110. In the work of Bajrakova *et al.* with 4.1-MeV neutrons (22) discussed in paragraph 105, no irradiations were carried out at high dose rates, and consequently the question of whether a dose-rate effect is present with that kind of neutron cannot be answered. However, their data show that at high exposures of 98 and 150 rad delivered at 0.0013 rad/mm (80 mrad/h), the frequencies of translocations remained at approximately the same level as after 52 rad. This finding is in marked contrast to that with 0.7-MeV neutrons (518) administered at about the same dose-rate as in the experiments of Bajrakova *et al.* (22), where a markedly high translocation yield (21.7 per cent at 214 rad) was recorded.

3. Dose fractionation

111. As was mentioned earlier, fractionation of the radiation exposure affects the yield of translocations recovered from irradiated spermatogonia and this depends on the magnitude of the doses and the fractionation procedures used. For convenience, the various results obtained will be considered under the headings "short intervals" (less than 24 h), "medium intervals" (24 h to a few days) and "long intervals" (a few weeks). The earlier results reviewed in the 1972 report will be briefly summarized to facilitate comparisons. Unless otherwise stated x irradiation was used.

(a) *Short intervals*

112. Léonard and Deknudt (282) studied the induction of translocations in mouse spermatogonia by using an x-ray exposure of 500 R divided into two equal fractions separated by time intervals from 60 min to 24 h. It was found that after a single 500-R exposure, the incidence of spermatocytes carrying translocations was 8.1 per cent; with an interval of 2 h between the fractions, the frequency fell to 5.7 per cent, rose to 8.8 per cent at 4 h, fell again to 4.4 per cent at 7 h, rose to 8.4 per cent at 16 h, with some suggestion for a further fall to 6.8 per cent at 24 h. In the study of Searle *et al.* (515), in one experiment, when a total dose of 300 rad was delivered in two equal fractions separated by a 30-min interval, the frequency of affected spermatocytes was 8.1 per cent compared with 14.5 per cent observed after the unfractionated exposure. (As the authors themselves point out, the latter frequency is higher than the one expected at this dose (7.5 per cent) on the basis of their earlier studies.) With a 2-h interval, the frequency rose to 10.8 per cent, a just significant increase. In the next experiment, there was again an initial fall from 8.8 per cent (unfractionated) to 6.6 per cent (60 min) and a rise later to 8.1 per cent at 6- and 8-h intervals; none of these changes was statistically significant.

113. In the experiments of Preston and Brewen (420), an unfractionated exposure of 500 R gave a yield of 17.2 per cent; with intervals of 30, 90 and 150 min between the two 250-R fractions, the yields appeared to decline to 16.2 ± 1.8 per cent, 14.0 ± 1.5 per cent, 12.5 ± 1.4 per cent, respectively. In further experiments reported in the same paper, the authors investigated the effects of fractionation of a 1000-R exposure (an exposure which is on the descending part of the dose-effect curve) into two equal fractions separated by intervals of 3, 6 and 18 h. The yield of translocations following a 1000-R single exposure was 5.2 per cent; following fractionation however, the yield increased to 17.1 per cent for a 3-h interval and reached a maximum of about 41 per cent for an interval of 18 h when it was equal to the yield expected on the basis of additivity of yields of two separate 500-R exposures. On the basis of these results and the finding that the yields decreased with 48- and 72-h intervals to 23.8 and 19.5 per cent, respectively, the authors suggest that the pattern of response observed in the above experiments could be explained in terms of the killing of cells in the sensitive stage of the cell cycle by the first exposure, resulting in a partially synchronous population being irradiated by the second exposure. The stage of the cell cycle in which the population exposed to the second fraction is expected to be in, will vary with time between the two fractions, assuming that over the time period used in these experiments, the cells are still partially synchronous. Preston and Brewen predicted that with a time interval of, say, 96 h one would expect the yield to return to that for 1000 R. The results obtained by Cattanach and Moseley (92) indeed show that the expectation is fulfilled (para. 118).

(b) *Medium intervals*

114. The early experiments of Lyon and Morris (311) demonstrated that the yield of translocations after two 500-rad doses to spermatogonia (24-h interval), was not enhanced above that extrapolated from lower single doses, although it was above that for a single 1000-rad dose, which was beyond the maximum of the humped dose response curve. In further work with similar fractionation procedures, Morris and O'Grady (345) adduced further evidence which showed that the yields after fractionated exposures involving total doses from 100 to 600 rad were remarkably close to those for single ones (i.e., no enhancement); at higher doses (up to 1400 rad) the yields continued to increase approximately linearly after fractionation and were consistent with the additivity of yields of the two respective fractions. These observations are in marked contrast to those made by W. L. Russell (471), which showed that after fractionation of an exposure of 1000 R (two fractions, 24 h apart) the yield of specific locus mutations was much greater than expected by extrapolation from lower single doses. The suggested explanation for the enhancement of specific locus mutations was that the first radiation dose synchronized the cell divisions of the surviving spermatogonia in such a way that at the time of the second dose 24 h later, they were particularly sensitive to gene mutations. Morris and O'Grady speculated that the difference in response between specific lcous mutations and translocations could be understood if it is assumed that in the latter case, the cells were synchronized at a stage with relatively unchanged sensitivity to chromosomal damage (see the 1972 report (589) for details of the data).

115. The work of Wennström (605), in which the effects of fractionation of a 200 rad dose into two, three, four or six fractions (24-h interval between fractions) also demonstrated that the yields with these different régimes were not significantly different from the one obtained after a single dose of 200 rad. (The finding that, with four or six fractions there was no change in the yield relative to that of the single dose is at variance with that of Lyon *et al.* (315), which showed that with a 300-rad total dose split into five daily fractions of 60 rad, there was a reduction in frequency from 6.3 to 3.4 per cent.)

116. Van Buul and Léonard (71) examined the extent to which the magnitude of the first fraction of a split dose affected the subsequent response of the cells 24 h later to the second fraction. In these experiments, male mice were irradiated with a total x-ray exposure of 600 R delivered either singly or in two equal fractions or in two unequal fractions of 100 and 500 R or 500 and 100 R. Translocations were scored 70-120 days after the completion of the radiation treatments. The results showed that when the irradiation was delivered either singly or in two equal fractions, the frequencies of abnormal cells were not significantly different (7.6 compared with 8.4 per cent), as had been found by other workers. With the 100 + 500 R régime, the frequency was 10.2 per cent (1600 cells scored), whereas when the order of the exposures was reversed, it was 4.9 per cent (1700 cells scored). These data suggest that the net result of interaction between the postulated cell synchronization by a first fraction of a dose and the alteration of the sensitivity of the surviving spermatogonial cell population is dependent on the magnitude and sequence of the exposure fractions.

117. In a more recent paper, Cattanach, Heath and Tracey (93) adduced further evidence for the thesis that with 24-h intervals, the size and sequence of the exposure fractions determine the radiosensitivity of the stem cells to translocation induction. They found that when 1000 R was administered as 100 R followed by 900 R, the recovered translocation yield (22 per cent) was similar to that which can be obtained by extrapolation from lower exposures and also that of a 500 R + 500 R, 24-h fractionation. However, when the 900 R preceded the 100 R, the response was much lower (7.4 per cent), yet still higher than that produced by a single 1000 R treatment (4.5 per cent). The same order of effectiveness was observed for the length of the sterile period. From these results the authors have concluded that 24 h after the initial exposure (a) the surviving stem cells are more sensitive than formerly, both to killing and genetic damage, and (b) they are no longer heterogeneous in their radiosensitivities so that increasing yields of genetic damage may be obtained with increasing exposures.

118. Cattanach and Moseley (92) irradiated males with a single x-ray exposure of 800 R or in two fractions of 500 and 300 R (in that order), separated by intervals

ranging from 24 h to 12 days. Translocations were scored in spermatocytes descended from the irradiated gonia, 100 days after the completion of the irradiation treatment. The data showed that the 24-h fractionation increased the translocation yield significantly above that of the acute treatment (18.3 per cent compared with 7.9 per cent) but not higher than expected on the basis of additivity of individual fractions; with a 48-h interval, the frequency was 16.0 per cent, still being consistent with the expectation of additivity. On the other hand, with intervals of 3-12 days, the translocation yields were much lower and little different from that obtained after acute exposure. These latter results are consistent with the prediction made by Preston and Brewen (420) on the basis of their experiments in which a 1000-R exposure was given in two fractions separated by periods ranging from 3 h to 3 days (para. 113).

119. In the work of Cattanach *et al.* (93) discussed in paragraph 117, evidence was also obtained showing that the subadditive translocation yields recorded with the 800-R treatments (500 R + 300 R, and in that order with intervals of 3-12 days) was maintained with further intervals of up to 15 days and that additivity was regained by the end of the third week. Sterile period data indicated that with these intervals (of up to 15 days), the germinal epithelium had recovered sufficiently from the first fraction for spermatogenesis to restart before the second fraction was given. These results permitted the authors to conclude that (a) 3-15 days after the first exposure, the surviving cells proliferate rapidly to repopulate the testes and at this time they are either resistant to genetic damage (though still relatively sensitive to killing) or are sensitive to both, but with the two events being correlated, and (b) the onset of spermatogenesis is associated with the re-establishment of a heterogeneity in radiosensitivity among the stem cells.

120. Earlier work from Lyon's laboratory (315) had shown that when repeated small radiation doses are delivered to mouse spermatogonia, the yield of translocations was less that that after the same total dose given in a single exposure. Two main explanations were considered: (a) each individual small dose has less effect than the comparable fraction of a large single dose, and (b) repeated irradiation in some way changes the spermatogonial cell population so as to either decrease the sensitivity to induction or increase the elimination of mutational changes. The evidence obtained for (b) was the following: a dose-response curve was plotted for varying numbers of 10-rad doses (total dose ~620 rad). The form of the curve suggested that later doses were having less effect than earlier ones and hence was consistent with the idea that the spermatogonial cell population was becoming more resistant with repeated irradiations. If this were true, one would expect that if a single exposure to a large dose of irradiation were given *after* a succession of repeated small doses, it would have less effect than if the procedure were reversed.

121. Lyon, Phillips and Glenister (317) tested the above possibility in experiments by comparing the yields of translocations obtained with a dose of 300 rad of gamma rays to spermatogonia administered before, 24 h after, or 8 days after exposure of the animals to 30 daily doses of 10 rad each. The results showed that under conditions when the 300-rad single exposure was given 24 h after the 30 X 10-rad exposure, the yield was significantly lower (7.3 per cent) relative to those from the other two régimes (9.4 per cent: 300 rad + 30 X 10 rad; 9.7 per cent: 30 X 10 + 300 rad, 8 days later). That is consistent with the hypothesis that the repeated irradiation had temporarily increased the resistance of the spermatogonial cell population to translocation induction. The authors consider the above interpretation tentative.

(c) *Long intervals*

122. So far, there have been only four reports on the effects of dose fractionation on translocations induced by x rays in spermatogonia where the interval between the doses was of the order of several weeks. The first of these relate to the work of Ford *et al.* (170), who found that when an exposure of 1200 R was administered in two equal fractions separated by a period of 8 weeks, the yield of translocations was high (being 41.6 and 32.5 per cent in two different experiments) but not higher than what would be expected from additivity of yields, although much higher than what had been found following single acute exposures of similar magnitude. Similarly, Pomerantzeva *et al.* (415) found that when a total exposure of 900 R was given in three equal fractions separated by 4-week intervals, the frequency of translocations was 9.1 per cent, this being roughly three times that after a single 300-R exposure (3.3 per cent) and about twice that after a single 900-R exposure (4.7 per cent).

123. More recently, Pomerantzeva and Ramaiya (412) made a study with fractionated gamma-ray exposures delivered to mouse spermatogonia (900 R in three equal fractions) and varied not only the interval between the exposure fractions (1 to 4 weeks) but also the interval between the completion of the irradiation and the sampling of the spermatocytes (12 to 48 weeks). Considering first the effect of *sampling interval*, increasing it from 12 to 28 weeks led to no significant change in translocation frequency (9.3 ± 1.2 per cent compared with 10.0 ± 1.4 per cent; pooled data: 9.7 ± 1.0 per cent). However, when the interval was extended to 48 weeks, there was a slight decrease in the frequency (7.3 ± 0.8 per cent compared with 9.7 ± 1.0 per cent). The latter finding is qualitatively similar to that recorded earlier by Evans *et al.* (163), namely, that after a single dose of 800 rad the frequency fell from 20.5 per cent with an 11-week interval to 12.8 per cent with a 30-week interval. (See table 11 in the 1972 report, Annex E.)

124. Concerning the effects of *interval between exposure fractions* on the yield of translocations, Pomerantzeva and Ramaiya found that, with a 7-day interval between the fractions (12-week sampling interval), the frequency was 8.6 ± 0.8 per cent and did not change with a 28-day interval (9.3 ± 1.2 per cent). In either case, the yield was lower than expected on the basis of additivity (yield after a single 300-R exposure: 5.2 ± 0.6 per cent). The first of these findings is similar to that of Cattanach *et al.* (93 and paragraph 119) whereas the second one is not: Cattanach *et al.* noted

that with a total exposure of 800 R administered in two unequal fractions of 500 and 300 R, additivity was regained 21 days after the completion of the radiation treatment, whereas this has not been the case in the work of Pomerantzeva and Ramaiya. One possible reason for the discrepancy between the two sets of results may be that, since both the total exposures and the fractionation régimes are different, the pattern of recovery of the germinal epithelium under these conditions is also different (see paragraph 125).

125. In their experiments (500 + 500 R), Preston and Brewen (420) found (see also paragraph 113) that with an 18-h interval, the yield was equal to that expected on the basis of additivity (40.7 per cent compared with 2 X 17 = 34 per cent) but dropped to 23.8 per cent with a 48-h interval and remained at approximately the same level up to an interval of 4 weeks. By 6 weeks, additivity was once again regained (32 per cent compared with 2 X 17 = 34 per cent).

126. In other experiments reported in the same paper, Preston and Brewen irradiated male mice with repeated 400-R x-ray exposures up to a total exposure of 2800 R, the interval between successive exposures being 8 weeks. The expectation was that under such conditions, the interval between one exposure and the next would be long enough for the cells to re-assort back to a normal cycle, with cells present at all stages, and consequently additivity of yields should be obtained. The data presented in table 22 show that the expectation is indeed realized. The time elapsed between irradiation (after different numbers of exposures) and the sampling of spermatocytes was adjusted to sample the first wave of meiotic cells following the recovery and repopulation of the geminal epithelium, as emphasized in an earlier publication (419). This varied from 6 weeks following four 400-R exposures up to 17 weeks following the last 400-R exposure of the 2800-R total exposure. As will be obvious, the interpretation for the observed effect in this kind of experiment, involving long intervals between exposures, is different from that advanced for similar effects observed with fractionation régimes involving 24-h intervals.

4. Interaction with chemicals

127. The 1972 report presented the data of Ehling (148, 152, 153) and of Pomerantzeva and colleagues (209, 411) on the effects of pre-treatment with different chemicals, such as chloramphenicol, mitomycin C, aminoethylisothiourea (AET), 5-methoxytryptamine and cysteamine, on radiation-induced dominant lethals. Similar studies have now been carried out to examine the effects of chemical pre-treatment on radiation-induced yield of translocations in spermatogonia. Léonard and Deknudt (283) who studied the effects of AET pre-treatment, found that the compound exhibited no protective effect and explained the failure of AET to modify the rate of translocation induced by x irradiation on the basis of some germinal selection or, more likely, the stage specificity of AET (Ehling's finding was that a protective action was manifest only in early spermatids). In a subsequent paper, Léonard and Deknudt (284) demonstrated that a mixture of reduced glutathione (GSH), AET, mercaptoethylamine (MEA), cysteine and serotonin creatinine sulphate or 5-hydroxytryptamine (5-HT) did have a protective effect: the frequency of abnormal spermatocytes in the "radiation alone" series was 8.1 per cent and that in the "mixture plus radiation", 5.9 per cent (500-R exposure to spermatogonia). Using Adeturon (ATP salt of AET), Bajrakova (21) found that this chemical did offer some protection against radiation-induced translocations in spermatogonia. The frequencies of abnormal cells after radiation alone or radiation plus chemical are, respectively, 2.6 per cent and 1.6 per cent (150 R), 4.8 per cent and 2.5 per cent (300 R) and 6.1 per cent and 2.6 per cent (450 R). Between 800 and 1000 cells were scored for each data point.

128. In a further elaboration of earlier work (411), Pomerantzeva and Vilkina (413) examined the effects of pre-treatment with cysteamine on gamma-ray induction (100, 300 and 600 R) of translocations in spermatogonia. No protective effects were found. However, in parallel experiments on dominant lethal induction in post-meiotic and meiotic stages, the pre-treatment led to a reduction in induced dominant lethality after 300 R. The effect was negligible after 100 R and completely absent after 600 R.

5. Comparison between cytologically observed and genetically recovered frequencies of reciprocal translocations

129. Despite the phenomenal progress that has been made in the cytological screening for radiation-induced reciprocal translocations induced in spermatogonia, there is a great paucity of experiments designed specifically to examine the relationship between the frequencies obtained in spermatocytes and those observed in genetic tests of F_1 male progeny. In the only paper thus far published, Ford *et al.* (170) determined this relationship at a high exposure (600 R + 600 R, separated by 8 weeks; adult males were irradiated and the frequencies of translocations in spermatocytes derived from irradiated spermatogonia were determined, and in parallel experiments the frequency of heritable translocations in the F_1 progeny of similarly irradiated males was also ascertained). It was found that the frequency of transmissible reciprocal translocations was only about one half of that expected on the basis of the cytological data. The interpretation was that this discrepancy could arise if some selection process operated on translocation-carrying diploid (rather than haploid) genomes between the meiotic metaphase and fertilization.

130. For better use of the latter kind of data in hazard evaluations, information on whether or not the relationship found at high exposures will hold at lower levels and the extent to which this is likely to be modified under other conditions of radiation exposure (low dose rate, fractionation etc.) is of paramount importance. To rectify this deficiency in our knowledge, Generoso *et al.* (186) and Brewen *et al.* (56) have embarked on an extensive study aimed at determining, for a series of acute exposure levels (150, 300, 600 and 1200 R of x rays), the frequencies of translocations in spermatocytes and those of translocation heterozygotes in the F_1 male progeny, in parallel cytological and genetic tests.

131. The data available until now are given in table 23. It can be seen that (a) the frequency of translocation heterozygotes (genetic tests) increases with exposure up to 600 R (although the difference between the yields after 150 R and 300 R is not significant), followed by a marked falling off at 1200 R; this humped characteristic of a exposure-frequency curve is in general agreement with the cytologically scored reciprocal translocations; (b) at exposure levels of 300 R and above, the ratio of translocation recovery in the genetic tests to cytologically determined frequency is roughly one eighth, as was found earlier by Ford *et al.* (170); and (c) at the lower exposure level of 150 R, this ratio is one quarter (although not significantly different from one eighth in view of the still relatively small number of F_1 males tested). Thus at the exposure level of 150 R, there is a suggestive indication that, on the basis of the conditions assumed by Ford *et al.* (170), the rate of recovery of balanced translocations among progeny might be that which is expected from the cytological frequency.

132. In a recent study in which male mice were given fractionated gamma-ray exposures (3 X 300 R, separated by 28-day intervals between fractions), Pomerantzeva, Ramaiya and Vikina (416) found that the frequency of cytologically diagnosed translocation heterozygotes among F_1 males (derived from irradiated gonia) was 2.8 ± 0.9 per cent (9/319). Although no direct determination of the translocation frequency was made in the irradiated males themselves, such data collected by the same group of workers in another study (para. 123) under similar radiation conditions may be used to compute the ratio of the frequency of translocation heterozygotes in the F_1 to the frequency of translocations in irradiated males. This ratio, 0.28 (2.8/10.0), is not significantly different from either 0.25 or 0.125, in view of the small number of F_1 males screened.

6. Summary and conclusions

133. Since the publication of the 1972 report of the Committee, a sizeable amount of information has accumulated from studies on the induction of reciprocal translocations. Most of this has come from continuing studies with mice.

134. In contrast with the results from earlier work in which the frequency of reciprocal translocations induced in spermatogonia (and scored in spermatocytes) by x irradiation at high dose rates was found to show a linear dose-effect relationship, the results of Preston and Brewen (and those of Wennström to some extent) show that the data best fit a model which incorporates both a linear and a quadratic component. In the work of Preston and Brewen, the interval between irradiation and killing of the mice was varied (depending on the dose) in such a manner that the time of sampling of the spermatocytes coincided with the first wave of meiotic activity following recovery of the germinal epithelium; in earlier work, most often, a single sampling time (irrespective of the dose and depending on the laboratory) had been used.

135. With chronic gamma irradiation delivered at a rate of 0.007 R/min, the exposure-frequency relationship is linear over the entire exposure range investigated (up to 1200 R). Further lowering of the exposure rate to 0.003-0.004 R/min does not lead to any significant reduction in the rate of induction. An analysis of all the available data obtained with chronic gamma irradiation at low dose rates down to 0.003 rad/min (with doses varying from 100 to 1200 rad) shows that the minimal rate of induction is unlikely to be lower than $1.0\ 10^{-5}$ rad^{-1}. At these very low dose rates, the efficiency of chronic gamma irradiation is at least an order of magnitude lower than that of acute gamma irradiation or acute x irradiation.

136. Irradiation of mouse spermatogonia at high dose rates with 2-MeV neutrons is about four times as effective for translocation induction as similar irradiation with 250-kVp x rays. Neutrons at 14 MeV appear to be much less efficient in this respect. The dose-effect relationship for chronic neutron irradiation (4.1 MeV) is consistent with linearity up to 52 rad, after which a saturation effect is observed. Relative to chronic gamma irradiation, similar irradiation with 4.1-MeV neutrons is about 20 times more efficient. No dose-rate effect can be demonstrated with 14-MeV neutrons in the range 0.01-1.67 rad/min.

137. Fractionation of the irradiation exposure affects the yield of translocations recovered from irradiated spermatogonia in a way that depends on the magnitude of the radiation dose and the fractionation régimes employed.

138. With total doses below 600 rad (i.e., those on the ascending part of the humped dose-effect curve), irradiation in two equal fractions separated by intervals of up to about 2 h leads to a decrease in the yield of translocations (relative to single doses). This might be due to two reasons: (a) the change in the characteristics of the spermatogonial population caused by the first fraction of the dose (for instance, the killing of cells in certain phases of the spermatogonial cell cycle and the consequent synchronization of the remaining cells), the degree of which may vary with the dose and (b) the decreasing possibility of interaction between chromosome lesions produced by the first fraction and the subsequent one. The former possibility seems, however, most unlikely.

139. When the interval between the fractions is equal to or more than the maximum time that seems to be required for rejoining of the chromosome lesions produced by the first fraction (2.5-4 h), the total yield is approximately equal to the sum of the yields of individual fractions, as expected. The limited data beyond the 4-h interval between fractions in short-term fractionation studies suggest that there is a further drop in the frequency (7-h interval) followed by a tendency for an increase (16-h) and then a decrease (24-h). Such a cyclical response may be interpretable on the assumption that with the different fractionation intervals, the partially synchronized cells receiving the second fraction may be in sensitive or resistant phases of the cell cycle.

140. With a high total dose such as 1000 rad (which is on the descending part of the humped dose-response curve), administered in two equal fractions and with time intervals ranging from 30 min to 72 h, again, there is a cyclical pattern of response; but this is a different one. With a 30-min interval the yield is close to that of

the total single dose of 1000 rad. With increasing intervals, the frequency increases up to a maximum with an 18-h interval when it is equal to the yield expected on the basis of additivity. The yield subsequently decreases and after 72 h, falls back to the level expected from a single 500-rad exposure. With extended intervals of up to 4 weeks, the increase is only gradual, and by 6 weeks, additivity is once again regained.

141. With unequal fractions (500 R + 300 R and in that order), additivity of yields is first observed with a 24-h interval (intervals shorter than this were not used) followed by a drop and a slow rise in the yield (with intervals ranging from 3 to 15 days), and by the end of the third week, additivity is once again regained. These results are in general agreement with those described in the preceding paragraph.

142. The interpretation of these results (paras. 140-141) might be that (a) the spermatogonial stem cells have different sensitivities in the different stages of the cell cycle; (b) the 500-rad fraction kills the most sensitive cells, leaving a partially synchronized population which passes to a cell cycle stage in which the cells are sensitive (18 h); (c) the subsequent decline in yield indicates a progression into a more resistant stage; and (d) by about 6 weeks after the first fraction of the dose, the cells have become re-assorted to a normal ("asynchronous") population.

143. In experiments involving a total irradiation exposure of 2800 R administered in seven equal fractions of 400 R and separated by 8-week intervals, additivity of yields is expected and in fact has been found.

144. With unequal fractions separated by 24-h intervals (100 R + 500 R, 500 R + 100 R, 500 R + 300 R, 100 R + 900 R, and 900 R + 100 R), the recovered translocations yields are dependent on the size and sequence of the exposure fractions. With a small fraction preceding the large one, the yield is high and is equal to that extrapolated from lower exposures. With the reversed sequence of exposures, the yield is low, but higher than that after a single acute exposure. These observations are interpreted on the assumption that 24 h after the first fraction, the surviving stem cells are in a more sensitive stage than before, both to killing and to translocation induction and that they are less heterogeneous in their radiosensitivities at the time they receive the second fraction (the degree of synchrony being dependent on the magnitude of the first fraction).

145. When total dose as large as 300 rad is split into several small fractions (30 of 10 rad or 60 of 5 rad) and administered over daily intervals, the frequency of translocations recovered is much lower, being only about one quarter of that after the single dose. This finding has been explained on the assumption that the spermatogonial population becomes progressively radioresistant under conditions of repeated irradiation. The possibility was tested in experiments in which a 300-rad gamma-ray dose followed an exposure régime involving 30 daily doses of 10 rad each and vice versa. The yield under the first set of conditions was lower than under those of the second.

146. Pre-irradiation injection with chemicals such as Adeturon or a mixture of reduced glutathione, AET, MEA, cysteine and serotonin creatinine sulphate has a protective effect with regard to the induction of translocations in spermatogonia. However, cysteamine has no effect.

147. A comparison of the frequencies of cytologically observed reciprocal translocations and genetically recovered ones (following spermatogonial irradiation) has shown that at exposure levels of 300 R and above, the ratio of translocations recovered in the genetic tests to cytologically determined ones is about 1 to 8; at a lower exposure of 150 R, this ratio is 1 to 4, though this result is not significantly different from 1 to 8. In another study involving a total exposure of 900 R delivered in three fractions separated by 4-week intervals and cytological examination of the parental males and their F_1 sons (thus no semi-sterility tests), the ratio of the frequency of translocation heterozygotes in the F_1 males to the frequency of translocations in the parental males was 1 to 4, but again, the result was not significantly different from 1 to 8.

7. Other male germ-cell stages

148. Searle *et al.* (520) have reported on the kinetics of dose response for the induction of reciprocal translocations in mouse spermatozoa. In these experiments, adult male mice were given gonadal doses of 0-1200 rad acute x-irradiation (nine levels) and mated the same day. The 531 sons conceived within a week after irradiation were tested for fertility and their testes examined cytologically for chromosome aberrations in spermatocytes. A total of 55 of the 57 diagnosed as semi-sterile and 35 out of 40 of those diagnosed as sterile were judged to be heterozygous for one or more reciprocal translocations. There was a close agreement between fertility diagnosis and the presence or absence of reciprocal translocations. Numbers of 0, 1, 2, . . . translocations per mouse showed a good fit to a Poisson distribution, in contrast to previous finding with spermatogonial irradiation. Again, in contrast to findings after spermatogonial irradiation, the translocation frequency after spermatozoal irradiation steadily rose with dose and showed no decline at higher levels.

149. The equation of the straight line that fit the data best was

$$Y = (4.78 \pm 0.43)\ 10^{-4} D$$

where Y is the yield and D the dose. Although the fit to linearity was good ($P = 0.57$), it was noted that deviations of observed values from expectations were all negative at low doses (50-400 rad) but positive at the higher doses of 1000 and 1200 rad; this suggested that the true relationship was curvilinear. The equation of best fit to a quadratic model was

$$Y = (2.25 \pm 1.03)\ 10^{-4} D + (3.09 \pm 1.26)\ 10^{-7} D^2 \quad (P = 0.84)$$

and to a power law model was

$$Y = (3.03 \pm 3.98)\ 10^{-5} D^{(1.41 \pm 0.20)} \quad (P = 0.87)$$

150. Data on the types and relative frequencies of aberrations induced in spermatocytes by different x-ray exposures (50-400 R) have been reported by Wennström (605). They show that when testes preparations were made 1 day after irradiation of the mice (to sample spermatocytes treated at the diplotene stage), the frequency of cells with multivalents increased non-linearly ($Y = 0.2805\ 10^{-2} + 0.746\ 10^{-6}\ D^2$); this was also true of chromatid breaks and fragments. In one experiment in which the time interval between irradiation and killing of the mice was varied from 2.5 h to 7 days, maximum yields of all aberrations were obtained with the 1-day interval (3.3 per cent multivalents, 3.7 per cent chromatid breaks and 11 per cent fragments) followed by a decline thereafter. The decrease for multivalents at the 3- and 7-day intervals (sampling of spermatocytes irradiated at early and late pachytene stages, respectively) was not significant.

151. In a similar study, Tsuchida and Uchida (579) found that in preparations made 1 day after irradiation with 300 R of gamma rays, the frequency of multivalents was 6 per cent; those of chromatid breaks and fragments were respectively 6.4 and 10.5 per cent. Five days after irradiation (sampling of mid-pachytene stages) the frequency of multivalents was nearly the same (7 per cent) whereas those of chromatid breaks and fragments increased (15 and 10 per cent). The overall frequency of abnormal cells was 20.7 per cent with the 1-day interval and 32 per cent with the 5-day interval.

152. Although most of the studies on translocation induction in male mice had been concerned with the irradiation of adult males, some studies have been carried out using males of other ages. Fazylov and Pomerantzeva (164) reported that the sensitivity of the germ cells of new-born male mice was only one third of those in the adult (as judged by cytogenetic analysis of spermatocytes) and that the exposure frequency relationship was linear in the range 20-400 R. Ivanov and Léonard (245) irradiated male mice soon after birth or when 90 or 450 days old with x-ray exposures of 100, 200 or 300 R (100 R/min). One hundred days after the exposure, the animals were killed and meitoic preparations of the testes were made. The results that Ivanov and Léonard obtained however, were at variance with those of Fazylov and Pomerantzeva: there were no differences in sensitivity between gonocytes and spermatogonia at any of the exposure levels. Data similar to those of Ivanov and Léonard have also been collected by Brewen and Preston (53) (50-300 R; five levels); again there were no significant differences in sensitivity between new-born and adult male mice.

153. Another finding of Fazylov and Pomerantzeva (164) relates to their work on irradiation of 16-day-old foetal males (*in utero* irradiation; translocations scored later in spermatocytes of adults). At the 20-R level, the translocation frequencies were higher in foetal than in adult males; at exposure levels of 50 R or more, the reverse was true. The authors concluded that the reason for the lower mutation frequency in foetal males was that there was a positive correlation between mutational response and radiosensitivity to cell killing and that at exposures of 50 R and above, only gonocytes with a lower mutational response survived. They did not, however, take full account of an important feature of their data, namely, the likely occurrence of clusters. Clusters of translocations in a few males could have explained the higher frequency of translocations they found following the 20-R exposure, thereby invalidating their statistical analysis and their conclusion (526).

154. In similar work but with irradiation of 13.5-day-old male foetuses (this stage was chosen because at day 13.5 of gestation, the sex cords are just developing) at x-ray exposure levels of 100, 200 and 300 R, Ivanov *et al.* (246) failed to obtain any evidence for translocation induction. Tsuchida and Uchida (578) also reported essentially similar results after 150 R of gamma irradiation to 12-day-old male foetuses (*in utero* irradiation). The aberrations scored included multivalents, chromatid breaks and fragments. The data obtained by Brewen and Preston (53), however, are at variance with the above in showing that translocations can be induced in the dividing gonocytes present in the 13.5-day-old foetus. The frequencies were: 0.24 per cent (50 R), 1.4 per cent (100 R), 0.90 per cent (150 R), 2.8 per cent (200 R) and 3.4 per cent (300 R). These results demonstrate that the gonocytes in the 13.5-day-old foetus are about one half as sensitive as those of adult spermatogonia, at least at exposure levels of 150-300 R.

8. Female mice

155. While a number of studies have been carried out in recent years on the induction by radiation of translocations in male germ cells of the mouse, our knowledge of similar effects in female germ cells has remained meagre. The reasons for this contrast have been more connected with technical difficulties than with any expectation that the level of translocation induction would be negligible. In the 1972 report, mention was made of the early work of L. B. Russell and Wickham (463) and of the preliminary results of Searle and Beechey in Harwell. In the former experiments (carried out before the technical advances which made cytological examination possible), after maternal x-ray exposure to 400 R, 1 out of 320 F_1 male progeny was judged to be a semi-sterile offspring and thus presumably heterozygous for a reciprocal translocation. However, a few others were sterile and so could have carried translocations.

156. Searle and Beechey (513) have now completed their experiments, and in addition, two papers by Gilliavod and Léonard (192, 193), one by Tsuchida and Uchida (579) and another by Brewen, Payne and Preston (58) have appeared in the literature; besides, some preliminary results of Krishna and Generoso (267a) have also become available. In the first experiments of Gilliavod and Léonard (192), female mice were irradiated with 50 or 200 R of x rays (whole-body, high dose rate) and caged individually with unirradiated males for one year. The F_1 male progeny were killed when mature and meiotic preparations of the testes were made. In parallel experiments, female mice irradiated at similar x-ray exposure levels were killed 24 h after irradiation and meiotic chromosome preparations of the oocytes were made. Although such preparations of the oocytes themselves showed the presence of translocation configurations in some first meiotic metaphases (2 out

of 50 in the 50 R series and 0 out of 50 in the 200 R series), no translocations could be diagnosed in the spermatocyte preparations of the F_1 males examined (101 sons in the 50 R series and 78 sons in the 200 R series).

157. In their subsequent paper, Gilliavod and Léonard reported on cytological observations on control and irradiated oocytes at exposure levels of 25, 50, 100 and 200 R. The frequencies of translocation configurations observed (R-IV and/or CH-IV) were (per cent): 0 (0/101, 0 R); 3.2 (2/63, 25 R); 3.7 (4/108, 50 R); 1.0 (1/100, 100 R); and 0 (0/85, 200 R). At the 100-R level, there were 6 oocytes bearing chromosome fragments. The authors attribute the finding that the frequency of oocytes carrying translocation configurations declines already at 100 R (in contrast to the observations of Searle and Beechey (513) to be described later) to the relatively small numbers of dividing oocytes that could be examined, although one cannot rule out sensitivity differences in the strains used by the two groups of investigators (C57BL in the experiments of Gilliavod and Léonard and F_1 females from C3H/HeH X 101/H in the work of Searle and Beechey).

158. In the experiments of Tsuchida and Uchida (579), a comparison was made between the radiosensitivity of the dictyate oocytes and of spermatocytes in diplotene and mid-pachytene. Gamma-irradiated (300 R) female mice (2-3 months old) were killed 1 and 5 days after irradiation and the oocytes collected cultured *in vitro;* they were then processed for the scoring of aberrations at metaphase I. (No hormonal treatments were administered to stimulate oocyte maturation or superovulation.) The results showed that there were no significant differences in the frequencies of abnormal cells at the two time intervals (18.9 per cent compared with 21.6 per cent; number of cells analysed, 366 and 352). At the first interval, the frequencies of chromatid interchanges, fragments and chromatid breaks were respectively 4.4, 7.4, and 10.7 per cent. At the second interval, the comparable frequencies were 6.3, 9.1, and 8.8 per cent. Thus, in terms of both the overall frequencies of abnormal cells and of the kinds of aberrations, the dictyate oocytes were found to be somewhat less sensitive than mid-pachytene spermatocytes (see paragraph 151).

159. Brewen, Payne and Preston (58) irradiated female mice 2-3 months old with x rays and used hormonal treatments to induce superovulation. Attention was focused on (a) correlating the yield of aberrations with the time interval between irradiation and ovulation, (b) studying the relationship between exposure and the yield of aberrations at the time interval in which highest frequencies of aberrations were observed, and (c) estimating the frequency of translocation heterozygotes in the F_1 progeny of irradiated females from cytogenetic observations on irradiated oocytes. Data on the first problem are given in table 24. It can be seen that the frequency of interchanges is low at the 1-, 3- and 5-day intervals, increases 6-fold at the 7-day interval and finally reaches a peak at the 14-day interval followed by a decline thereafter. The observation that very few interchanges are recovered with 1-, 3- and 5-day intervals is in accordance with the results of Gilliavod and Léonard (192, 193; 1-day interval). The variation in yield of aberrations as a function of time between irradiation and ovulation agrees well with the variation in sensitivity to dominant lethal induction over the same time period (458, 513).

160. Results that bear on the exposure-frequency relationship obtained in the above study are given in table 25. Only the 14-day interval was used. It can be seen that the frequency of chromatid interchanges increases faster than linearly with the exposure, indicating a significant two-track component. An examination of whether or not the distribution of cells with various numbers of interchanges fit a Poisson distribution revealed that the fit was good at all the exposures except at 300 R where there was an excess of cells with two interchanges and a deficit of those with one interchange. The authors attribute this deviation to the low numbers of cells scored.

161. At the 300-R level, 50 metaphases were stained for C-bands and analysed. Of the 11 interchanges found, 5 had two centromeres on one chromatid plus an acentric fragment and were classified as asymmetrical interchanges. The other 6 were classified as symmetrical interchanges since each chromatid had a single centromere. Thus, these very limited preliminary data indicate that the two interchange events are recovered at the 14-day interval.

162. The 400-R data were used to estimate the expected proportion of oocytes carrying a balanced translocation (that will be transmitted) as well as the amount of dominant lethality that will be generated. The assumptions used were the following: (a) symmetrical and asymmetrical interchanges occur at about the same frequencies; (b) there is no preferential segregation of exchange or non-exchange chromatids into polar nuclei; (c) the inclusion of any deleted chromosome, dicentric chromosome, or duplication deficiency in the mature ova will result in dominant lethality. Of the 100 metaphase-I oocytes analysed, 36 had no visible aberrations; 18 had a single isochromatid break or, rarely, a chromatid deletion; 19 had a single interchange; 6 had a single interchange plus a single deletion; and 8 had two interchanges. The remaining 13 cells contained three or more aberrations (exchanges and/or deletions) and were not considered in estimating the frequency of transmissible translocations; however they were included for calculating dominant lethality.

163. The estimated frequency of transmissible balanced translocations was 1.8 per cent; if the same calculations were made for the 300-R data, the predicted recovery rate was 0.6 per cent, in very good agreement with the observed rate recorded in the genetic tests of Searle and Beechey (513): 4 out of 680 progeny of irradiated females (0.6 per cent) given 300 rad 1-42 days prior to conception (para. 166). The predicted dominant lethality at the 400-R level was about 43 per cent, consistent with the figure of 35 per cent post-implantation mortality (although somewhat lower than that of 59 per cent total dominant lethality) recorded in the experiments of Searle and Beechey (table 17) after 400 R given to females 21 days before conception.

164. The experiments of Searle and Beechey (513) were designed to study the induction of reciprocal translocations in oocytes. In one set of experiments, mature

females were irradiated with 300 rad of x rays and mated after irradiation. Up to two litters were produced before sterility ensued. The sons were tested for fertility by mating to outbred females, and the method of Carter *et al.* (84) was used for fertility diagnosis. The daughters were crossed to males and those giving small litters (less than 9 in the first, less than 12 in the first two) were allowed to continue breeding, further tests for fertility being performed in their offspring. The production of 12 or less new-born in three litters was considered as presumptive evidence for semi-sterility. The diagnosis of translocation heterozygosity (or XO condition) in these tests was cross-checked by making appropriate chromosome preparations. As in the experiments of Gilliavod and Léonard (193), meiotic preparations of the oocytes of irradiated females (100 and 400 rad) were also made and screened for exchange configurations, fragments etc.

165. The second set of experiments involved exposure to 0.7-MeV fission neutrons (100 and 200 rad; 49-55 rad/min). Mature females were irradiated and both sons and daughters were tested for fertility as before. In addition, sons and daughters of females exposed *in utero* to fission-neutron irradiation in an earlier study of Searle and Phillips (514) (108.5 rad with 20.5 R gamma contamination: exposure period of about one week to pregnant females between days 0.5 and 11, post-coitum; oogonial irradiation) were also tested for fertility by the same methods as described for the x-ray experiments.

166. The results showed that 0 out of 386 sons of females given 300 rad of x rays showed evidence of semi-sterility or translocation heterozygosity, but 9 out of 294 daughters were diagnosed as semi-sterile because of the small size of their litters. Further tests led to good evidence for translocation in 3. In the others, the semi-sterility was not proved heritable. At least one of these probably carried a translocation but the induction of XO females or other causes seemed more likely to be responsible for the low litter size in the rest. The frequency of translocations that can be estimated from the total data (sons and daughters combined) is 4 out of 680, or 0.6 per cent, at 300 rad. Correcting for the spontaneous frequency (3/1443 when contribution by both males and female gametes is considered or 1.5/1443 for females; see Lüning and Searle (302)) and assuming linearity, this would correspond to a rate of $0.16\ 10^{-4}$ rad^{-1} per gamete. This rate is roughly one half of that estimated in the male for spermatogonial irradiation.

167. Examination of oocytes at metaphase I during the first and third week after irradiation with 100 and 400 rad of x rays revealed both multivalents (some of the ring quadrivalent type) and fragments. The aberration frequency in oocytes rose with dose and, at the 400-rad level, with time after irradiation, reaching a maximum of 10 per cent multivalents and 22 per cent fragments in the third week. As was mentioned earlier under "dominant lethals in female mice" the increase in levels of chromosomal damage with dose and time after irradiation was reflected in dominant lethals after the same radiation-conception intervals and doses.

168. In the neutron experiments (513), no evidence for the induction of translocations either in maturing oocytes or in oogonia was obtained, although there were indications for X-chromosome loss. However, sample sizes were small.

169. In the work of Krishna and Generoso (267a), a total of 288 female mice 11-17 weeks old received 300 R of x irradiation and were divided into four groups. Females from the first group were caged with males immediately after irradiation, while females from the other groups were caged with males on the 5th, 11th and 15th day after irradiation. They were kept together until the females ceased to produce young. With the radiation exposure used, 24 females from the first group and 12 females from the second (caged on the 5th day post-irradiation) produced two litters, while females in the other two groups produced only one litter.

170. Both male and female progeny are being tested for translocation heterozygosity. The currently available results from tests of 800 male progeny show that 4 (0.5 per cent) were partially sterile and 2 (0.25 per cent), completely sterile. The four partially sterile males were cytologically confirmed as translocation heterozygotes, and tests on the sterile males are not yet complete. Even if comparisons are restricted to partially sterile males only, these results indicate a significant induction of heritable translocations in dictyate oocytes that were recovered in male progeny (4 in 800 compared with 1 in 4392 in controls). These results may be compared with those of Searle and Beechey (513 and para. 166), who failed to find any translocation heterozygotes in 386 sons of female mice given 300 R. However, there is no statistically significant difference between the two sets of data ($P = 0.2$ by Fisher's exact test).

9. Other species

171. In the 1972 report, the data of Lyon and Smith (313) on translocation induction in pre- and post-meiotic germ-cell stages of golden hamster, guinea-pig and rabbit were presented and compared with those obtained in the mouse. The results showed that (a) translocations are induced in the spermatogonia in all the experimental species although the dose-effect relationship differs from that in mice; (b) in both rabbits and guinea-pigs, the overall dose-response curves are humped, as in mice, but the peak incidence occurs around doses of 200-300 rad (compared with 600-800 rad in mice); (c) the pattern of translocation induction in the post-meiotic male germ cells of the golden hamster (after 200 rad x irradiation) resembles that of the mouse showing (in the limited data then available) that spermatids are more sensitive than spermatozoa.

172. More data have now become available not only for the three species mentioned in the preceding paragraph, but also for the Chinese hamster and the marmoset. In addition, the available cytogenetic data derived from studies on translocation induction in human spermatogonia have also been published.

(a) *Post-meiotic cells*

173. Cox and Lyon (122) irradiated adult male golden hamsters with 200 or 600 rad of x-irradiation and mated them to females for four successive weeks; similarly,

adult guinea pigs and rabbits were exposed to, respectively 600 rad and 100 to 600 rad of x rays and likewise mated to females. The male offspring collected from these matings were cytogenetically screened for the presence of translocations; in the case of the golden hamsters irradiated with 600 rad, the F_1 female progeny were also kept and tested for the presence of translocations by examination of their male progeny.

174. After a dose of 200 rad to golden hamsters, the yield of translocations increased from week 1 to week 3 and fell in week 4 (1.5, 2.0, 6.4 and 3.9 per cent; the number of animals tested were, respectively 66, 50, 47 and 51). After 600 rad, there appeared to be a similar pattern but with higher yields, but the number of offspring obtained from matings in weeks 3 and 4 was very low. The pattern was roughly the same in tests of female F_1 progeny. In the guinea-pig too, there was a similar pattern of translocation induction after 600 rad, but again the number of animals tested was too small to make accurate estimates. In the rabbit, although translocations were found, too few offspring were tested, and precise estimates of the pattern of sensitivity change are not possible. Averaging the data over all weeks and doses, Cox and Lyon established a tentative rank order of sensitivity of the post-meiotic cells of the different species, taking into account the earlier mouse data. This is as follows: mouse > rabbit > guinea-pig > hamster.

175. Comparing these translocation data with those on dominant lethality collected in the same experiment (by the litter-size reduction criterion), the authors found that (a) the yields of both translocations and dominant lethals induced in spermatozoa were higher in the mouse than in guinea-pig; (b) in the golden hamster, the litter-size reduction was as high as in the mouse, but the translocation yield appeared lower. These comparisons suggest, as was mentioned in the 1972 report, that at present there are no sure grounds for extrapolating from one stage or type of genetic damage to another and from one species to another (see paragraphs 23 and 105, Annex E, 1972 report (589)).

(b) *Spermatogonia*

176. Our knowledge on the sensitivity of spermatogonia of mammals other than the mouse to the radiation induction of reciprocal translocations has considerably expanded since the publication of the 1972 report, in which the available data on guinea-pigs, rabbits and golden hamsters were reviewed. Additional information for those three species and new data for the rat, Chinese hamster, rhesus monkey, marmoset and man have now become available.

177. In work which is essentially an extension of that reported in an earlier paper (313), Lyon and Cox (309) investigated the response of the spermatogonia of the guinea-pig, rabbit and the golden hamster to the induction of reciprocal translocations. Adult male golden hamsters, guinea-pigs and rabbits aged 3, 6 and 9 months respectively, were given single acute x-ray exposures in the dose range 100-600 rad (88 rad/min; part-body exposures). After the irradiation, the animals were left for varying periods of time (3-7 months for the golden hamster, and 3-9 months for the guinea-pig and rabbit) to allow for recovery of spermatogenesis, after which cytological preparations were made of the testes of these animals.

178. The data that bear on dose-effect relationships are summarized in table 26 along with those of Brewen and Preston (54) for the guinea-pig and Chinese hamster. (In the latter case, young male guinea-pigs were whole-body irradiated and Chinese hamsters were given part-body irradiation; no details of when the testes preparations were made are given.) It can be noted that, in the experiments of Lyon and Cox (309) the frequency of translocations in guinea-pigs and rabbits increased with dose up to 300 rad and then declined sharply giving an overall humped curve, as in the mouse. (A similar increase is observed in the data of Brewen and Preston for the guinea-pig and the Chinese hamster, but the data at higher doses are not yet available.) The kinetics of increase in the dose range up to 300 rad is consistent with linearity. In the golden hamster on the other hand, although the mean translocation frequencies at all dose levels are higher than in the controls, they are not significantly different from each other, presumably due to a severe distortion of the primary dose-response curve. The net result is a flat-topped curve without any distinct peak. It may be noticed that in this species, the yields of translocations at 500 and 600 rad are higher than those in rabbit and guinea-pig.

179. Using the model $y = a + bD$, the authors estimated the values of the slopes (the b values)[12] up to 300 rad in the rabbit and guinea-pig and up to 200 rad in the golden hamster and found that these were significantly higher in rabbits than in the other two species (definite translocations: rabbit, $(1.48 \pm 0.13)\ 10^{-4}$ rad^{-1} compared with $(0.94 \pm 0.07)\ 10^{-4}$ rad^{-1} in guinea-pigs and $(0.93 \pm 0.09)\ 10^{-4}$ rad^{-1} in the golden hamsters; definite plus possible translocations: rabbit, $(1.70 \pm 0.14)\ 10^{-4}$ rad^{-1} compared with $(1.10 \pm 0.10)\ 10^{-4}$ rad^{-1} in guinea-pigs and golden hamsters).

180. Lyon and Cox (309) compared their data with those obtained in the mouse by other authors (163, 280, 353), who also found that the dose-effect relationship up to doses below the peak of the humped curve was consistent with linearity; that showed that irrespective of whether the data were expressed in terms of translocations per cell or proportion of cells with translocations, the slopes of the mouse lines were higher, except for the comparison of rabbit data with the mouse data of Léonard and Deknudt (280). In the latter situation, the slopes (rabbit, mouse) were not significantly different. On the basis of all these, it can be concluded that in the dose range up to 300 rad, the rank order of sensitivity is golden hamster $\cong$ guinea-pig $<$ rabbit $\leqslant$ mouse.[13]

[12] The slopes estimated are for translocations per cell; "possible translocations" refers to cells containing a configuration which resembles a multivalent, in size and shape but in which the individual chromosomes are not distinct; "definite translocations" are those in which the identification is unequivocal.

[13] The authors' conclusion: golden hamster < guinea-pig < rabbit < mouse.

181. The results of Brewen and Preston (54) for the guinea-pig (table 26) show that at comparable exposures, their frequencies are higher than those of Lyon and Cox (309); the frequencies in Chinese hamsters are roughly similar to those recorded for the mouse by Preston and Brewen (419).

182. Gilliavod and Léonard (191) compared the induction of translocations in mouse and rat spermatogonia after an x-ray exposure of 300 R and found similar yields in both species. Lyon *et al* (314) and van Buul (70) have recently published some data on the induction of translocations in the spermatogonia of the rhesus monkey *(Macaca mulatta)*. The experiments of Lyon *et al.* were carried out on two colonies, one maintained in Birmingham, England (United Kingdom) and the other in Rijswijk (the Netherlands), whereas those of van Buul were on the latter colony only. The animals were irradiated (testicular exposures) unilaterally or bilaterally with x-ray doses of 100, 200 and 300 rad (about 63 rad/min for the English monkeys and 30 rad/min for the Dutch monkeys). The recovery of the testis from radiation injury was monitored by volume measurements and biopsies at different intervals after irradiation. The data are presented in table 27.

183. It can be seen that (a) there are between-colony, between-monkey and between-testis variations in the response to the induction of translocations; (b) when the pooled data of Lyon *et al.* as well as those of van Buul are considered, the dose-effect relationship suggests a peak at about 200 rad, but the differences in frequencies between the different doses are not statistically significant; and (c) the frequencies of translocations are clearly lower than those observed in the mouse (see table 21 for the latter). The authors noted that monkeys of both colonies showed seasonal variation in spermatogenesis and in addition, some monkeys of the Birmingham colony were not in breeding condition. The effect of this seasonal variation on the yield of translocations is not known but in any case could explain some of the variation in response observed between the different monkeys.

184. Brewen *et al.* (57) have now published their complete results on translocation induction in the spermatogonia of the marmoset and man. Mature marmosets were exposed to testicular irradiation with acute doses of 25, 50, 100, 200 and 300 rad of x rays delivered at high dose rates. At various intervals after irradiation (depending on the dose), bilateral castration was performed and preparations were made by the method of Evans, Breckon and Ford (162) with some modifications. Biopsy material was obtained from nine human volunteers who had received testicular irradiation with x rays at doses of 78, 200 or 600 rad (225). As in the marmoset, the interval between irradiation and sampling varied, depending on the dose. Cytological preparations were made using the same methods as those employed for the marmoset.

185. The results are given in table 28, where mouse data are also presented for comparisons. It can be seen that in the marmoset, peak yields are obtained at about 100 rad and the human data do not exclude such a possibility. Under the assumption that the sensitivity of the spermatogonia of both species is approximately the same and that the yield increases with dose up to 100 rad (and using both sets of data at and below 100 rad), the authors estimated that the average rate is $7.7\ 10^{-4}$ rad^{-1} per cell. A weighted regression analysis performed on the human and marmoset data (the 78-rad point for man and the 25-, 50- and 100-rad points for the marmoset, all considered together), assuming that the regression passes through the origin at zero dose, gives a good fit ($P = 0.2$) to the equation $Y = (6.94 \pm 0.92)\ 10^{-4}\ D$; however, the data also fit ($P = 0.1$) the model $Y = (7.64 \pm 3.94)\ 10^{-4}\ D - (0.0089 \pm 0.05)\ 10^{-4}\ D^2$, the negative quadratic component not being significantly different from zero ($P = 0.9$) (495). For this reason, the estimate of risks is based on the linear model.

186. It should be pointed out that the primate data, taken as a whole, show considerable heterogeneity (tables 27 and 28). Translocation frequencies obtained in the Rhesus monkey are much lower than those at comparable doses in man and marmoset, while there are discrepancies at the 100-rad level between the two sets of results on the Rhesus monkey. Yet in all these experiments, peak yields of translocations are found at lower dose levels (100-200 rad) than in the mouse. It is impossible to tell at present whether the marked differences in yields between the man and the Rhesus monkey (which are more closely related than man and the marmoset) are due to fundamental differences in radiosensitivity (akin to those already established within rodents) or just artefactual, in view of the limited amount of material and possible differences in techniques or irradiation and scoring (314).

187. Under these circumstances, it has been decided to use data from man and the marmoset (which are in close agreement) for the purpose of risk estimation. It should be stressed, however, that the amount of direct information on man is still very limited (table 28), so that any estimate derived from it must be regarded as only approximate. It should also be noted that this information would suggest that human germ cells are about three times as sensitive as those of the mouse with respect to translocation induction in spermatogonia, while the latest information (41) suggests approximately equal sensitivity with respect to the induction of dicentrics in lymphocytes in these two species.

(c) *Fractionation effects*

188. Experiments similar to those carried out in the mouse to study the effects of dose fractionation on the response of spermatogonia to the induction of reciprocal translocations have now been conducted in two other mammalian species, the golden hamster and the guinea-pig (308). The fractionation régimes chosen were similar to those already investigated in detail in the mouse. Male guinea-pigs were irradiated with a total dose of 400 or 600 rad of x rays given in 2 equal fractions separated by either 24 h or 8 weeks; in another series, a total dose of 600 rad was administered in 12 fractions of 50 rad at weekly intervals. In parallel experiments, golden hamsters received 400 rad divided into 2 equal fractions separated by either 24 h or eight weeks. In addition, total doses of 400 or 600 rad were delivered in

8 (or 12) 50-rad fractions delivered a week apart. The time interval between irradiation and cytological examination depended on the species and the fractionation procedures employed, but were similar to those used for single doses (309).

189. The results obtained are given in table 29 along with data collected at pertinent single exposures to facilitate comparisons. Considering first the data on 24-h fractionation, it can be seen that in both species the yields are higher than after single doses of comparable size. Statistically, the yields after fractionated exposures did not deviate significantly from those predicted by extrapolating the curves for single exposures (up to 200 rad in hamster and up to 300 rad in guinea-pigs) to higher doses. The estimated slopes for both the guinea-pig and golden hamster are the same, $(0.93 \pm 0.07)\ 10^{-4}\ \text{rad}^{-1}$. These results show that the situation after fractionation is the same as after unfractionated exposures. (The authors, however, considered that the guinea-pig was more sensitive than the golden hamster after single exposures up to 300 rad, and therefore the situation after fractionation was construed as being different.)

190. Turning now to the data obtained with fractionation at 8-week intervals, it can be seen that the yields are again higher than after unfractionated total doses of comparable size; however, at both the dose levels, 400 and 600 rad, the yields are lower than those obtained after 24-h fractionation, i.e., the yields are lower than those expected from additivity of the effects of the dose fractions. These differences (24 h compared with 8 weeks) are significant only for the guinea-pig at the 600-rad level. It may also be noticed that in the guinea-pig, the yield after 2 X 300 rad (8-week interval) is nearly the same after 2 X 200 rad (8-week interval), which in turn is similar to that in the golden hamster under the same conditions.

191. The finding in the mouse (420) that successive 400-R x-ray fractions to mouse spermatogonia (up to a total of 2800 R, separated by 8-week intervals) resulted in yields consistent with the additivity of effects of individual fractions favour the view that the 8-week interval is long enough for the spermatogonial cells to return to normalcy. In contrast, in the guinea-pig and the golden hamster, the translocation data as well as those on the lengths of the sterile periods observed in the 8-week fractionation series support the notion that such normalcy is not restored in these species within this interval of time.

192. In both the guinea-pig and the golden hamster, the results of multiple small fractions show that the translocation yields are much lower than those expected by extrapolation of the dose-response line for single exposures (up to 300 rad) to higher doses. In comparing these results with those obtained in the mouse with similar fractionation régimes, it should be borne in mind that although the total doses are the same (600 rad), in the case of the mouse, this dose point is still on the ascending part of the dose-response curve, whereas in the other two species, it is beyond the dose of peak yield. In the mouse, the yield after fractionation (12 X 50 rad) is roughly half that obtained after a single unfractionated dose of 600 rad (316); in the golden hamster, the yield after 12 X 50 rad is roughly twice that after the single dose of 600 rad; and in the guinea pig, after similar fractionation (600 rad) the yield is about six to eight times higher than after the unfractionated dose. Thus it appears that the response after fractionated small doses is dependent on whether or not the total dose administered is on the ascending or the descending part of the curve. Further data for the mouse using total doses greater than that which gives the maximum yield for single exposures administered in small fractions as above are required to confirm this suggestion.

10. Types of translocation and their effects on fertility and viability

(a) *The mouse*

193. From earlier work reviewed in the 1972 report it is known that (a) certain autosomal translocations recovered from treated post-meiotic male germ-cell stages may be fully viable in the heterozygous state and yet lead to male sterility through failure of spermatogenesis; (b) such failure may not be specific to a particular stage or cell type but occurs with variable incidence throughout the meiotic process and possibly at earlier steps in the germ-cell sequence and (c) all the known X-autosome translocations also cause sterility with failure of spermatogenesis and small testes.

194. Lyon and Meredith (310) found that in translocation lines where males were sterile, virtually all of the quadrivalents were chains rather than rings, in contrast to the "semi-sterile" lines in which almost two thirds were rings. The same tendency can be found in the data of Léonard and Deknudt (281) on translocation induction by post-meiotic irradiation. Searle (505), who analysed the data of Léonard and Deknudt (281) for single translocations, found that in those males with few or no spermatozoa, the frequencies of chain configurations (quadrivalent or trivalent) were almost twice that in males which had no obvious shortage of spermatozoa. Furthermore, there was a positive correlation between the severity of the sterility effect and the frequency of chain quadrivalents, the latter being 99 per cent when the sperm count was nil (507). In the F_1 males that were derived from post-meiotic germ-cell irradiation and which had enough sperm, the proportion of multivalent associations of the chain type (44.9 per cent) was decidedly higher than that found after spermatogonial irradiation (23.6 per cent), as calculated from previous results of Léonard and Deknudt (280). Thus there is evidence for a selective process which effects the frequency of chain quadrivalents and also for a qualitative difference between the types of translocation observed after post-meiotic and pre-meiotic irradiation.

195. Cacheiro *et al.* (73) made histological and cytological analyses of the testes of 42 sterile sons of males treated with ethyl methanesulphonate (EMS), butylated hydroxytoluene (BHT) plus EMS, or 200 R of x rays (treated germ cells: spermatozoa and spermatids). A very high percentage (36 out of 42) of these males carried chromosome aberrations and a majority of them carried translocations. While translocations are impli-

cated to explain partial sterility (which results in the death of the offspring of the carrier) and complete sterility (where the effects are on the carrier himself) the data of Cacheiro *et al.* (73) show that this difference is not due to single versus multiple translocations. The evidence indicates that the difference between translocations that cause sterility and those that cause partial sterility may be correlated with the position of the break points as revealed by cytological evidence: translocations that cause sterility in males appear to be those in which at least one of the breaks occurs close to one end of a chromosome (position effect). A similar suggestion, namely that breakage in or near centromeric heterochromatin is associated with male sterility, has been made by Searle (507).

196. These suggestions have now been confirmed, as shown by the recent results of Cacheiro *et al.* (74). In this work, 30 sterile F_1 sons of x-irradiated males were studied, 12 of which were derived from irradiated spermatids (158 F_1 males tested) and 18 from treated spermatogonia (4286 F_1 males tested). Cytological analyses were carried out in mitotic metaphases from dividing spermatogonia (orcein staining), kidney cultures (quinacrine and Giemsa banding techniques) and in meiotic cells at diakinesis wherever spermatogenesis proceeded to that point or beyond. Of the 12 sterile males derived from spermatid irradiation, 10 were found to carry reciprocal translocations as determined by banding (with 7 of these also revealed by conventional staining through the presence of a small marker chromosome): 2 of these had Y-autosome translocations and two others had two autosomal translocations each. Except where the Y was involved, at least one of the breaks in each male was close to the centromere (c) or telomere (t); in fact, all but two of these males had c/t-type translocations. Wherever diakinesis could be studied, it was found that only a small number of multivalent configurations were of the ring-IV type, in keeping with the breakpoint locations near chromosomal ends. Such c/t-type translocations often lead to long and short marker chromosomes and seem especially liable to give rise to viable tertiary trisomies which are usually sterile in the male (though not in the female) and may have specific abnormalities (310, 507).

197. In sterile sons derived from irradiated spermatogonia, however, only 4 out of 18 had translocations and, although at least one break was near a chromosomal end, none was of the c/t type. It thus appears that sterility here may be predominantly due to causes other than reciprocal translocations with near-end breaks; possibly small deficiencies or point mutations could play a role.

198. It is worth pointing out in this context that Jacobs *et al.* (248), who analysed the breakpoints of structural rearrangements in man (lymphocyte cultures, quinacrine and/or Giemsa techniques), noted that within chromosome arms there appeared to be an excess of breaks in the terminal regions, an excess of c/t translocations where ascertainment was through a balanced carrier, and a possible excess of terminal/median translocations where ascertainment was through an unbalanced carrier. The authors, however, were careful to point out that there might be observational biases. Similar observations showing an excess of breaks in the terminal region of chromosomes have been made by other human cytogeneticists (278, 580).

199. Although most of the translocations causing sterility in mice have been recovered from treatment of males, especially of post-meiotic stages, there is now evidence that such translocations could also be obtained from irradiation of oocyte stages of female mice (513).

(b) *Other species*

200. Among experimental mammals, most of the information thus far available on properties of reciprocal translocations has been collected from studies with mice. The work of Cox and Lyon (123) extends such information to guinea-pigs, golden hamsters and rabbits. These investigators made a cytological study of translocations induced by post-meiotic male germ-cell irradiation in the F_1 (and in some cases in the F_2) sons of irradiated males. It was found, as in the case of the mouse (see review by Léonard, 279) that the frequency of spermatocytes displaying multivalent configurations varied with the translocation, but the average percentage appeared to depend on the species, the latter being 57 per cent in the case of the hamster and 83 per cent in the case of the guinea-pig; too few rabbits were examined to make meaningful estimates of the kind or the average frequency of multivalents. Chain quadrivalents were more abundant than ring quadrivalents at meiosis for the guinea-pig and the hamster, in contrast to the mouse. An attempt was made to estimate the size of chromosomes involved in the various translocations from the size of the multivalent configurations in each of the animals. It appeared that in the hamsters, the longest, one of the shortest, and the X, as well as the long, medium and short chromosomes, had all been involved in translocations, although there was some suggestion that more exchanges tended to take place between the longer than the shorter chromosomes. This is expected if the longer chromosomes present a larger target for the radiation and if the effect of x rays is random. In the guinea-pig, the situation was roughly similar.

201. One possible explanation for the greater abundance of chain quadrivalents in hamster and guinea-pig translocation carriers would be that a greater proportion of breaks were near the ends of the chromosomes than in the mouse; if true, the cause could be in the greater number of chromosome arms (and hence chromosome ends) in these species than in the mouse or in the greater range of sizes of the chromosomes.

202. In all three species, as in the mouse, translocations were found which caused male sterility, due to partial or complete failure of spermatogenesis, although most translocations caused semi-sterility. In the hamster, chain quadrivalents were more abundant than ring quadrivalents of two of the sterile males, and in another sterile male only chain multivalents were obtained. However, translocations which lead only to chain multivalents are not necessarily associated with sterility here, since two other males for which all the quadrivalents were chains proved to be fertile. It is likely that sterility in the hamster is associated with the size of

the chromosomes involved, since the translocations in the four sterile males all involved the longer chromosomes, but more data are needed to substantiate this viewpoint.

203. In the guinea-pig, the situation was nearly the same: only chain quadrivalents were observed in the three sterile males; however three of the seven fertile males also carried only chain quadrivalents. Thus the presence of only chains in this species, as in the hamster, is not always associated with sterility. In contrast to the hamster, sterility here does not appear to be correlated with the size of the chromosomes involved in the translocation. In the rabbit, two of the four translocation carriers were sterile; one of the fertile males carried two translocations and the other, one. Both of them, as well as the two sterile males, carried translocations which involved the longer chromosomes. Hence, there is no evidence here of any association between size of chromosomes involved and sterility.

204. It is instructive to compare these results with those available in man. Only a very few human reciprocal translocations with known breakpoints have been studied at meiosis; however, in those which have been described, a preponderance of ring-IV configurations was found in three male translocation heterozygotes showing a normal spermiogram (98, 99, 100, 166) while chain-VI configurations were found in the majority of spermatocytes from a sterile translocation heterozygote (99). Unequal bivalents, indicative of telomeric breakpoints, occurred in one patient who was a t(Cp– Eq+) heterozygote, and he too was sterile through spermatogenic breakdown (99).

(c) *Embryonic mortality in the progeny of translocation heterozygotes*

205. If the chromosomes involved in a translocation between non-homologous chromosomes segregate randomly at anaphase-I of meiosis, four classes of gametes are produced in the proportion 1:1:2 of balanced normal, balanced-translocated and unbalanced. Thus, about 50 per cent of the zygotes derived from a mating of a balanced translocation heterozygote and normal animal will die. As the number of translocations per cell increase, the proportion of unbalanced gametes will also increase (see for instance table 1 in Ford *et al.*, 170). Mice heterozygous for a single translocation are therefore expected to be semi-sterile whereas those heterozygous for two or more translocations would be expected to show a much higher order of infertility, it not outright sterility, due to death of unbalanced embryos.

206. In their translocation experiments involving irradiated mouse spermatozoa, Searle *et al.* (520) compared the embryonic lethality in the progeny of males with or without detectable types of chromosomal aberrations (mainly translocations). As the data given in table 30 shows: (a) the mean number of live embryos per female in the cytologically abnormal category is less than one-half that in the normal category; (b) the mean number of implants is also markedly reduced by a clearly significant amount. That suggests that some pre-implantation loss is occurring, which may be in part due to reduced fertilization of eggs and in part due to early death of some very unbalanced zygotes. The embryonic survival (in terms of live embryos per female) in those with one reciprocal translocation is 42.4 per cent of the survival in those without detectable abnormality (3.08/7.3). Since a value of 50 per cent is expected with normal disjunction, the observed figure suggests an average level of adjacent-2 disjunction of around 15 per cent (519). However, this must be regarded as an upper limit, for the comparative embryonic survival in terms of the ratio live embryos/total implants is 50.1 ± 1.9 per cent (ratio 369/806 for translocation carriers divided by the ratio 6161/6743 for normal males).

207. Cox and Lyon (123) have presented similar data for the golden hamster and guinea-pig. They found that, in general, both the frequency and the time of embryonic death in the progeny were the same as in the mouse. In the hamster (table 31), although with some translocations, the number of implants per female was lower than in the controls; on the average, the difference was relatively small (10.3 compared with 11.1). However, there was a large increase in the number of small moles among the translocation series, suggesting that for all these males, the death of unbalanced zygotes was occurring predominantly in the early post-implantation period. Thus, the golden-hamster resembles the mouse in this respect (170, 245). Inspection of table 31 will also reveal that among females mated to some males (Nos. 3, 4 and 13) there is a slight reduction in the number of implants which could be due to some excess pre-implantation loss. In 6 of the 7 animals with one translocation, the frequency of post-implantation loss was close to 50 per cent which is as expected if chromosomal disjunction is normal and unbalanced zygotes die; in the single male with two translocations, the post-implantation death was 75 per cent, which again is as expected. The remaining male with one translocation (male No. 8) had a low proportion of embryonic deaths, 34.9 per cent, and the mean number of live embryos in females mated to him was 6.9, or 75 per cent of the control value.

208. In the guinea-pig, the data are limited, most of the results pertaining to 3 of the 7 males tested. In general, the number of implants per female was similar to that in controls, but there was a marked increase in small moles suggesting that here too, the death of unbalanced translocation products occurs mainly in the early post-implantation period. For male No. 6, post-implantation death was 50 per cent, but for Nos. 4 and 9, it was significantly less than 50 per cent. These latter results and similar ones obtained in the golden hamster can be explained on the assumption that one of the unbalanced translocation zygotic types is viable, although other interpretations cannot be excluded. In the mouse, at any rate, there is evidence for the survival of some unbalanced zygotes (89, 310, 334, 335).

11. Summary

209. After spermatozoal x irradiation in mice, the frequency of translocations increases with dose and does not show a decline at high dose levels; this finding is in

contrast to that after spermatogonial irradiation, where the frequency increases with dose up to about 700 rad followed by a decline thereafter.

210. There does not appear to be any significant differences in sensitivity to the induction of translocations between new-born and adult male mice. Contradictory data have been reported with regard to the induction of translocations in the germ cells present in male foetuses 12-13.5 days old, some showing that translocations can be induced and others showing that they are not. In those experiments in which positive evidence has been obtained, the data show that the germ cells in the foetuses are about one half as sensitive as adult spermatogonia.

211. Studies on the induction of translocations in female mice have gained momentum during the last few years. The development of techniques for culturing oocytes has facilitated this line of inquiry. Oocytes derived from irradiated females 14 days after irradiation show the highest response in terms of aberration recovery: the frequency of chromatid interchanges induced in oocytes increases faster than linearly with x-ray dose. The frequency of genetically recoverable translocations (after irradiation of females) predicted from the kinds and number of aberrations observed cytologically are in accordance with one another, at least at the 300-R level.

212. In terms of both the overall frequencies of abnormal cells and of the kinds of aberrations, mid-pachytene spermatocytes (sampled 5 days after irradiation) are more sensitive than dictyate oocytes if the same sampling interval is used; however, if the sensitivity of the latter at the 14-day interval is used, the reverse is true.

213. For the x-ray induction of translocations in post-meiotic male germ cells, the mouse is more sensitive than the rabbit, the latter more sensitive than the guinea-pig, and the guinea-pig more sensitive than the golden hamster. After spermatogonial irradiation, the rank order of sensitivity is mouse $>$ rabbit $>$ guinea pig $\cong$ golden hamster.

214. Human spermatogonia and those of the marmoset appear to be roughly three times as sensitive as those of the mouse for the x-ray induction of translocations. In contrast, the spermatogonia of the Rhesus monkey appear to be less than one half as sensitive as those of the mouse. The primate data as a whole shows considerable heterogeneity. In using the data from marmoset and man for hazard evaluations, the Committee wishes to stress the uncertainties involved; it further notes that the estimate so derived can only be regarded as approximate.

215. In the guinea-pig and the golden hamster, as in the mouse, the effects of dose-fractionation on the yield of translocations (after spermatogonial irradiation) are dependent on the time interval between the fractions and the size of the fractions.

216. In translocation lines where the males are sterile (derived from irradiation of post-meiotic male germ cells in the mouse), there is a predominance of chain quadrivalents in contrast to the semi-sterile lines, which are characterized by a predominance of ring quadrivalents; in addition, there is a positive correlation between the severity of the sterility effect and the frequency of chain configurations, the latter being 99 per cent when the sperm count is nil.

217. With banding techniques, the breakpoints involved in the translocations that were recovered have been localized. In male-sterile translocations obtained from post-meiotic germ cell irradiation, at least one of the breaks was close to the centromere (c) or telomere (t) and the majority of the translocations were of the c/t type. In sterile sons derived from irradiated spermatogonia, however, this was not the case.

218. Apart from the qualitative difference between translocations recovered from irradiated post-meiotic versus spermatogonial cells, there is also a quantitative difference in that, in semi-sterile sons, there are more ring than chain quadrivalents after spermatogonial irradiation, whereas the reverse is true after post-meiotic germ-cell irradiation.

219. In the golden hamster and the guinea-pig, in translocation lines in which male semi-sterility is found (derived from post-meiotic germ-cell irradiation), chain quadrivalents are more abundant than ring quadrivalents, in contrast to the situation observed in the mouse (see paragraph 216 above).

220. In the golden hamster, guinea-pig and rabbit, although most translocations recovered from post-meiotic germ cell irradiation cause semi-sterility in males, there are some which cause male sterility; in the hamster, sterility is not necessarily associated with translocations leading to chain multivalents, and the situation is the same with the guinea-pig. In the hamster, sterility seems to be associated with the size of the chromosomes involved in the translocation (involvement of longer chromosomes) but this is not true in the guinea-pig or rabbit.

C. INVERSIONS

221. Roderick (436) and Roderick and Hawes (438) have published the results of a continuing study concerned with the identification, recovery and genetic properties of chromosomal inversions in mice. (Earlier work by the authors was reviewed in the 1972 report (589) in paragraphs 126-132 of Annex E.) So far, 26 paracentric inversions have been induced (by x rays or other mutagenic agents), out of which 18 seem to be simple autosomal ones, with almost no deleterious effect on viability. In animals homozygous or heterozygous for any two inversions on different chromosomes, there was no significant lowering of reproductive performance. However, there were two instances in which the animals heterozygous for two inversions on different chromosomes were sterile (437).

222. Using inversion In(1)1Rk on chromosome 1 (earlier designation, In(13)1Rk), which has now been demonstrated to be about 43 cM long (3.5 per cent of the genome), Roderick (436, 437) has uncovered two

recessive mutations in a sample of 400 chromosomes tested. One of them causes lethality at various stages of embryonic development and hours after birth. The other mutation may be allelic with the *leaden* (ln) locus.

223. In the course of an experiment designed to measure sex-chromosome loss after x-irradiation of spermatogonia, L. B. Russell *et al.* (454) found, within the presumed X^MO (i.e., paternal loss) class, a female that had a submetacentric chromosome in a complement of 39. Further genetic and cytological work showed that the submetacentric segregated independently from the 39-chromosome (XO) condition, indicating that the abnormal chromosome was wholly autosomal. Meiotic preparations from animals heterozygous for the submetacentric failed to yield multivalent configurations and had only 20 bivalents. Since the short arm of the metacentric is of considerable length, multivalent configurations would be expected, if the abnormal chromosome were the result of a reciprocal translocation. A pericentric inversion was, therefore, suggested by this finding. The suggestion has been tentatively confirmed by the results of cytological banding studies which indicate that the affected chromosome is No. 8. A breeding stock has now been established, and homozygotes have proved to be viable and fertile. Current attempts are directed at introducing chromosome-8 markers in order to determine the effects of the presumed inversion on recombination. The submetacentric may prove to be a useful cytological marker chromosome.

224. Evans and Phillips (161) recently reported on the finding of an X-chromosomal inversion among the descendants of a male that had been exposed to a fractionated dose of x irradiation (12 X 50 rad separated by weekly intervals; spermatogonia). It was found associated with Bare-patches *(Bpa)*, a mutation which proved to be sex-linked and male-lethal (509). The original *Bpa*/+ females produced amongst their progeny considerable numbers of XO daughters, all of which were of the rare OX^P type. This enhanced capacity to produce XO progeny was subsequently shown to be separable from *Bpa* and was given the symbol *Fxo* (410). The presence of *Fxo* also suppressed crossing over between *Bpa* and *Ta* or *Blo*, and it was suggested that a structural change of the X-chromosome might be involved; this suggestion has now been confirmed cytologically in *Bpa Fox*/++ animals and shown to be absent from *Bpa*+/++ animals. Consequently, the symbol *Fxo* has now been withdrawn and replaced by In(X)1H in accordance with the standardized nomenclature for the mouse (117).

225. Preliminary observations suggest that this X-chromosomal inversion is a long one, covering about 85 per cent of the physical length of the X-chromosome; the genetic data obtained are consistent with a length greater than 48 cM (the map distance between the markers *spf* and *Blo*). Strong crossover suppression occurs between *Bpa* and *Ta*, between *Bpa* and *Blo* and between *Bpa* and *spf* as well. The latter result indicates that there is crossover suppression on both sides of *Bpa*. In addition, recombination between *Bpa* and either of the markers *Ta* or *spf* leaves In(X)1H on the unmarked chromosome. This evidence implies that *Bpa* lies within the inversion and is separable from it by a double crossover (one exchange on either side of *Bpa*). The frequency of such separation has been estimated to be about 8 per cent. The authors believe that while the occurrence of a double crossover would reduce the efficiency of the use of the inversion in the detection of sex-linked lethals, the inversion may still prove useful in experiments aimed at estimating rates of induction with more accuracy than has hitherto been possible.

D. TANDEM DUPLICATION

226. In the course of studies on induced mutations involving the mouse haemoglobin loci, L. B. Russell *et al.* (460) found the daughter of an x-irradiated female (SEC/Rl, Hba^b/Hba^b; Hbb^s c^{ch}/Hbb^s c^{ch}) and an unirradiated male (101/Rl, Hba^a/Hba^a; Hbb^d C/Hbb^dC) whose haemoglobin was not of the usual type by the criteria of electrophoretic pattern (fast-moving band relatively fainter), solubility (low), and crystal pattern. The presumed mutant was also of small stature. The abnormal haemoglobin pattern was not transmitted in backcrossing to SEC/Rl (although the small size was), but was transmitted in backcrossing to 101/Rl, together with the small size. Crosses of the presumed mutant to an albino stock (Hbb^dc/Hbb^dc) yielded offspring which were c^{ch}/c^{ch} in coat colour (instead of the expected c^{ch}/c), possessed the abnormal haemoglobin phenotype, and were of small size. Subsequent cytological analysis by the use of quinacrine banding clearly showed a chromosome 7 which was approximately 20 per cent longer than normal and in which there was a repetition of the bright E band and adjacent sub-bands (D and F). The combined genetic and cytological findings indicate a tandem duplication within chromosome 7 which involves a segment including at least the *Hbb* and *c* loci. The abnormal haemoglobin phenotype is consistent with the presence of two doses of c^{ch} and one of *c*. This tandem duplication, the first recorded in experimental mammals, provides a valuable new tool in mouse genetics, for example, in the study of gene-dosage effects, and has the advantage that involves the *c* locus region, which is well characterized as a result of complementation analysis and also is involved in a number of X-autosome translocations.

E. LOSS OR ADDITION OF CHROMOSOMES

1. Sex-chromosome losses

(a) *Spontaneous rates*

227. L. B. Russell (450) has recently reviewed the results that bear on the spontaneous incidence and rates of induction of numerical sex-chromosome anomalies in mammals. In this paper, among other things, data on spontaneous frequencies which have accrued from the controls of various mutagenesis experiments, from the treated groups of mutagenesis experiments where the anomalous type must have originated in the untreated parent and from the routine maintenance of stocks that carry X-linked markers have been compiled. They show that for maternal X-chromosome losses (scored as OX^P

exceptions), the overall average based on 49 176 females in these various sets (excluding those in which the pre-existing XO condition was not ruled out) is 0.053 per cent. The corresponding figure for paternal X-chromosome losses (scored as X^MO exceptions), as judged from a comparison of the frequencies of X^MO and OX^P exceptions (in crosses where these could be simultaneously scored), is 5-10 times higher.

(b) *Induction in male germ cells*

228. The complete results of the sex-chromosome loss experiment carried out by L. B. Russell and Montgomery (reported in a preliminary form in the 1972 report) have now been published (450, 457). In this study the incidence of sex-chromosome anomalies after x irradiation of mouse spermatogonia and spermatozoa was studied. A 600-R x-ray exposure was used, delivered either singly or in two fractions, 100 R and 500 R, separated by a 24-h interval. The breeding scheme involved crossing irradiated or control (101 X C3H)F_1 males to females homozygous for the dominant sex-linked gene, Greasy *(Gs)*; this permitted the phenotypic detection of paternal or maternal sex-chromosome losses (by the occurrence of X^{Gs}/O or O/X^+ female progeny, respectively), paternal non-disjunction ($X^{Gs}/X^+/Y$ progeny) and certain translocations. All exceptional progeny were examined cytologically and through breeding tests. Mothers of presumed XO progeny were likewise tested. It turned out that in 9 out of 14 cases of O/X^+, there was a pre-existing XO condition indicating the importance of performing such tests.

229. The results obtained confirmed the conclusions reached in the 1972 report, namely, that (a) there were no significant differences between the effects of single or fractionated exposures; (b) after spermatozoal radiation (pooled data of the single and fractionated exposure series), 2 exceptional females were recovered among 421 offspring (0.48 per cent); there was none in the controls. The induction rate (on the assumption of linearity) is therefore 0.8 10^{-5} R^{-1} per gamete; (c) after spermatogonial irradiation, the frequency of sex-chromosome loss was 0.20 per cent (16/8155), which is not significantly different from that in controls (0.24 per cent (12/4994)).

(c) *Induction in female germ cells*

230. In the 1972 report, the data of W. L. Russell *et al.* (489) on the induction of X-chromosome losses in female mice irradiated with 400-R gamma rays at exposure rates of 80 R/min and 0.6 R/min were presented. They showed that the frequency was significantly lower at the lower exposure rate. These results have now been confirmed and extended to a lower dose rate of 0.006 R/min and besides, additional data, hitherto unpublished, have become available (450). These are summarized in table 32.

231. It can be seen that (a) the exposure-frequency relationship for the induction of X-losses (in maturing dictyate oocytes sampled up to 6 weeks after acute irradiation) is non-linear, (b) there is a continuous drop in the frequency with the lowering of the exposure rate, and (c) the interval effect which had earlier been documented for the induction of specific-locus mutations is even more pronounced for the induction of X-losses: in mice irradiated with 400 R at 0.006 R/min, the exceptional progeny are almost exclusively recovered from conceptions that occurred during the first 6 weeks followed by a steep decline to control levels thereafter. These data thus confirm the earlier observations with reference to specific locus mutations and extend them to yet another measure of genetic damage. From the standpoint of hazard evaluations, these findings are of great importance: (a) the rate of induction at low exposure rates, such as 0.006 R/min, is extremely low (even after a high total exposure); (b) there is a marked interval effect; (c) after relatively low exposures, such as 50 R, delivered at high exposure rates, the rate of induction is negligible.

2. Non-disjunction

232. In recent years, there has been a growing interest in the study of non-disjunction. The reasons are (a) the increasing realization that non-disjunction is an important cause of spontaneous abortion in man (autosomal trisomies and X-monosomy together constituting over 20 per cent of karyotyped abortuses and over 70 per cent of all those that are chromosomally abnormal (45, 127 and tables 12 and 13)); (b) the findings that about 0.4 per cent of live-born children carry sex-chromosomal and autosomal numerical anomalies (table 11); and (c) the fact that, with the exception of maternal age, the roles of factors affecting the frequency of non-disjunction (including the effects of radiation) are not unequivocally established in our species.

(a) *Mouse*

(i) *Male germ cells*

233. Spontaneous non-disjunction of sex-chromosomes at meiosis in the male mouse is an exceedingly rare event (450, 457, 462). L. B. Russell and Saylors (462) and L. B. Russell (452) used a breeding scheme which would allow the genetic detection of XXY mice as males heterozygous for the sex-linked dominant gene Tabby (*Ta*). Only one such exceptional mouse was recovered from irradiation of spermatocytes (200 R of x rays) in 6214 classified offspring, compared to none in controls.

234. In a cytological investigation with male mice carried out by Ohno *et al.* (384), every one of the 1460 second meiotic metaphase divisions examined contained either a single X or a single Y and not one instance of abnormal segregation which might lead to the formation of XY or O sperm was noted. In a recent cytological study, Szemere and Chandley (558) examined the effects of radiation on non-disjunction in male mice. Mice of the random-bred Q strain were irradiated with 100 or 200 rad of x rays; half of the irradiated animals were killed 5 days after irradiation (to sample metaphase-II cells treated at the pachytene stage of the meiotic prophase), the remainder being killed at 12 days (to sample cells treated at pre-leptotene). In the 200-rad

series, one group of males was killed 43 days after irradiation to sample cells treated as early spermatogonia. Estimation of the irradiation-to-killing intervals was made using timings established earlier for the Q strain of mice (261). Additional experiments at 100 rad involved mating of irradiated males to females, first after 4 weeks for a 1-week period (to sample cells treated as early spermatocytes) and subsequently remating them for another week (to sample late spermatogonia). The pregnant females were killed and dissected when the foetuses had reached 9 days of gestation. It was thought that the foetal age chosen would permit the detection of at least some of the trisomic offspring (168). Appropriate controls were maintained.

235. The estimates of non-disjunction frequencies were made on scores obtained at metaphase-II in control and irradiated groups as the ratio of the number of cells containing 19 and 21 dyads to the number of cells containing 19, 20 and 21 dyads. For each dose and treated stage, 200 cells were analysed. The results showed that in controls there were no hypoploid or hyperploid cells, in agreement with the data of Ohno *et al.* mentioned earlier. In the x-irradiated groups, aneuploid cells were found, particularly in cells treated as pre-leptotene spermatocytes, 12 days prior to scoring. The non-disjunction frequency for this treated stage was 4.5 per cent at 100 rad and 6.0 per cent at 200 rad; the frequencies for other stages were relatively lower. The foetal karyotyping gave no evidence for pure trisomics although some mosaics were present. In addition, and of special interest, was the finding of two triploid ($3n = 60$) foetuses in the treated group; both were from matings in week 5 and could have therefore arisen following the irradiation of early spermatocytes.

(ii) *Female germ cells*

236. Yamamoto *et al.* (626) examined the maternal age-dependence of chromosome anomalies in unirradiated mice. The procedure was briefly as follows: female mice (strain CF 1) were mated at ages of 3-5 months (control), 11-13 months, and 14-16 months to young adult males. On day 10.5, the pregnant mice were sacrificed and the foetuses recovered and analysed cytogenetically. The proportion of aneuploid foetuses was 2/149 in the control, 5/117 in the 11-13 month group and 5/39 in the 14-16 month group. In the young group, both the aneuploids were mosaic monosomies and in the two, the breakdown was 3 trisomies, 1 monosomy and 6 mosaics. The incidence of aneuploidy in the two "old groups" considered together was significantly higher than in controls. However, a comparison of the control with the 11-13 month group alone did not reveal any significant difference in frequency whereas that of the control with the 14-16 month group showed that in the latter it was higher.

237. In a subsequent study, Yamamoto *et al.* (627) irradiated female mice of different ages with 5 R of x rays and conducted a cytological study similar to the one described in the preceding paragraph. Chromosome analyses revealed that the number of aneuploid foetuses was 2 (1.3 per cent), 4 (3.6 per cent), 10 (6.4 per cent) and 7 (16.3 per cent) in the groups, non-irradiated young, x-irradiated young, non-irradiated aged and x-irradiated aged, respectively. The number of foetuses examined in the different groups was 149, 111, 156 and 43, respectively. While the difference in the incidence of chromosome abnormalities between non-irradiated and x-irradiated young adults was not significant, there appeared to be a definite increase in the incidence of aneuploid foetuses in the x-irradiated aged as compared with the x-irradiated young. The authors concluded that the incidence of aneuploid foetuses in aged mothers is further increased by 5 R of x irradiation. Of the 7 aneuploids in the aged group (irradiated) there were 4 trisomies, 1 double trisomy and 2 mosaics (39/40 and 40/41).

238. Gosden and Walters (197) have reanalysed the above data statistically for evidence of interaction between age and x irradiation using three procedures: (a) comparing the appropriate function of the percentages with its standard error; (b) partitioning the three degrees of freedom into an age, irradiation and interaction effect; (c) examining the proportionate increase apparently due to irradiation. None of these tests showed any significant difference of the kind claimed by Yamamoto *et al.* (627). The other objection which Gosden and Walters raise to the conclusion of Yamamoto *et al.* pertains to the fact that the authors have used as controls the earlier published results detailed at the beginning of this section; such a procedure would be open to question in view of possible differences in environmental conditions.

239. Uchida and Lee (582) made use of the recent advances in the technique of culturing mouse oocytes *in vitro* to obtain preparations of meiotic chromosomes (in metaphase II) of oocytes derived from irradiated females. C3H X ICR/Swiss F_1 hybrid females aged 3 and 6 months were exposed to 10, 20 and 30 R of whole-body gamma irradiation; the irradiated females and their paired controls were sacrificed and the ovaries removed within one week of radiation exposure. The oocytes were teased out of the ovaries and those containing a germinal vesicle were incubated in foetal calf serum for 18-23 h to obtain cells in metaphase II and subsequently processed for cytological examination.

240. In a total of 15 713 viable oocytes collected, 1151 and 1054 metaphase-II oocytes (in the irradiated and control groups, respectively) were analysable (428 oocytes at 10 R, 368 at 20 R, and 355 at 30 R). Since there were no significant differences between the two age groups used, the results were combined. Six of the irradiated oocytes had an extra chromosome (i.e., 21 chromosomes), Two of these were in the 10 R series, three in the 20 R series and one in the 30 R series. No hyperploid cells were found among the controls. Assuming that for each oocyte with 21 chromosomes, a complementary cell with 19 chromosomes must have been produced (and formed the polar body) and barring preferential segregation of one type of abnormal product into the polar body, there should be an equal number of hyperploid polar bodies with their complementary hypohaploid oocytes. The total number of non-disjunctional products should therefore be closer to twice the observed frequency of hyper-haploid oocytes, i.e., 12 (1 per cent) among the irradiated oocytes. The

numbers of non-disjunctional events in the sample are still too scanty to permit comparisons between the different exposure levels. From the work of Uchida and Lee, it would therefore appear that non-disjunction can be induced in young females by *in vivo* radiation exposure.

241. Uchida and Freeman (581a) have now performed another experiment on the same lines as that of Uchida and Lee described above, but with the use of older female mice, aged 12 months instead of 3-6 months. The frequency of hyperhaploid metaphase-II oocytes was significantly higher than in controls and was also higher than in young females. The incidence of non-disjunction among aged controls was 0.6 per cent, increasing to 2.7 per cent on irradiation, as compared with a rate of 1 per cent in irradiated young females. The authors consider that these results support the suggestion that the risk of producing trisomic offspring among humans is increased with exposure of the abdomen to diagnostic x rays. They point out that 9 out of 11 epidemiological studies have shown an increase in non-disjunction with radiation exposure, although in some series these increases were not statistically significant.

242. In a genetic study on the effects of maternal age on spontaneous and x-ray-induced (200 R) sex-chromosome non-disjunction and loss in the mouse, L. B. Russell and Montgomery (457a) compared the response of mice about 3 months old with that of mice about 9 months old. The experiments, which are still continuing, have so far generated no unequivocal instances of maternal non-disjunction, although there has been one case of paternal (spontaneous) non-disjunction. In a new series, also still in progress, in which the females are even older (11.5-12 months at the time of irradiation and/or mating), no cases of maternal non-disjunction have so far been recovered (457a, 467).

243. Lüning, Eiche and Lüning (303) conducted some pilot experiments with the CBA strain of mice to check whether or not exposure of females to low doses of x rays induce non-disjunction in oocytes; should this be the case, then the nullosomic and disomic gametes that result from non-disjunction should lead to the production of aneuploid foetuses. Such foetuses, except possibly some trisomies, are expected to die *in utero* and the frequency should be ascertainable under proper conditions. The experimental scheme included (a) irradiated and control females of various ages, with and without a history of having produced a few litters prior to the commencement of the experiments; (b) acute exposures of 2, 4, 8, 12, 16 and 32 rad to females as well as fractionated doses (4 X 4 rad; 2 X 8 rad at 1-week intervals), (c) exposure of foetuses at various times before parturition; and (d) intervals ranging from 0 to 182 days between radiation exposure and mating. The females were killed 11-20 days after mating for uterine examination.

244. The results obtained in this study show that (a) in the irradiated series, there is no excess intra-uterine death at a more or less late stage in development and (b) the age of the females at the time of mating has a considerable effect on the intra-uterine death rate (varying from about 8 per cent in young females to 25-30 per cent in older females) in both the irradiated and control series. It should be pointed out that conclusion (a) cannot be considered a definitive one; in spite of the variety of pilot tests performed, the absolute numbers in any one series are relatively small and this makes it difficult to detect small increases in intra-uterine death.

(b) *Hybrids between the house mouse and tobacco mouse*

245. The diploid chromosome complement of the tobacco mouse, *Mus poschiavinus*, consists of only 26 chromosomes, 14 of which are metacentric (206) in contrast to the all-acrocentric complement of 40 in the house mouse. The fundamental numbers are the same ($2n = 40$), however, and both meiotic (572) and mitotic studies (628) with the two species and their F_1 hybrids have demonstrated that the chromosomes are, in fact, homologous. It is believed that the tobacco mouse metacentrics were derived from acrocentric chromosomes of the house mouse by Robertsonian fusion/translocation. During the last few years, stocks of mice have been constructed each carrying a different metacentric chromosome derived from *M. poschiavinus*. These are being extensively utilized to examine systematically the involvement of specific chromosomes in meiotic non-disjunction and as a good model system to gain an insight into the conditions leading to aneuploidy in mammals, including man.

246. The F_1 hybrids between the house mouse and the tobacco mouse are fully viable, but have greatly reduced fertility. Studies on first meiotic division cells have shown that the seven metacentrics regularly form trivalents with the 14 homologous *M. musculus* acrocentrics. The finding that in the F_1 hybrids more than one half of the metaphase II figures are genetically unbalanced suggests that anaphase-I disjunction is disorderly leading to gametic aneuploidy, which in turn leads to the production of aneuploid inviable zygotes (572). Tettenborn and Gropp (572) suggested that the non-disjunction observed in the hybrids could result either from genetic heterozygosity *per se* or from structural heterozygosity leading to trivalent formation.

247. Cattanach and Moseley (91) found that in males, each of the 7 tobacco mouse metacentric chromosomes when carried heterozygously with the house mouse acrocentrics led to non-disjunction, but the frequency was not the same for each chromosome. In addition, considerable heterogeneity existed between individuals heterozygous for any one metacentric and the non-disjunction frequencies did not appear to be correlated either with chromosome size or centromere position. The authors also obtained some evidence of non-disjunction in metacentric homozygotes, small testis size and reduced sperm production among homozygotes and crossover suppression between the metacentrics and the homologous acrocentrics in heterozygotes. On the basis of these data, they concluded that a large part of the non-disjunction observed when the tobacco mouse metacentrics are carried heterozygously with the house mouse acrocentrics may result not from structural heterozygosity *per se*, but rather from other genic or

minor chromosomal differences which reflects the fact that the chromosomes are derived from two different species.

248. The results obtained by Ford and Evans (169) and Gropp, Giers and Kolbus (204) in the backcross progeny of single metacentric heterozygotes are essentially the same: depending on the metacentric involved, heterozygous males caused different rates of non-disjunction and the estimates based on metaphase-II counts and on karyotying of pre- and post-implantation embryos were in agreement with one another. The work of Gropp, Giers and Kolbus (204) also demonstrated that aneuploidy (trisomy) of the zygotes was considerably more frequent in the progeny of heterozygous females than in those of heterozygous males and has led to the suggestion that this disparity might be the result of a higher non-disjunction rate in female gametogenesis. The authors have entertained the possibility that mechanisms of selection against unbalanced male germ cells might operate on a small scale. Ford and Evans, however, suggest that in their work there was no evidence of selective elimination of spermatids or spermatozoa with unbalanced genomes up to the third day of gestation.

249. So far, all the trisomic conditions reported in this system cause pre-natal death, which in some of them occurs at an early stage (day 10-13) while in others, at a later one (day 14-16), and the developmental profiles differ considerably according to which individual autosome is involved (169, 203, 204, 205). Consistent with this, Ford and Evans found a considerable reduction in the number of trisomic embryos between the earlier gestational period (8-11 days) and the later period (12-15 days). Taken together, these observations with primary trisomics contrast with the findings with partial (tertiary) trisomics (in the house mouse) which may be viable and not infrequently fertile (40, 154, 310). One further finding relates to the observation that very few monosomic zygotes survived to be identified subsequent to implantation in the *M. musculus* X *M. poschiavinus* heterozygotes for any of the metacentrics thus far tested (169).

(c) *A method to measure non-disjunction in the laboratory mouse using Robertsonian translocations*

250. Lyon *et al.* (319) have recently devised a method for measuring non-disjunction in mice using Robertsonian translocations of the tobacco mouse. Since a high frequency of non-disjunction occurs spontaneously in mice heterozygous for Robertsonian translocations (see the preceding section), it was thought that it should be possible to measure this by a method similar to that used for measuring adjacent-2 disjunction in mice with reciprocal translocations. In the latter method, animals heterozygous for the translocation and homozygous for different alleles of a marker gene are mated together. Offspring homozygous (rather than typically heterozygous) for the marker arise through adjacent-2 disjunction (or non-disjunction) and their frequency can be recorded (519).

251. In the scheme of Lyon *et al.*, homozygotes for the Robertsonian translocation are crossed to homozygotes for the chosen genetic market, and the offspring intercrossed. The intercross progeny are tested for the presence of the translocation by biopsy of the testis, spleen or ear skin. By this means a stock homozygous for both the translocation and the marker is constructed. Animals from this stock are crossed to homozygotes for the marker, but not carrying the translocation. All the offspring from these matings will then be heterozygous for the translocation and homozygous for the genetic marker and are used in the experiments. They are mated *inter se* and the young are observed at birth, 7-14 days later, and at weaning for the presence of recessive markers. All such marker-carrying young are tested for fertility and their karyotypes are determined by biopsies of ear, skin or corneal preparations.

252. Using this method, Lyon *et al.*, estimated that the non-disjunction frequencies ranged from less than 5 per cent to about 15 per cent in the different crosses. In addition, the finding that all the marked young were heterozygous for the Robertsonian translocation suggests that the gametes involved are derived from non-disjunction at the first meiotic division. A search for genetic or environmental factors affecting the frequency of exceptional progeny revealed that with one Robertsonian translocation, the frequency increased steadily with increasing maternal age whereas with another, the maternal age of the marked young was not significantly below that of the total progeny.

(d) Microtus oeconomus

253. Another mammalian species which may be potentially useful in the study of non-disjunction, specifically of the sex-chromosomes, is the northern vole, *Microtus oeconomus*. The use of C-banding techniques have shown that in this species with a diploid chromosome number of 30, while all the 14 pairs of autosomes exhibit tiny dots of centromeric heterochromatin, the X-chromosomes have large blocks of these and the Y-chromosome is C-band positive along its entire length (636).

254. In an exploratory study, Tates, Pearson and Geraedts (570) found that in testes preparations processed for C-banding, cells having a single X or Y, two Ys, two Xs and XYs can be identified in early and mid-term spermatids (some of the spermatids were larger in size and appeared to be polyploid). In a subsequent study, Tates (569) irradiated males with 50, 100 and 200 R of x rays and made preparations 1, 2, 4, 8 and 12 days after irradiation. Such a procedure would enable the sampling of cells irradiated as spermatocytes and possibly as spermatogonia (in the later interval series). There is definite evidence for the induction of non-disjunction even at the lowest level of exposure used, but the calculation of the exact frequencies is complicated by the occurrence of great variability between animals within exposure levels, and within and between the different sampling intervals. The author is at present collecting more data.

3. Summary

255. Additional data on the x-ray induction of sex-chromosome losses in mouse spermatogonia that have accumulated since the publication of the 1972

report support the conclusion reached earlier, namely that there is no evidence for an increase in the frequency at which exceptional XO progeny are recovered (relative to controls) after spermatogonial irradiation (600-R level). After spermatozoal irradiation however, the frequency is significantly higher than in the controls.

256. X-chromosome losses can be readily induced by irradiation of mouse females at high dose rates; there is a marked dose-rate effect in that a lowering of the exposure rate from 80 R/min to 0.6 R/min down to 0.006 R/min (total exposure of 400 R) results in a progressive reduction in the frequency. This continuous reduction in frequency with lowered dose rates parallels the results obtained for the induction of specific-locus mutations; in addition, the frequency of X-chromosome losses in conceptions occurring later than a few weeks after irradiation is not significantly higher than in the controls. Thus there is evidence for the operation of an interval effect for this end-point of genetic damage as well.

257. Studies on non-disjunction have been receiving more attention during the past few years. In male mice, the results show that non-disjunction can be induced by irradiation of pre-leptotene spermatocytes. In female mice, although there are indications for the radiation induction of non-disjunction in oocytes, the data do not permit reliable risk estimates to be made.

258. Use has been made of the presence of the seven pairs of metacentric chromosomes in the tobacco mouse to construct mouse stocks carrying known metacentric chromosomes to study the process of non-disjunction in more detail. Although up to now no radiation experiments have been carried out with these stocks, the studies have provided interesting insights into how the frequencies of non-disjunction vary depending on which metacentric is involved, the time of death of the different trisomics and their developmental profiles.

259. A new method has been developed to measure non-disjunction in mice using Robertsonian translocations of the tobacco mouse. This is likely to prove valuable in studying radiation-induced non-disjunction in mice.

260. Attempts are being made to study non-disjunction of the X and Y chromosomes in the males of the northern vole, *Microtus oeconomus*, in which techniques are now available to score for non-disjunctional spermatids derived from spermatocytes and spermatogonia.

F. POINT MUTATIONS

1. Specific-locus mutations in male mice

261. The complete results of the work of Selby (discussed in the 1972 report in a preliminary form, Annex E, paragraph 174) on the x-ray induction of specific locus mutations at the seven loci in the germ cells of male mice of different ages (new-born, and age groups from 2 to 35 days[14] after birth at irradiation) have now been published (526, 527) (table 33). These results, with only a slight increase in the number of progeny tested (over those presented in the 1972 report) confirm the conclusions reached earlier: (a) for new-born mice, the rate is $1.37\ 10^{-7}\ R^{-1}$ per locus, which, statistically, is significantly lower than that of $2.91\ 10^{-7}\ R^{-1}$ per locus for spermatogonia in adults (300-R level for both). The former rate does not significantly differ from the one reported by Carter *et al.* (194) ($1.83\ 10^{-7}\ R^{-1}$ per locus, 200-R level) for 17.5-day-old foetal males; (b) none of the mutation rates in the other age groups was significantly higher than that of the adult, although this conclusion does not rule out the possibility that individual age groups may have mutation rates somewhat different from that of the adult.

262. The combined mutation rate for the nine age groups of young males (day 2-35), $2.63\ 10^{-7}\ R^{-1}$ locus, is significantly higher than that of the new-born males, $1.37\ 10^{-7}\ R^{-1}$ per locus, and almost the same as that of similarly irradiated adults. An examination of the data for the different age groups suggests that the change in mutational response may have occurred by day 8; day 8 has the second-highest mutation frequency of all nine groups. All three age groups before it have lower mutation frequencies than the adult. The mutation frequencies on days 2 and 4 are the lowest found among the nine groups, both being very similar to the rate found for new-born males. The point estimates for the data are arbitrarily grouped according to their indication in table 34, in which estimates for new-born and adult are also shown for comparison.

263. The incidence of clusters of specific-locus mutations following irradiation of new-born males was significantly higher than the cluster incidence reported by W. L. Russell for similar irradiation of adults. This presumably indicates the survival of relatively fewer reproductive cells following irradiation of the day-0 testes. In the other age groups, clusters were found only on day 21 (two clusters of two mutations each). In new-born males, although there were suggestive indications for differences in the distribution of mutations among the loci studied (relative to that in the adults) the differences were not significant: for the other age groups, the distribution appeared similar to that in adults.

264. Cattanach and Moseley (92) investigated the effects of irradiating mouse spermatogonia with a total exposure of 1000 R of x rays delivered in two equal

[14] Between birth and 35 days of age, the testis undergoes many developmental changes, and by 35 days, the cell population resembles that of the adult. Widmaier (609) found that primary spermatocytes were commonly observed 7-8 days after birth in the mouse strain he studied. Some spermatids were present by 20 days and at 25 days, almost all tubules contained secondary spermatocytes and spermatids. At 30 days, the germinal epithelium was fully developed. Widmaier concluded that the first cycle of the seminiferous epithelium begins on day of birth in the mouse and that the cycle proceeds essentially as described by Oakberg (368). Oakberg (369) has shown that the time required for type-A spermatogonia to develop into mature spermatozoa averages 34.5 days in the adult male. However, spermatogenesis has been shown to proceed more rapidly in juvenile rats than in the adult (236).

fractions separated by 4 and 7 days; the yields of specific-locus mutations (at the loci) were compared with those obtained in the experiments of W. L. Russell (472) with single 1000-R exposures, two 500-R exposures separated by 2 and 24 h and two exposures of 600 R and 400 R; 15 weeks apart. These are shown in table 35 from which it can be seen that (a) neither the 4- nor the 7-day interval results in yields which are similar to that of the 24-h fractionation, (b) the frequencies are higher than after the single acute exposure of 1000 R, and (c) the data for the 4- and 7-day fractionation periods are consistent with the expectation of additivity of yields such as that seen in the long-term fractionation experiments of W. L. Russell (472), 600 R + 400 R, > 15 weeks apart.

265. One of the early attempts to screen for biochemical variants induced by irradiation of the mouse was that of Feinstein *et al.* (165) who devised a rapid semi-quantiative screening method for blood catalase; in the progeny of irradiated male mice (derived from W. L. Russell's experiments), the authors observed two with low blood catalase in a total sample of 12 000 mice.

266. A programme designed to study the radiation-induction of haemoglobin variants in the mouse, initiated a few years ago at Oak Ridge is continuing and has produced some interesting results (461, 492). The work consists of screening blood samples of F_1 progeny from experiments in which either 101 or SEC strain mice are x irradiated and mated to non-irradiated mice of the other strain. The parental strains differ from each other for alleles at the *Hba* chromosome 11 and *Hbb* loci chromosome 7. The haemoglobin characters of F_1 offspring analysed included electrophoretic pattern, solubility and crystal pattern. Blood samples were also checked for possible alterations in serum albumin and red-cell lysis.

267. Of a total of 8621 F_1's so far analysed for these characters, 6918, 875 and 828 were derived from irradiated spermatogonia, post-spermatogonial stages and oocytes, respectively. Five haemoglobin variants have been found. Two of these appear phenotypically to be alpha-chain deletions or inactivations, the third a sterile male (with spermatogenic block in pachytene), a result of an independent translocation T(3;16), the fourth a tandem duplication (para. 226) involving *Hbb*, and the fifth presumably carries two No. 7 chromosomes from the 101 mother and none from the irradiated SEC father. No serum albumin mutants were detected and four anaemic F_1's probably did not transmit their abnormality. The authors note that the per-locus mutation rate based on the 3 *Hba* mutants (which may be either small deficiencies or intragenic changes) are not out of line with earlier specific-locus results, although confidence limits are still very wide.

268. Work similar to that outlined above, but using nine electrophoretically detectable markers (*Es*-1, *Es*-3, *Gpd*-1, *Gpi*-1, *Id*-1, *Mod*-1, *Pgm*-1, *Dip*-1 and *Hbb*) is currently underway at Research Triangle Park (321a, 591, 592). Irradiated DBA/2J mice (500 R + 500 R gamma rays, 24 h apart, spermatogonial irradiation) were crossed to C57BL/6J and the F_1 progeny screened by electrophoretic methods for variants. Thus far, 4 mutants (two of which are haemoglobin variants) have been found in 2600 progeny. Work is continuing.

269. In two recent papers, Kohn and Melvold (262) and Kohn, Melvold and Dunn (263) have summarized the results of their x-irradiation mutagenesis studies in mice using the histocompatibility *(H)* system. Before describing the results, it will be useful briefly to review the system and the methodology. This system is comprised by a group of co-dominant histocompatibility genes that are located throughout the genome and on whose action the acceptance or rejection of dermal grafts depends. For operational reasons, the *H* loci are divided into two classes which can be distinguished from one another in the F_1 hybrid of the B6 and C lines that are employed (B6 = C57BL/6Kh; C = BALB/cKh). The class-I loci, 30 in number[15] have different alleles in the parental lines and are therefore heterozygous in the F_1 hybrid. The class-II have similar alleles in the parental lines and are therefore homozygous in the hybrid. The number of class-II loci is unknown.

270. The *H*-test involves five major steps (264, 266): (1) mating of selected parents, one of which can be treated with a mutagen or x irradiated (C♂ X B6♀); (2) skin-graft testing of the F_1 progeny; each animal exchanges one graft with each of two other animals in a "reciprocal circle"; (3) identification of suspected mutants; (4) backcrossing of each of these to a parental line; (5) graft-testing of the resultant backcross progeny to establish the transmission of the suspected mutation.

271. The mutations are classified on the basis of their graft-rejection patterns as "gains" (appearance of a new antigenic specificity, i.e., grafts donated by the putative mutant rejected), "losses" (loss of a specificity, i.e., grafts placed on the putative mutant rejected) and "gains and losses" (one specificity replaced by another, i.e., reciprocal rejection occurs between the putative mutant and other animals). Class-I mutations are distinguished from class-II by their loss or gain-and-loss phenotypes for loci on autosomes and X-chromosomes: class-II mutations could produce only gains unless the Y-chromosome was involved.

272. Male mice (C-line) were x irradiated (60-65 rad/min; 350, 500, 650 and 800 rad acute x irradiation; unequally fractionated doses of 500, 650 and 800 rad) and mated to the B6 line. The F_1 progeny (derived from irradiated spermatogonia) were graft-tested, the mutations identified and subsequently verified as mentioned in the preceding paragraph. The results showed (262) that among a total of 13 614 F_1 progeny, including 11 279 experimental (all radiation groups) and 2335 controls, a single class-I mutation was recovered, which was of the "gain-and-loss" type (in a series in which the male parents were irradiated with a fractionated dose of 300 + 500 rad, 24 h apart). The mutant rejected skin from the C parental line but accepted skin from the B6 maternal line. No class-I mutations were detected in the controls. Four other class-I mutations that were detected (1 loss and 3 gain-and-loss) had occurred in the B6 alleles, i.e., in the unirradiated maternal gametes.

[15] Minimum number of loci at which the B6 and C strains differ (19).

273. In tests for class-II mutations (263), a total of 36 mutants was found, of which 8 were in the controls and 28 in the different irradiated groups. Neither the frequency of mutations in any of the irradiated groups nor the total frequency of mutations recovered was significantly different from the control frequency.

274. The failure to obtain evidence for radiation-induction of histocompatibility mutations is attributed by the authors, not to the failure of the system to detect mutations, but rather to the very low mutability of these loci (relative to the seven or the six loci used in the Oak Ridge and Harwell studies) after radiation exposures. They surmise that this can happen if x-ray-induced histocompatibility mutational lesions are more efficiently repaired or if spermatogonia carrying x-ray-induced histocompatibility mutations fail to result in viable progeny. Obviously, further research is needed. It would be especially of interest to determine if similar results would be obtained after spermatozoal irradiation.

275. In a subsequent paper, using target theory considerations, Kohn (265), estimated the sizes of genes involved in mutation experiments with specific loci in the mouse and in other organisms. The author's main conclusions were: (a) mutation rates tend to be much lower than predicted by target theory; (b) selection and/or repair are major factors that determine the rates; and (c) the mouse seven-loci test, which provides a principal data-base for the standards of human radiation protection, may not provide adequate overall representation of the mutability of the mammalian genome. However, since the author himself points out "estimates of gene size by target theory most likely will be incorrect, depending on the magnitude of balancing of a number of factors", it does not appear profitable to enter into a detailed discussion of this paper. Furthermore, in this report, the Committee has used the specific-locus data from the mouse only in the context of assessing the effect of various physical and biological variables on mutation rates, in the sense they were originally intended to be used (480).

2. Dose-rate effects

276. Lyon, Phillips and Papworth (318) published a paper in 1972 in which they re-examined the published data on dose-rate effects with low-LET irradiation for the induction of specific-locus mutations in mouse spermatogonia besides some new data from Harwell hitherto unpublished. Based on earlier results, the conclusion was that in adult spermatogonia, the maximal effect of reducing the exposure rate is already obtained at 0.8 R/min (namely a reduction of the yield to about 30 per cent of that at high exposure rates), such that a further reduction in exposure rate has no measurable effect. The paper of Lyon *et al.* (318) raises questions about this conclusion.

277. The arguments are as follows: (a) in Russell's work, the mutation rate per unit of exposure at an exposure rate of 0.001 R/min is actually higher than at 0.009 R/min, suggesting an inverse relationship between mutation rate and exposure rate, but the difference is not statistically significant; (b) from work at Harwell, new data (recorded in the paper) at low dose rates have become available, and the same trend towards higher mutation rates at very low dose-rates is observed; (c) when, using all the available data, the induced mutation rates are plotted against $\log_e I$ (where I is the exposure rate), some kind of curvilinear relationship is indicated. Statistically, the data fit well a model in which the mutation rate varies continuously with the exposure rate and in which there is a dose-rate I_{min} at which the mutation rate is minimal. The maximum likelihood estimate of I_{min} is about 0.03 R/min (95% confidence limits, 0.002 and 0.09); (d) although the quadratic model used gives a good fit to the data, the model of zero slope below exposure rates of 0.8 R/min also fits the data; (e) an examination of whether the true relationship is not a smooth curve but rather two independent straight lines, one with a negative slope over the range of 0.001 and 0.02 R/min, and the one with a positive slope thereafter, reveals that the data also fit this model.

278. In the opinion of Lyon *et al.*, the biological basis for two separate mechanisms that might conceivably operate (one on either side of I_{min}) may be related to the number of cell cycles, duration of the irradiation and cell population changes. A relevant consideration may be that the position of I_{min} is such that at exposure rates below it, the period of irradiation necessary in order to give the total dose extends over many cell cycles, whereas above I_{min}, the total exposures are delivered within one cell cycle. Published results of Oakberg and Clark (375) suggest that at a rate of 0.001 R/min, the survival of type-A spermatogonia is much higher than at 0.009 R/min and above. At 300 R, the survival of type-A spermatogonia expressed as experimental/control ratio is 0.372 at 0.009 R/min and 0.846 at 0.001 R/min. The pattern of survival at 0.009 R/min resembles that at high exposure rates (600-R level).

279. The essence of the argument then is that cell killing may be a plausible explanation for the dip in the curve with relatively little depression of the mutation rate due to cell killing at 0.001 R/min and lower rates. At environmental levels of radiation, one might therefore expect a response more similar to the one at 0.001 R/min than at 0.009 R/min (see also Oftedal (383) for a discussion of the problem).

280. The implication of the analysis of Lyon *et al.* for hazard evaluation is this: on the basis of Russell's interpretation that the mutation rate remained constant at exposure rates below 0.8 R/min, it was reasonable to suppose that it would still remain constant at environment radiation levels (0.1 R/year or $1.9\ 10^{-7}$ R/min). This means that for low-dose conditions applicable to man, the assumption that the induction rate is one third of that seen at higher dose rates is justified. On the other hand, if the efficiency of the irradiation increases at very low dose rates, the rate used in risk evaluations should need upward revision.

281. The paper of Lyon *et al.* has been re-examined by W. L. Russell (467, 481). This reanalysis bears out the following conclusions: (a) at rates below 0.8 R/min, the Oak Ridge data for induced mutation rates do show an upward trend; however, the confidence intervals are sufficiently large such that they fit the model of zero slope; (b) the Harwell data at low dose rates show a less

pronounced upward trend if Harwell controls are used to correct for spontaneous rates; furthermore, the confidence limits for the Harwell data are also wide, indeed very wide, for the 0.001-R/min point. Thus there is no firm evidence for a negative slope at lower dose rates.

282. Additional data that have since become available seem to lend support to the earlier conclusion of W. L. Russell that at exposure rates below 0.8 R/min to mouse spermatogonia there is no further significant reduction in mutation rate and that at low exposure rates (0.8 R/min or lower) the induction rate is about one third of that obtained at high dose rates. In experiments specifically focusing attention on the problem of determining mutation rates at very low exposure rates, W. L. Russell and Kelly (486, 487) irradiated male mice with a total gamma-ray exposure of 300 R (^{137}Cs) at rates of 0.0007 R/min and 0.0056 R/min (delivered over a 10-month and a 38-day period, respectively). Two factors that were not considered in earlier experiments have been controlled in the current series: (1) in the earlier work, animals of all groups entered the experiment at about the same age. Thus, those that required the longest exposure time were irradiated over a more advanced age than the rest; (2) their matings did not start until they were considerably older.

283. In the new experiments, the animals exposed at 0.0056 R/min for 38 days were divided into four groups. The exposure period of these groups was distributed at approximately 3-month intervals of age to cover the age range involved in the 0.0007-R/min group that was exposed for over 10 months. All groups, including controls were not mated until the 0.0007-R/min group had received its exposure.

284. The data thus far available show that at a rate of 0.0007 R/min there are 11 presumed mutations in 42 020 offspring and at 0.0056 R/min 19 presumed mutations in 74 842 offspring. The frequencies are highly significant above the controls and differ from each other by less than one mutation from that expected on the null hypothesis of no difference between the two groups. The tests are continuing.

285. In studies initiated to complement those of W. L. Russell and Kelly (discussed in the preceding paragraphs) on spermatogonial stem cell survival, Oakberg and Palatinus (378) demonstrated that there was no reduction in the stem cell population after 300 R of ^{137}Cs gamma rays given to mouse spermatogonia at a rate of 0.0007 R/min, whereas it was 37 per cent of controls after the same exposure delivered at 0.0056 R/min. Thus, in these experiments, a change in cell killing has not been accompanied by a change in mutation frequency, contrary to the arguments presented in paragraphs 278-279.

3. Specific-locus mutations in female mice

(a) *Dose-fractionation effects*

286. In earlier studies (reviewed in the 1972 report), W. L. Russell (476, 480) had found that a single exposure of 50 R of x rays to female mice gave a lower mutation rate per unit exposure (conceptions within the first seven weeks after irradiation; maturing oocytes samples) than those of 200 or 400 R and that the yield after 8 X 50 R (75-min interval between the fractions) was 8 times that of a single exposure (i.e., much lower than the effect of a single 400-R exposure; see the 1972 report, Annex E, table 16).

287. Lyon and Phillips (312) have now investigated the mutational response of maturing oocytes to irradiation with a total dose of 200 rad given in 20 fractions of 10 rad each, over a period of five days (10 rad at a time, four times a day; interval between fractions in a day, approximately 2 h) or over four weeks (10 rad per day for five days in a week (Monday through Friday) 24-h interval between fractions). The effects observed were compared with those in females irradiated with single doses of 200 rad, of which there were two groups. One group was mated soon after irradiation and the other after a week's delay. All x irradiations were delivered to mice 9-10 weeks old at about 52 rad/min. The offspring conceived within seven weeks (and later) after the irradiation were scored for mutants at the seven loci of the PT stock. There were no controls.

288. The results showed that there were no significant differences in mutational yields between the two single-exposure experiments (although in one, mating of the irradiated mice was delayed for a week) and between the two fractionation régimes (although in one, the irradiation was delivered in five days and in the other, over four weeks). Therefore, the data of the two acute groups were pooled and, likewise, those of the two fractionation groups were pooled; these data are given in table 36. Inspection of table 36 will reveal that (a) among the offspring conceived within seven weeks after irradiation, the mutational yield after single exposures is 9/34 813 (a rate of 1.85 10^{-7} rad^{-1} per locus) and after fractionation, 1/39 887 (a rate of 0.18 10^{-7} rad^{-1} per locus); and (b) if the comparisons are restricted to the progeny conceived within the first three weeks after irradiation, the corresponding figures are 7/21 578 (a rate of 2.32 10^{-7} rad^{-1} per locus) and 1/20 398 (a rate of 0.35 10^{-7} rad^{-1} per locus). Thus, there is a reduction in mutation frequency by factors of about 10 or 7, depending on which progeny groups are included in these comparisons.

289. The rates given above have not been corrected for controls.[16] If this is down, the induction rates will be even lower. For instance, the induction rate obtained at the 200-rad level (even by correcting with the minimal spontaneous rate) is lower than that of W. L. Russell at the same exposure: for the first seven-week conceptions, W. L. Russell obtained a rate of 3.95 10^{-7} R^{-1} per locus, which is twice that which can be estimated from the data of Lyon and Phillips (1.75 10^{-7} rad^{-1} per locus). The latter authors suggest two possible reasons

[16] The Oak Ridge control data currently stand at three independent mutations (one of which was a cluster of six) among 166 826 progeny. This, combined with the earlier data of Batchelor *et al.* (28) (no mutations among 37 813), bring the total number of progeny scored to 204 639. Based on the method used in the 1972 report (Annex E, paras. 145-146) a minimal and an upper rate of spontaneous mutations can be estimated. These are, respectively, 2.1 10^{-6} per locus per gamete and 5.6 10^{-6} per locus per gamete.

for this discrepancy: (a) the stocks of mice used (originally descended from those of Russell) have come to differ in the twenty-year period since they were founded, and (b) there was a difference in the dose rates used: about 90 R/min in W. L. Russell's experiments and about 53 rad/min in those of Lyon and Phillips. W. L. Russell (467) has pointed out that when his oocyte data are split up into those pertaining to "older" and "younger" females the discrepancy between his data and those of Lyon and Phillips is very much reduced.

(b) *Dose-rate effects*

290. One of the difficulties in measuring the effect of protracted irradiation on mutation frequency in maturing oocytes of mice is that the length of radiation exposure time necessary to accumulate a sizeable dose may approach the duration of the oocyte stage being studied. This was recognized in the earliest work on mutation induction in females by W. L. Russell. When he later discovered (475a) that the mutation frequency apparently drops to zero for conceptions occurring more than six or seven weeks after irradiation, he pointed out, at that same time, that the lowness of a total mutation frequency in offspring collected during a period of several weeks after the end of a chronic irradiation exposure could have resulted partly from an effect of low dose rate on maturing oocytes and partly from a portion of the dose having been given to oocytes in immature stages, more than six weeks before conception. However, it was shown that a very low mutation frequency from chronic irradiation, compared with acute, would be demonstrated, even for maturing oocytes, by restricting the comparison to conceptions occurring within a short time after accumulation of the dose.

291. In order to utilize data collected from conceptions occurring over a longer period, and still restrict the measurement to maturing oocytes, it is necessary to compute the proportion of the dose received while the oocytes are in maturing stages. This was done, in a crude approximation, in computations used to arrive at the figure of 1/20 which was accepted in the 1972 UNSCEAR and BEIR reports as the ratio of effects of chronic to acute irradiation in maturing oocytes.

292. W. L. Russell (483a) has now presented previously unpublished data which have enabled him to make more precise estimates of the effects of protracted irradiation on maturing oocytes. The data shown in table 37, were collected to determine as sharply as possible the time interval after irradiation at which mutation frequency drops, and to find out if this is a sudden or gradual change. No mutations were obtained in conceptions occurring more than six weeks after irradiation, and the frequencies in the fifth and sixth weeks showed no decline compared with earlier weeks. Thus the drop in mutation frequency with time after irradiation is very sudden. Russell also points out that, on the basis of these and other data, offspring conceived in the first week after irradiation appear to have a lower mutation frequency than those conceived during week 2-6 after irradiation.

293. On the basis of the above results, an "effective dose" can be computed for offspring conceived at various intervals after a period of protracted irradiation. By "effective dose" is meant the portion of the total dose that was received six weeks or less before ovulation. Russell applied this analysis, computing a weighted mean effective dose, to his own experiments and to the data of Lyon and Phillips (312) and Carter (84a), as shown in table 38. A mutation rate for protracted irradiation of mature and maturing oocytes was then determined by fitting a weighted least-squares regression line to the frequencies for all six irradiation experiments and the control. Actually, four regression slopes were calculated, one set of two based on all the data and the other set excluding an experiment that used only old females. Each set had two fits, one for each of the two different estimates of the control mutation frequency.

294. The mutation rates estimated in this way for low-level irradiation of mature and maturing oocytes, when compared to the mutation rate for his 400-R acute irradiation data, yield ratios of 1/18, 1/24, 1/29 and 1/46. The ratios might have been even lower if the proportion of oocytes that received most of their dose in the first week before ovulation (when mutational sensitivity is somewhat less) had been as high in the chronically irradiated animals as it was in the acutely irradiated ones. In any case, with the more precise estimation of the effective doses than was available for the preparation of the 1972 UNSCEAR and BEIR reports, and with the addition of the new data of Lyon and Phillips, it turns out that the Committees' statements of a ratio of 1/20, for the relative effectiveness of chronic to acute irradiation, did not underestimate the risks from low-level irradiation of mature and maturing oocytes.

295. In his paper, Russell also compared the specific-locus mutation rates obtained for mature and maturing oocytes with the mutation rate for chronic irradiation of spermatogonia. The mutation rate, for the same seven loci, in mouse spermatogonia irradiated at dose rates of 0.0009 R/min and below, was calculated in the review paper by Searle (506) to be $6.59\ 10^{-8}\ R^{-1}$ per locus. The four rates for low-level irradiation of mature and maturing oocytes estimated by Russell are only 0.17, 0.27, 0.33 and 0.44 times as effective, and only in the highest of these is the induced rate in oocytes significantly above the control rate. Thus the ratio of effectiveness to the spermatogonial mutation rate could be zero. Similarly, the ratio of effectiveness to acute irradiation given in the previous paragraph could also be zero.

296. With regard to the validity of extrapolating mutation rates in mouse immature arrested oocytes to human immature arrested oocytes, which has been questioned because of marked differences in the sensitivity of these oocytes to cell killing, Russell indicates that his data have an indirect bearing on this problem. The mutation frequency is lower for the most mature oocytes, those which produced the offspring for week 1 in table 37, than for the less mature oocytes that produced the offspring listed for weeks 2-6. The fully mature oocytes are less sensitive to killing than the less mature ones. Thus here there is a positive correlation between killing and mutational sensitivity. That is in contrast to the negative correlation found for immature arrested oocytes, which give no evidence of mutation

induction but which are highly sensitive to killing. It appears from the lack of consistent correlation, that mutation induction and killing are independent events. In support of this view, Russell cites the new data of Cox and Lyon (121), on x-ray induction of dominant lethal mutations in mature and immature oocytes of guinea-pigs and golden hamsters. In both species, they found lower mutation yields from immature than from mature oocytes, despite the fact that the immature oocytes of the guinea-pig are less sensitive to killing than the mature ones, while the reverse is true for the golden hamster, which, therefore, resembles the mouse. Thus, as these authors state, there is "no general pattern ... of correlation, either positive or negative, in the sensitivity of oocytes to killing and to dominant lethal induction".

297. In Russell's view, there would now seem to be less reason than before for rejecting an application of data on the mouse immature arrested oocyte to the human immature arrested oocyte. In the immature oocytes, the specific-locus mutation frequency in the mouse and the dominant lethal frequency in guinea-pig and golden hamster are all low compared to the frequencies in mature oocytes. The fact that this is so, despite the tremendous differences in sensitivity to cell killing, and in chromosomal morphology, in the immature oocytes of these species, weakens the contention that the sensitivity to cell killing of the mouse immature oocyte is an argument against using it to predict the mutational response of the human immature oocyte.

298. Russell concludes that if, on the side of caution, one continues to consider the possibility that the human immature arrested oocyte might be as mutationally sensitive as the most sensitive of all oocyte stages in the mouse, namely the maturing and mature oocytes, then one can use his estimates of mutational frequency from low-level irradiation in these stages. The rates range from 0.17 to 0.44 times that in spermatogonia, but it should be kept in mind that in three of the four estimates the frequencies are not significantly above control values. Thus, even in the event that the human immature arrested oocyte does not respond like the mouse arrested oocyte, but more like the most sensitive oocyte stages in the mouse, it seems likely that the genetic hazard of radiation in the female will still be less than in the male.

4. Mutation processes at low and high radiation doses and dose rates: criticism of a current model

299. Since the discovery of the dose-rate effect with low-LET irradiation for the induction of specific-locus mutations in mice in 1958 (491), the question of whether the phenomenon mainly involves the repair of only two-track mutational events or primarily the repair of one-track events has been repeatedly discussed (473, 475, 477, 479). In their 1958 paper, W. L. Russell *et al.* pointed out that one-track events can show a dose-rate effect (and a supra-linear dose-effect curve at high dose rates) if the repair system is damaged or saturated at high doses and at high dose rates. For various reasons that have been enumerated in detail (473, 475, 477, 479; also discussed in the 1972 report, Annex E, paragraphs 182-195) the hypothesis of repair of one-track mutational events has been favoured.

300. In 1967, Wolff (617) listed several arguments (based essentially on dose-rate effects and RBE considerations) which in his opinion lend support to the view that mutations scored in specific-locus experiments are predominantly chromosome rearrangements that result from two-track events. More recently, this view has been modified in papers by Wolff (618) and Abrahamson (3) and Abrahamson and Wolff (4a) in which the mutationed lesions are assumed to be a mixture of one- and two-track events. Attention will be focused on the last paper since this contains the most definitive account of these authors' views.

301. Abrahamson and Wolff fitted the specific-locus data obtained in the mouse to an equation of the form $Y = C + \alpha D + \beta D^2$, where Y is the expected yield of mutations, C = control rate, D = the dose of sparsely ionizing radiations, and α and β the linear and quadratic coefficients, respectively. For the oocyte data, the α and β terms were estimated by a least-squares regression analysis of the data obtained at 50 R, 200 R and 400 R (acute x-ray exposures). The estimated values, if a cluster of six mutants was counted as one mutation, were $C = 1.67\ 10^{-6}$, $\alpha = 1.26\ 10^{-7}$ R^{-1} and $\beta = 1.14\ 10^{-9}$ R^{-2}. From these, the expected number of mutations in other experiments was computed. For spermatogonial data, Wolff and Abrahamson used all the low dose-rate data available (below 1 R/min to derive α, and this was then used with the 300-R acute x-irradiation data to derive β. The values so obtained were $C = 8.3\ 10^{-6}$; $\alpha = 6.88\ 10^{-8}$ R^{-1} and $\beta = 6.57\ 10^{-10}$ R^{-2}. These values were used to calculate expected frequencies of mutations in the other experiments.

302. Considering first the oocyte data, the predicted and observed mutation frequencies were similar except in three low dose-rate experiments (in which exposures lasted for 12, 20 and 31 days, respectively) and in an acute irradiation experiment from Harwell (312) in which the yield of mutations was lower than expected from Oak Ridge data. Abrahamson and Wolff suggested that the low observed frequencies in the chronic exposure experiments "are the consequence of some of the oocytes having been irradiated during the less mutable stages rather than resulting from repair of pre-mutational damage in a static cell population". The authors made some "crude corrections" to allow for this postulated admixture with less sensitive stages, which brought the expected numbers into reasonable agreement with the data.

303. Turning now to the spermatogonial data for acute irradiation, many discrepancies were found between observed and expected values. However, these were mainly in single or fractionated irradiation experiments with individual exposures of more than 500 R and with a general pattern of less than expected yields. The authors attributed these discrepancies to differential cell killing and selection, in line with previous views (e.g., ref. 470).

304. The main implications of this reanalysis for the evaluation of radiation hazards are the following: with sparsely ionizing radiations at low doses and low dose rates, it is the linear component that predominates, and the magnitude of the risk of induction of mutational

damage will be determined by this. For males, where the hazard evaluation is in fact based on the *observed* linear dose-effect relationship (506, 617) at low dose rates over a wide range of doses, the above reanalysis adds nothing new. For females however, the risk (on some methods of calculation) will be expected to be higher than what had been hitherto assumed by UNSCEAR (589) and BEIR (34).

305. The above model and, especially, the modifications of the mouse data which the authors perform to fit their model have been criticised by W. L. Russell (482, 483, 483a). With regard to the model itself, Russell points out that the data also fit his hypothesis, in which the mutational lesions themselves are one-track events, but multiple tracks are involved in damaging or saturating the repair process. The data will fit still other models. Therefore, Russell argues that the fit of the data to the model proposed by Abrahamson and Wolff does not prove their hypothesis to be superior to other hypotheses which also give acceptable fits. He contends that other criteria which he has discussed elsewhere (473, 475, 477, 479) provide more cogent evidence on the nature of the mutational lesions.

306. Russell's strongest objection is against the modification of the mouse oocyte data carried out by Abrahamson and Wolff. The two fits preferred by the authors fail to give good agreement with the low dose-rate experiments considered by them, essentially the data of Carter and Russell's 258-R and 400-R data shown in table 38. Abrahamson and Wolff recognize this and, in an extensive discussion, try to explain away the discrepancy by claiming that the effective doses in the chronic irradiation experiments are very low, much lower than the values calculated by Russell (paras. 293-294 and table 38). Russell claims that errors arose when they tried to compute the effective dose on the basis of number of oestrus cycles and an oocyte maturation scheme which, according to Russell, seems to have no basis in reality. Thus they compute that the effective dose in the Carter experiment would be only one half or less of the dose given. The irradiation time in this experiment was 12 days, and all matings occurred within two weeks of the end of irradiation. In view of the data in the table and the well known fact that maturation and loss of oocytes occurs at the same rate in breeding and non-breeding females (370a), Russell finds it hard to see how any of the oocytes in Carter's experiment could have received less than the total dose during the maturing stages that are sensitive to acute irradiation. It is also noted by Russell that the two mutations in the 283-R experiment in table 38 were from conceptions occurring in the 5th week after the end of irradiation, a period long after the time when Abrahamson and Wolff would have had the effective dose down to zero.

307. Although Abrahamson and Wolff include the new Lyon and Phillips data for a single 200-R dose of acute irradiation, they omit any consideration of the fractionated exposures. Russell states that if Abrahamson and Wolff had computed their expected value (assuming cluster = 0) for this set of data, it would have been 9.5 mutations expected where only 1 was observed. With a correct adjustment for effective dose they would still have predicted 7.8 mutations.

308. Abrahamson and Wolff, on the one hand, admit that their corrections for effective dose are crude, but on the other hand, conclude "it is reasonable to assume that the wide discrepancies [between their theoretical expectations and the actual data] are caused by some of the radiation occurring during less mutable stages". Since the data shown in table 38 have already been adjusted for this factor using Russell criteria, it is of interest to see how much discrepancy is still left between his corrected observed values and the Abrahamson-Wolff prediction.

309. Of the two Abrahamson-Wolff fits preferred by them, the slope of one (cluster = 0) exceeds the slopes of the four regression lines derived by Russell (paras. 293-294) by multiples of 4.8, 6.5, 8.0 and 12.7, and the slope of the other Abrahamson-Wolff line (cluster = 1) exceeds the slopes of the Russell lines by 4.3, 5.7, 7.1 and 11.2. Russell calculates that both Abrahamson-Wolff slopes are significantly above all the slopes of the actual data with a high degree of confidence. The lowest t value in these comparisons is 7.84, where the critical value of t for 5 per cent probability is 2.57.

310. Thus the Abrahamson-Wolff derivation from acute irradiation of the mutation frequency theoretically expected, on their hypothesis, for low-level irradiation exceeds the observed value by a factor of 4-13. Russell concludes that their approach is not a reliable one for estimating hazards.

5. Nature of specific-locus mutations

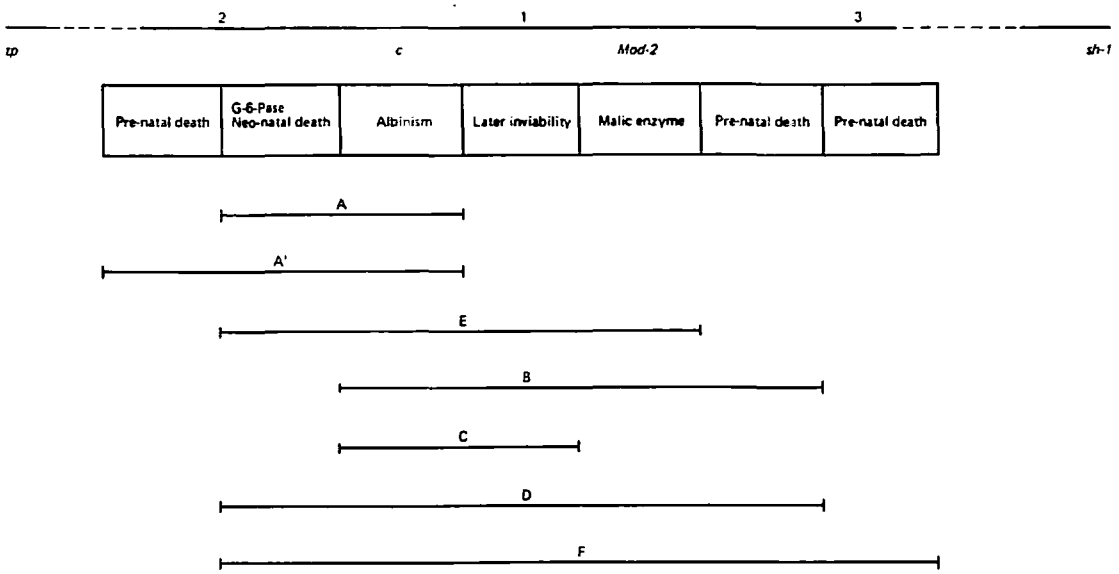
311. The 1972 report considered in some detail the work of L. B. Russell (453), who analysed, by means of complementation tests, the mouse chromosome 9 region between and surrounding *d*, *se* and *sv* (recombination frequency *d-se*, 0.16 per cent; *se-sv*, 2 per cent). This analysis revealed the existence of 16 complementation groups spanning eight or nine functional units. It was found that (a) there was a strong effect of the irradiated germ-cell stage, as well as the type of radiation, on the locus-spectrum, i.e., on the relative frequencies of events involving *d*, *se* or both, and on the involvement of single functional units as against that of two or more functional units; (b) the frequency of mutations interpreted as aberrations (deficiencies) ranged from 13.5 per cent in most x- or gamma-irradiated spermatogonia to 42.3 per cent in post-spermatogonial stages and 65.6 per cent in oocytes; and (c) the recombinational length of most of the aberrations was very small, 75-80 per cent of them spanning less than two crossover units. Even in the groups that had a high total frequency of aberrations (post-gonial stages and oocytes), no more than 23 per cent of all mutations exceeded this length and the frequency was for x- and gamma-irradiated spermatogonia (excluding the 24-h fractionation group).

312. The type of analysis discussed in the preceding paragraph has now been extended by L. R. Russell to another locus, the *c* (albino locus), located in linkage group I, chromosome 7 (213); the mutations used in the present work, as in the earlier one on *d-se* were derived from the specific locus experiments of W. L. Russell and

co-workers and were recovered in the heterozygous state with the c^{ch} allelle carried by the tester stock. Since all but one of the 103 completely, and 12 partially, tested mutants are distinguishable in colour from c^{ch}, testing consists of crossing the original mutant to c^{ch}/c^{ch} and then intercrossing the heterozygotes, for tests on viability, and in the case of lethals, time of death.

313. The results available thus far show that (a) among the 9 control mutants, 8 were viable and 1 subvital in the homozygous condition; (b) among 50 mutants derived from x- or gamma-irradiation experiments (spermatogonia), 35 were viable, 3 subvital and 12 lethal in the homozygous condition (there was no significant effect of dose rate, fractionation or of x irradiation compared with gamma irradiation in the distribution of mutants in the three classes); (c) neutron irradiation of spermatogonia appears to produce a shift in the sense that now 7 out of 19 tested mutants are lethal, 1 subvital and 11 fully viable; and (d) the data for the post-spermatogonial and oocyte stages are limited and the numbers in the subgroups too small to compare the spectra between gamma or neutron irradiation, but, out of a total of 25 mutants tested, 12 are viable in the homozygous condition and the rest are lethal.

314. L. B. Russell *et al.* (454a, 464, 465) carried out complementation and deficiency-mapping tests on a total of 30 independent lethal mutations involving the *c* locus. It was found that these lethal mutants group themselves into at least seven complementation groups. The authors suggest that at least seven functional units must be postulated to account for all the interaction effects on a linear basis. The complementation groups have been designated as A, A', E, B, C, D, and F. Their properties and their relationship to the *c* locus and adjacent markers used in the complementation study can be diagrammed as follows:



(G-6-Pase: glucose-6-phosphatase deficiency; *Mod-2:* mitochondrial malic enzyme (*m*alate *o*xidoreductase *d*ecarboxylate); *tp:* taupe; *sh-1:* shaker-1).

315. Five of the *c*-lethal mutants (A-group) do not involve *Mod-2* (only 1 cM distant from *c*). However, the finding that complementation for neo-natal death can occur without complementation for albinism and separate from complementation for various kinds of pre-natal death suggests that even these mutants may be small deficiencies involving several cistrons. Since the neighbouring marker *tp* is not involved, their maximum length must be less than 3 cM. Among proven deficiencies, the two longest were at least 4 but less than 8 crossover units in length (454a). The remainder of the *c*-lethal mutations were at least 1 but probably much less than 6 cM long. It is likely that the 66 viable *c*-locus mutations found are not deficiencies.

316. Four of the 30 *c*-locus lethal mutants have been studied cytologically using both quinacrine-mustard and Giemsa-banding (454a). In one of these, a B complementation-group mutant, no loss of cytological material was detectable. The two F-group mutants (deficient for *sh-1* as well as *c)* were found to lack most of one of the major bands of chromosome 7 (the E band), one being slightly longer than the other. One of the D-group mutants lacks an amount of chromosome 7 that is almost equivalent in length, but is located more proximally, overlapping with the F-group mutants with regard to cytological sub-band E1. This serves to locate the *c*-locus cytologically within E1 and its flanking markers, *sh-1* and *tp* in E2 (or E3) and proximal to D1, respectively. This finding, and evidence from cytological studies of other chromosome-7 aberrations, indicate that relative cytological lengths in that region of the genome may not correspond closely with relative genetic lengths (454a).

317. Again, on the basis of complementation tests, Erickson *et al.* (160) and Gluecksohn-Waelsch *et al.* (195) concluded that all six lethal albino alleles that they examined which included three of Russell's, could be overlapping deficiencies of various sizes at and around the albino locus. The fact that no complementation could be observed in combinations of c^{25H} with any of the other five permitted these authors to infer that c^{25H} may be the biggest deletion of all.

318. Using Q- and G-banding methods, Miller *et al.* (338) demonstrated cytologically that the above inference is in fact true: in heterozygous animals, the two No. 7 chromosomes could be distinguished from one

another, and the one carrying c^{25H} was found to be 7.6 ± 1.5 per cent shorter than its homologue, providing a direct estimate of the size of the deletion. Since the total genetic length of the mouse genome is about 1250 cM (589) and since chromosome 7 makes up about 5.4 per cent of the haploid genome, a deletion of 7.6 per cent of this chromosome might be expected to be about 5 cM long (1250 X 5.4% X 7.6%); this value is in the range of length based on the available genetic recombination data. However, there are indications that cytological length may not be a good indicator of genetic length for this portion on the genome (see paragraph 316).

6. Autosomal recessive lethals

319. Since the publication of the 1972 report, some new data on recessive lethals in mice (spontaneous and radiation-induced) have become available (298, 299, 300, 416). In addition, several specific problems and statistical difficulties involved in the design and evaluation of experiments on autosomal recessive lethals have become apparent, such as the presence and detection of pre-existing lethals in inbred strains and in the control and experimental groups derived from them, the basis and magnitude of fluctuations from generation to generation in the frequency of heterozygotes for recessive lethals, and what steps need to be taken to make a proper assessment of spontaneous and induction frequencies of these lethals (269, 299, 493).

320. In a recent paper on testing for autosomal recessive lethals, Lüning (198) elaborated further on the methodology that he described earlier (296), with a reconsideration of several aspects that are involved. Among these may be mentioned (a) the identification of individual lethal heterozygotes, (b) the identification of families carrying pre-existing recessive lethals by analysing 10 or more F_1 brothers, and (c) the variance of the rate of heterozygosity for recessive lethals in inbred strains in successive generations and its relevance for estimates of the mutation rate per genome.

321. The general scheme for individual and familial identification of recessive lethals can be diagrammed as follows:

P_1 generation ♂ X ♀

↓

F_1 generation ♂ X ♀♀♀ (at least 10 F_1 sons per parental cross to be tested)

↓

F_2 generation ♀♀♀ X F_1 father (backcross)

Uterine contents of pregnant females are examined to assess the amount of pre-natal mortality; identification of heterozygosity for lethals dependent on the rate of intra-uterine mortality, which is expected to be higher in crosses where a lethal is involved, than in those where it is not.

If an F_1 male is heterozygous for a recessive lethal, then 50 per cent of his progeny will carry the same lethal, therefore, in a backcross involving father-daughter mating, the expected mean mortality is 12.5 per cent over and above the normal mortality of 8 per cent, or a total of 100–(0.875)92 = 19.5 per cent. In practice, this involves the identification of each individual case as belonging to a distribution with a mean mortality of 8 or 19.5 per cent, the precision of which is dependent on the number of implants examined per backcross.

322. The model presented by Lüning (298) enables the identification of lethal heterozygotes and lethal-free animals in the backcross test of F_1 males to their respective daughters. According to the model, when a minimum of 50 implants (50-60; mean, 53) are analysed for each backcross of the F_1 male to his daughters, those which gave 9 or more dead are judged to be heterozygous for a recessive lethal; those crosses which resulted in 4 or less dead are considered lethal-free. An increase of the number of implants analysed increases the accuracy of the above procedure to identify lethal heterozygotes and lethal-free animals.

323. It is known that in inbred strains of mice there are large variations in the spontaneous frequencies of autosomal recessive lethals between one generation and the next. The earlier analysis by Lüning and Searle (302) of three sets of control data (controls for radiation experiments) revealed considerable differences in frequencies between them, and the authors estimated that the mean rate was $2.9\,10^{-3}$ with an upper 95% confidence limit of $6.5\,10^{-3}$ per gamete. In a subsequent paper, Lüning (299) examined the control data accumulated over the years 1964-1971 in his laboratory (and which pertain to four different series, including the three that were considered by Lüning and Searle) and concluded that the mean rate was $5\,10^{-3}$ per gamete with an upper limit of $1\,10^{-2}$. In relatively small experiments involving three strains of mice (CBA, C3H and 101) and their hybrids, Lyon (306) likewise found variability in the frequencies of autosomal recessive lethals and stated that "allowing for sampling error, the results are not incompatible with the hypothesis that in all three strains, recessive lethal genes arise with a frequency of 0.1 per gamete" (an approximate upper limit).

324. Haldane (211) first drew attention to the fact that, although spontaneous recessive lethals arise at a finite rate, the average frequency of heterozygotes for lethals can vary within a strain depending on how the parents are selected to prepetuate the strain and dealt with the problem from a theoretical standpoint. In the case where a pair of full-sib parents heterozygous for the same recessive lethal leave three quarters as many offspring as the others not carrying the lethal, he showed that the average accumulation of lethal heterozygotes is equal to $9.3\,\mu$ where μ is the mutation rate per genome. In the extreme case where the number of offspring from heterozygous parents is not reduced at all, the average accumulation would be equal to $12.7\,\mu$. At the other extreme, where the heterozygous parents leave no offspring, Lyon (306) showed that the average accumulation would equal $6.0\,\mu$. Thus, depending on the breeding scheme, the average frequency of lethal heterozygotes in an inbred strain would be between 6.0 and $12.7\,\mu$. These calculations, however, are based on

the assumption that the strain in question is constituted by an "infinite" number of breeding pairs, a theoretical situation. In practice, due to economic and spatial reasons, a given strain is propagated with only a limited number of breeding pairs. This restriction will cause drastic fluctuations in the frequency of heterozygotes for lethals in the strain when sampling is done at different periods of time, as has actually been observed in the experiments discussed by Lüning and Searle (302) and by Lüning (299).

325. Ryman (493) conducted a computer-simulation study to investigate the magnitude of temporal variation in the frequency of heterozygotes for autosomal recessive lethals in inbred strains, a problem to which little attention has been devoted so far. The simulation studies were performed with special reference to the mouse with the following assumptions: (a) the number of breeding pairs for strain continuation is 10, 20 or 50; (b) each pair produces 1 or 5 litters in every generation; (c) the minimum number of live-born young from a pair whose offspring can be selected to continue the inbred strain is 6 or 0 (1-litter situation) and 30 or 0 (5-litter situation) (The offspring not used to form breeding pairs in the strain were "surplus" and used for "experimentation", and the frequency of lethal heterozygotes was determined in the "surplus" group.); (d) the sex ratio is 1 to 1; (e) the mutation rate of autosomal recessive lethals per generation and the pre-weaning mortality are 0.5 and 16 per cent, respectively, these values being the long-term averages for the inbred CBA strain in the Stockholm Laboratory of Radiation Genetics; (f) lethal homozygotes die before birth.

326. The computer was programmed to trace the temporal pattern (over 200 or 500 generations) in the frequencies of heterozygotes for lethals under the different conditions mentioned above and to estimate the means and variances. The results showed that, with the 200-generation trials with "surplus" animals, there were large and sudden changes in the frequencies of lethal heterozygotes (0-40 per cent) under conditions when the number of breeding pairs per generation was 10. This variation became much less (0-12 per cent) when the latter was 50. The means over all generations and their respective variances were 0.046 (4.6 per cent) and 0.00573 with 10 breeding pairs and 0.038 (3.8 per cent) and 0.0006 with 50 breeding pairs. The estimated variance of the differences between consecutive generations was, as would be expected, much higher under the first set of conditions than under the second (0.00878 compared with 0.00092).

327. The results of simulations for 500 generations (with different maximum number of breeding pairs for the continuation of the inbred strain) revealed that with a low number of breeding pairs (such as 10), the variance of the mean frequency of lethal heterozygotes, as well as that between successive generations, is quite large, irrespective of the number of litters per pair and of whether selection against small litters is practised or not. Furthermore, the number of generations in which there were no lethal heterozygotes ("lethal-free" generations) was also appreciable. An increase in the number of breeding pairs and/or an increase in the number of litters per pair leads to a decrease in the variation and the number of lethal-free generations also becomes reduced.

328. The practical implications of these findings are the following:

(a) Since the maintenance of an inbred line is not an end in itself, great care must be taken in choosing an optimal breeding régime in relation to the type of experiments that are proposed to be conducted;

(b) Since heterogeneity within an inbred line may be considerable, the use of an inbred strain does not automatically guarantee a homogeneous genetic background;

(c) Estimates of spontaneous or induced rates of mutations to recessive lethals will be reliable only when the experiment is repeated at different time intervals or when pre-existing mutations are identified and taken into consideration;

(d) If the strain is not very large, the replications are expected to yield statistically heterogeneous results and it is justifiable to pool the results obtained with a given strain at different time intervals to get a realistic estimate of mutation rates, as was done earlier by Lüning and Searle (302) and by Lüning (299).

329. New data on the x-ray induction (500 R acute) of autosomal recessive lethals in mouse spermatogonia come from the experiments of Lüning and Eiche (300) and those of Pomerantzeva *et al.* (416). Lüning and Eiche used the technique outlined in paragraph 310 and found that the rate of induction (after correcting for the spontaneous rate of $0.5\ 10^{-3}$ per gamete) was $0.9\ 10^{-4}$ rad^{-1} per gamete. This is in complete agreement with the earlier estimate made by Lüning and Searle (302) based on three different sets of data (see the 1972 report for details). In the work of Pomerantzeva *et al.* (416) a total exposure of 900 R of gamma irradiation was administered to male mice in three equal fractions separated by 4-week intervals, and the frequency of autosomal recessive lethals was determined. In one of the two experiments, the induced frequency was 22.65 per cent (or $2.5\ 10^{-4}\ R^{-1}$) and in the other, 5.4 per cent (or $0.6\ 10^{-4}\ R^{-1}$). Pooling the controls and likewise pooling the radiation data, the induced frequency can be estimated as 9.93 per cent which corresponds to a rate of $1.1\ 10^{-4}\ R^{-1}$. As will be obvious, this rate is quite close to that recorded by Lüning and Searle (302) and by Lüning and Eiche (300).

7. Dominant mutations

330. Since the publication of the 1972 report, some new data have become available from studies on dominant mutations in mice. These pertain to the work of Selby and Selby (528), who investigated the gamma-ray induction and transmissibility of dominant mutations affecting the skeleton. Before considering the results of Selby and Selby, it is profitable to examine the background of this kind of work and place it in the perspective of earlier work done in this area.

331. The rationale was, and continues to be, based on the following considerations:

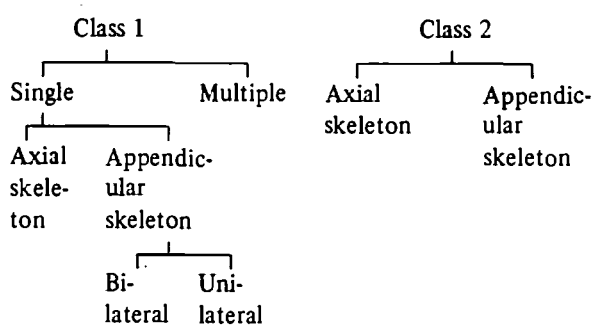
(a) For the evaluation of genetic radiation hazards to a population, it is desirable to obtain more information on the frequency of induced dominant mutations;

(b) Information on dominant visible mutations which has been generated as a by-product of mutation rate studies with specific loci continues to be limited;

(c) The skeleton is a complex system formed over an extended period of development and differentiates in specific ways in various parts of the body to form permanent structures. It is therefore subject to modification by gene action at very many loci;

(d) Consequently, studies on the radiation induction of dominant genetic changes affecting the skeleton are useful because they uncover a portion, perhaps a substantial one, of the overall genetic damage induced by irradiation.

332. In their first studies, Ehling and Randolph (147) showed that, in skeletal preparations of F_1 progeny of irradiated male mice (x rays and neutrons; pre- and post-meiotic germ-cell stages), it was possible to distinguish between the effects of newly induced skeletal variation and that which is normally present in the strains employed. Thus, they demonstrated the feasibility of using skeletal abnormalities as a criterion of radiation-induced, presumed dominant genetic damage and set the stage for further work (149, 150). The abnormalities were classified into Class 1 (those that occurred only once in the whole experiment) and Class 2 (those that occurred more than once). The further subdivision of these classes can be diagrammed as follows:



333. Since the sample sizes in these experiments were such that not more than one mutation would be expected from any particular gene locus, it was thought that the classification into Class 1 and Class 2 would provide for the optimum separation of the existing natural variation from that caused by newly occurring genetic changes. The results showed that there was a statistically significant increase in the incidence of Class 1 abnormalities after irradiation; among these, multiple abnormalities (those with at least one Class 1 abnormality plus others, regardless of whether Class 1 or Class 2) and single bilateral abnormalities of the appendicular skeleton were considered to provide the most sensitive indicators of mutational damage. There was no significant increase in Class 2 abnormalities after irradiation.

334. In the earlier experiments of Ehling (149, 150), since the F_1 mice were killed for making skeletal preparations at four weeks of age, breeding tests of the presumed mutants could not be carried out. Subsequently, however, Ehling (151) designed experiments to permit such breeding tests, the F_1 offspring being sacrificed only after they had produced a litter; 3 out of 5 presumed mutations were found to be transmitted to the second and later generations. In similar work carried out by Tutikawa (quoted in the Committee's 1972 report) in which 11 presumed dominant skeletal mutations were observed, 2 which showed externally visible effects were given breeding tests and both were found to be transmitted. Since the transmission of only a few skeletal mutations had been studied at the time of writing the 1972 report and the transmission pattern of a majority of them did not permit an unequivocal conclusion of dominance, the Committee stated, "It seems probable that many of the presumed dominant mutations may be heterozygous manifestations of recessive mutations".

335. In their work Selby and Selby (528, 528a) focused attention on the problem which had hitherto not been studied in depth, namely, that of the transmissibility of the presumed dominant mutations affecting the skeleton. Male mice received a fractionated gamma-irradiation exposure (100 R + 500 R, separated by 24 h; 60 R/min; the choice of this radiation régime was dictated by Ehling's finding (150) that this gave maximal response for spermatogonial irradiation). The F_1 sons sired subsequent to the sterile period were processed for examination of their skeletons after they were allowed to produce progeny. Thirty-seven of the 2646 F_1 males (1.4 per cent) were judged to have dominant mutations that caused one or more rare skeletal abnormalities; 31 of these were shown to be mutants by breeding tests and the remaining 6, having no progeny, were counted as mutants based only on criteria supported by the data. The frequency of 1.4 per cent recorded in this study is similar to the 1.8 per cent (5/277) obtained by Ehling (150) under similar radiation conditions.

336. In breeding tests, Selby and Selby found that the dominant mutations affecting the skeleton showed variable expressivity and incomplete penetrance for many or all of the effects that they caused. A number of them severely affected viability. With the experimental procedure used, both incomplete penetrance and decreased viability would have caused an underestimate of the mutation rate. Thus, some of the F_1's would not be counted as mutants because they do not show the effect of the mutation they carry and others would not be counted because the mutation they carried caused their death before they could be examined.

337. In comparing the results of Selby and Selby (528) with those of Ehling (149, 150), the following comments are in order. Ehling expected that a critical determination of which of the skeletal abnormalities are actually heritable would reveal that his criteria for detecting presumed mutations would, on the one hand, miss some mutations altogether and, on the other hand, wrongly classify some abnormalities as mutants when in fact they were not. The degree to which these errors might occur was not known at the time Ehling

conducted his studies, but it was hoped that they would not be large. The finding of only one presumed mutation in the control group of Ehling (1/1739) indicated that the second kind of error could not have contributed substantially to the large number of presumed mutations observed in the experimental groups. The work of Selby and Selby (528) indicates that, as expected, the use of Ehling's criteria would lead to some false positives and some false negatives when estimating the mutation rate. It is difficult to estimate, from the Selbys' data, the extent of the two kinds of error, but it appears that they might have approximately balanced each other, since there is close agreement between the total rates obtained by Ehling and the Selbys.

338. The mutation frequency in the experimental series of Selby and Selby is 1.4 per cent. No controls were run, since the main thrust of their work was to find out if the general types of skeletal abnormalities classified as presumed mutations by Ehling's criteria would in fact be transmitted to descendants. However, the authors point out that, although a reliable estimate of the spontaneous mutation frequency needs to be made, Ehling's results indicate that this frequency is very low and would probably not appreciably affect the assumption that 1.4 per cent is close to the induced rate. The authors further conclude that, for the reasons given in paragraph 324, taking 1.4 per cent as the induced rate is more likely to be an underestimate than an overestimate of the true value.

339. While it is true that the number of dominant mutations of spontaneous origin present in any generation must be considerably higher than the spontaneous mutation frequency per generation, owing to accumulation in the ancestral mouse populations, it is important to realize that the experiments of Ehling and of the Selbys were designed to exclude most, if not all, such accumulated mutations in the mutation frequencies recorded in the F_1. For example, in Ehling's experiments any abnormalities caused by mutations accumulated in the stocks should have occurred more than once in his large samples. Thus, they would have been classified as Class 2 abnormalities, and the animals containing them would have been considered non-mutants. In the Selbys' experiments, skeletal examination of the parents, as well as the sibs, of the mutant individuals was performed and supported the conclusion that most, and perhaps all, of the reported mutations were of new origin.

340. In humans, partial trisomies and monosomies are often associated with skeletal abnormalities (see, for instance, references 208 and 349). Although it cannot be ruled out that some of the skeletal abnormalities in the mouse may have resulted from partial trisomies and monosomies, it is unlikely that such chromosomal aberrations made an important contribution to the number of mutations reported, because most of these aberrations are male sterile and derive from spermatozoal rather than spermatogonial irradiation (507). Thirty-one of the 37 mutants reported in the Selbys' experiment proved to be fertile.

341. Many of the anomalies found in the above study are similar to rare dominant and irregularly inherited dominant conditions in man. As will be recalled (chapter I), regular dominant and irregularly inherited dominant diseases (together with multifactorial ones and congenital anomalies) constitute a very substantial proportion of human disorders. Studies on the effect of radiation in inducing mutations affecting the skeleton of mice may thus lead to an independent and direct estimate of the rate of induction by radiation of dominant mutations in man.

342. Bartsch-Sandhoff (27) studied the incidence of skeletal abnormalities in mouse embryos 19 days old derived from germ cells of irradiated males (600 R of ^{137}Cs gamma irradiation). This work was undertaken to verify the presumption that some of the skeletal mutations may be incompatible with post-natal survival and would not have been represented in the four-week-old mice examined in the earlier experiments of Ehling and Randolph (147) and Ehling (149, 150). It must be stressed that not all Class 1 abnormalities in four-week-old mice are presumed dominant mutations as determined by Ehling, and that only the total frequency of Class 1 abnormalities is comparable with the data of Bartsch-Sandhoff.

343. The small sample sizes in the Bartsch-Sandhoff investigation permit only limited quantitative conclusions. The incidence of Class 1 anomalies for the irradiated postspermatogonial stages (9/371) is significantly higher than that for all unirradiated controls (5/1190 in 19-day foetuses; 14/1739 in four-week-old animals), and not significantly different from the incidence (18/569) scored in four-week-old mice for the same irradiated cell stages. The frequency after spermatogonial irradiation (4/343) does not differ significantly either from the controls or from the corresponding frequency in four-week-old mice (13/597). However, there was an important qualitative conclusion. In the 19-day foetuses there were several new abnormalities hitherto undetected in four-week-old animals, some of which were so drastic that they could conceivably have caused death before four weeks of age.

344. Comparing the results of the Bartsch-Sandhoff study with those obtained by the other investigators, it can be concluded, on the one hand, that Ehling and the Selbys would not have seen those skeletal abnormalities which, although apparent in foetal stages, were too severe to survive to the ages studied by them. On the other hand, most of the anomalies scored by Ehling and the Selbys would not have been detected in the 19-day foetuses, owing to the limited degree of ossification present at that stage. Thus the total load of dominant skeletal abnormalities induced by radiation is likely to be greater than the number which can be detected at any one particular stage.

8. Summary and conclusions

345. In the germ cells of new-born male mice, mutations at seven specific loci are induced by x rays at the rate of $1.37\ 10^{-7}\ R^{-1}$ per locus, which, statistically, is significantly lower than the $2.91\ 10^{-7}\ R^{-1}$ per locus recorded for spermatogonia in adults (300-R level in both). In young males 2-35 days old, the rate is $2.63\ 10^{-7}\ R^{-1}$ per locus.

346. When a total x-ray exposure of 1000 R is administered to male mice in two equal fractions (spermatogonial exposures) separated by intervals of 4 and 7 days, the frequencies of specific locus mutations observed are similar to those seen in long-term fractionation experiments (interval between fractions about 15 weeks) and are consistent with the additivity of yields from two separate fractions. These frequencies, however, are higher than those after a single exposure of 1000 R and lower than that after two fractions of 500 R separated by a 24-h interval.

347. The limited data that have been collected on the radiation induction of biochemical variants using nine electrophoretically detectable markers in the mouse show that such mutations can be induced in spermatogonia. Likewise, studies on the induction of haemoglobin variants (at two loci) by x-irradiation of mice (spermatogonia, post-spermatogonial stages and oocytes) have yielded positive results: a total of five haemoglobin variants have thus far been found in a sample of over 8000 F_1 animals screened.

348. In mouse spermatogonia, the rate of x-ray induction of mutations in a large group of histocompatibility loci is very much lower than that at the seven specific loci.

349. The reanalysis of the data on dose-rate effects for the induction (by low-LET irradiation) of specific locus mutations in mouse spermatogonia by Lyon and colleagues raised the possibility that at dose rates below 0.03 rad/min the mutation rate might be higher than that at 0.8 rad/min. Recent work that is being carried out by W. L. Russell at Oak Ridge to test this (at rates of 0.0007 R/min and 0.0056 R/min, 300-R gamma-ray exposure) shows, however, that in over 40 000 and 74 000 F_1 progeny so far scored at these two exposure rates, the mutation frequencies are the same.

350. Histological studies carried out by Oakberg and Palatinus demonstrate that the survival of type A_s spermatogonia (stem cells) is practically unaffected when a gamma-ray exposure of 300 R is delivered to the testis at a rate of 0.0007 R/min, whereas it is reduced to 37 per cent of that in controls when the irradiation is delivered at 0.0056 R/min. This result, viewed in conjunction with the mutation data reported in the preceding paragraph, suggests that the cell-killing interpretation of Lyon *et al.* proposed to explain the possible differential yield of mutations at low and lower dose rates may not be tenable.

351. In female mice, fractionation of an x-ray dose of 200 rad into several small fractions leads to a very pronounced reduction (an order of magnitude or more) in the yield of specific-locus mutations relative to unfractionated irradiation. These data, along with the earlier data on chronic irradiation of the same oocyte stages, indicate that the mutation rate in mature and maturing oocytes is lower than that of spermatogonia. The results therefore support the conclusion that, even if the mutational sensitivity of the human immature arrested oocyte is as large as that of the most sensitive oocyte stages in the mouse (the mature and maturing ones), the genetic hazards, under most conditions of human exposure, will be less in the female than in the male. At the same time, there appears to be stronger evidence than before for assuming that the immature arrested oocyte in the human may, like the same stage in the mouse, have a mutational sensitivity which, at most, is much less than that of the male.

352. Abrahamson and Wolff have attempted to fit the data on radiation-induced specific-locus mutation frequencies observed in mice to a simple quadratic equation. For chronic exposures of mature and maturing oocytes, the quadratic fit gave much higher expected frequencies than those actually observed. The authors attributed these poor fits to an admixture of mutationally less sensitive immature oocytes into the sampled population. However, W. L. Russell has shown, in several separate experiments, that the duration of the sensitive stage is longer than that assumed by Abrahamson and Wolff and that, therefore, their argument is not tenable. Thus, the mutational response, even of this sensitive stage, is low under conditions of protracted irradiation, and is not as high as theoretically predicted in the fit of Abrahamson and Wolff. In any case, this stage is not likely to be the best model for assessing the mutational response of the human immature arrested oocyte.

353. The analysis of the nature of specific-locus mutations (spontaneous and radiation-induced) which had earlier been carried out for mutations at the *d-se* region have now been extended to the *c* locus. A majority of the *c* locus mutations derived from x- or gamma-irradiation experiments (spermatogonia) are homozygous viable. Complementation tests have revealed that the lethal mutants group themselves into seven complementation groups.

354. Recent work on mice with spontaneous rate of origin of autosomal recessive lethals and their induction by x irradiation has produced results which confirm those presented in the 1972 report of the Committee: they show that the spontaneous rate is about $0.5\ 10^{-2}$ per gamete and, at the 500-R level, the rate of induction is $0.9\ 10^{-4}\ R^{-1}$ per gamete. In addition, computer-simulation studies designed to investigate the magnitude of temporal variation in the frequencies of heterozygotes for autosomal recessive lethals in inbred strains have shown that the frequencies can vary over an enormous range in the different generations and that the use of an inbred strain does not automatically guarantee genetic homogeneity. Because of this, in experiments aimed at determining spontaneous or induced frequencies of recessive lethals, care must be taken to ensure that the strain (from which the animals are derived for experimentation) is maintained with an adequate number of breeding pairs in every generation and furthermore, the experiments ought to be repeated at different time intervals.

355. Substantial progress has been made in the study of radiation-induced skeletal mutations in the mouse. The data show that the frequency of presumed mutations detected in the earlier work of Ehling is closely paralleled in studies by Selby and Selby in which the

actual inheritance of skeletal abnormalities of a similar type was determined by breeding tests. Another finding of considerable importance is that most of the mutations have pleiotropic effects with various degrees of penetrance.

G. EFFECTS OF INCORPORATED RADIOISOTOPES

356. In its 1966 report (587) the Committee briefly considered the genetic effects of internally deposited radioisotopes such as ^{90}Sr (in mice), ^{14}C and ^{3}H (as tritiated thymidine and tritiated deoxycytidine (in *Drosophila*)), and in the 1969 report (588) some attention was given to the incidence of chromosome aberrations in humans occupationally exposed to radioactive substances. Since then, interest in the study of effects of radioisotopes has increased, in part stimulated by the growth and anticipated expansion of the nuclear power industry. Results of experiments with mice on the genetic and cytogenetic effects of ^{239}Pu and ^{3}H have now become available, and these will be discussed in the following paragraphs.

1. Plutonium-239

(a) *Distribution of ^{239}Pu in the mouse testis*

357. Green *et al.* (199) studied the distribution of intravenously-injected ^{239}Pu (as a solution of the citrate salt) in the mouse testis. Four or 12 weeks after injection (a mean activity of 88 μCi per mouse, 3.2 mCi/kg body mass), the mice were killed and their testes suitably processed for radiochemical measurements and autoradiography. It was found that the amount of ^{239}Pu in the testes was roughly the same with the two intervals used (mean amount, (280 ± 45) pCi/g of testis and (350 ± 38) pCi/gm of testis after 4 and 12 weeks respectively). The results confirmed the earlier findings of Ullberg *et al.* (585) in demonstrating that the distribution of ^{239}Pu in the testis was inhomogeneous: in autoradiographs, about 90 per cent of the plutonium seemed to be deposited within the intertubular spaces and in the peritubular tissues surrounding them. Of the 12 000 alpha tracks counted, 42 per cent lay above the peritubular membrane or adjoining the layer of cells containing the spermatogonial stem cells, 47 per cent lay entirely above the intertubular spaces, and 11 per cent lay entirely within the peritubular membranes, but excluding those in the first group.

358. On the assumption that the testis consists of a closely packed series of cylinders of uniform diameter (the experimentally determined mean diameter was 206 μm), the authors calculated that the 10-μm shell of tissue surrounding each tubule and containing the spermatogonial stem cells constituted 17 per cent of the whole testis mass, yielding an estimated dose-inhomogeneity factor of 42/17 = 2.5, i.e., the radiation dose rate to spermatogonial stem cells is higher by a factor of 2.5 than the average for the testis as a whole, calculated directly from the total amount of ^{239}Pu deposited.

(b) *Induction of post-implantation loss through ^{239}Pu treatment of male mice*

359. Lüning and Frölen (301) and Lüning, Frölen and Nilsson (304) have reported on the induction of dominant lethals in male mice following the injection of plutonium salts. In the first series of experiments (E1 and E2), in which the males received ^{239}Pu nitrate solution (intravenous injection), there was no evidence of any significant increase in intra-uterine mortality over that observed in controls (10 255 and 7216 implants were analysed in the experimental and control groups, respectively). The situation was different however, when a solution of the citrate was used (experiments E3, E4 and E5). In these studies, the effects were examined over the range 0.05-0.5 μCi per mouse. After injection, each male was mated to three females each week for up to 24 weeks. Appropriate controls were run. The pregnant mice were dissected 18 days after the commencement of the matings for examination of their uterine contents. The number of living and dead implants was recorded; the latter group was further divided into early deaths (no foetus discernible) and late deaths (dead foetuses). In certain groups, the pregnant mice were allowed to go to term and the F_1 male progeny were used in dominant lethal and semi-sterility tests.

360. The data on the induction of dominant lethals in plutonium-injected males are given in table 39. The figures given are pooled over successive weeks. It can be seen that in the plutonium-injected groups, there is a significant excess of intra-uterine mortality, and this is unrelated to the amount of injected plutonium per male (range, 0.05-0.5 μCi). When the results of all the plutonium series (E3, E4 and E5) were combined (ignoring the amounts of Pu injected) and the pattern of mortality over the successive weeks was examined (figure 2 in reference 304), it was found that the mortality increased from an initial value of about 9 per cent (first week) to about 12-13 per cent during the fifth week, after which the changes were small and non-significant. The sperm utilized during the first five weeks would have been in post- and peri-meiotic stages at the time of injection while those utilized subsequently would have been in earlier stages. It thus appears that the increased mortality observed during the first five weeks is due to the induction of dominant lethality in post- and peri-meiotic stages of sperm development.

361. Another interesting finding that emerged from the analysis of the weekly records of mortality in the plutonium series was that there was a trend for an increasing proportion of late deaths in later weeks, one which was opposite to that found by Bateman (29) with x irradiation (200 R). The causal basis for the increase in late deaths is unknown at present.

362. Dominant lethal tests performed on F_1 males sired by fathers which received plutonium injection (and derived from matings during the ninth, fourteenth and sixteenth weeks) showed that here again there was (a) an increase in intra-uterine mortality relative to controls and (b) a trend for an increase in the proportion of late deaths.

363. In studies primarily aimed at comparing the cytogenetic effects of protracted exposures to alpha particles from ^{239}Pu and to gamma rays from ^{60}Co, Searle *et al.* (516) collected some data on the induction of dominant lethals. In the plutonium series, male mice were intravenously injected with ^{239}Pu citrate solution (4 μCi/kg body mass, or about 0.1 μCi per mouse) and kept for 21, 28 or 34 weeks. The estimates of the absorbed gonadal dose and dose rates (based on radioactivity counts and testis mass determinations at the end of the exposure periods) were 13 ± 1 rad (0.090 rad/day), 18 ± 2 rad (0.095 rad/day) and 18 ± 1 rad (0.088 rad/day), respectively. The means were 17 ± 1 rad and 0.088 rad/day. (The fraction of injected plutonium actually retained in the testis was unchanged from 21 to 34 weeks at 0.027-0.028 per cent.) In the gamma-ray series, the exposure period was 28 weeks, with an accumulated dose of 1128 rad delivered at a rate of 0.004 rad/min.

364. In both series, the irradiated males were mated to females during the last four weeks of exposure, for dominant lethal tests. In the gamma irradiated series, there was good evidence for the induction of dominant lethality, with a marked increase in both pre- and post-implantation losses, relative to controls. The induced frequency of post-implantation losses was 12.9 per cent. In the plutonium experiments, there was no significant heterogeneity between the amounts of embryonic lethality for the three exposure periods. The pooled data on post-implantation mortality suggested a slight non-significant increase, relative to controls. If the data are taken at their face value, the frequency of induced dominant lethality is 4.6 per cent.

365. Since nearly all the induced dominant lethality in the irradiation series would be expected to arise in the meiotic and post-meiotic stages, the frequencies mentioned above can be divided by the gonadal dose received in this maturation period of 28 days (mean doses of 161 rad in the gamma series and 2.5 rad in the plutonium series). The rates obtained are: $8.6\ 10^{-4}$ rad^{-1} per gamete (gamma) and $1.9\ 10^{-2}$ rad^{-1} per gamete (alpha). At face value, these results thus suggest that irradiation with alpha particles from plutonium is about 22 times as effective as chronic gamma irradiation for the induction of dominant lethals in the germ-cell stages mentioned. It should be noted that the alpha-particle dose of 2.5 rad is that to the testis as a whole. The dose to the germ cells at risk may be different from this because of dose inhomogeneity resulting from preferential deposition of plutonium in the interstitial tissue (199) but cannot be calculated at present.

(c) *Cytogenetic effects of ^{239}Pu in male mice*

366. In their first studies, Beechey *et al.* (33) investigated the cytogenetic effects of intravenously injected ^{239}Pu (10 μCi/kg body mass in 1% trisodium citrate solution, about 0.3 μCi per mouse). The mice were killed 6, 12 and 18 weeks after injection and their testes were used for radiochemical determinations (left testis) and cytogenetic analysis (right testis). Control mice injected with the citrate solution alone were processed likewise.

367. It was found that the fraction of injected plutonium retained in the testes changed very little over the period of the experiment; therefore, the radiation dose was taken to be the product of the assay-derived dose rate (≈0.0002 rad/min) and the time interval between injection and killing. The estimated doses and the results of cytological analysis of the spermatocytes are summarized in table 40. It can be seen that (a) although the frequency of cells with fragments was higher in each experimental group than in the controls, the difference between the overall fragment frequency after treatment, 3.4 ± 0.7 per cent, and the control frequency, 1.3 ± 0.7 per cent, did not quite reach a significant level ($P = 0.07$); (b) there is a significant increase in the frequency of cells with quadrivalent configurations in the plutonium series; while most of these were rings and chains of four arising from the chromosomal reciprocal translocations in spermatogonia (as in earlier low- and high-LET radiation studies), a few were similar to those observed after x irradiation of oocytes in female mice (513) and were considered to be the result of chromatid interchanges in spermatocytes during meiotic prophase; and (c) the yield of quadrivalents declines at the longest exposure period of 18 weeks.

368. The data on reciprocal translocations were used by Beechey *et al.* to obtain a rough estimate of the RBE of alpha particles relative to chronic gamma and neutron irradiation (0.7 MeV). For this purpose, only the data pertaining to the 6- and 12-week periods were used (the 18-week data were excluded since it was thought that the decline in frequency might be connected with preferential killing of the sensitive spermatogonial cells). To estimate the period of spermatogonial exposure, the authors subtracted 13 days from the actual exposure period, the former being the time taken for the germ cells to pass through meiosis to metaphase-I. When the "amended" doses of 10 and 25 rad (instead of 14 rad and 30 rad; see table 40) are used and linearity of response is assumed, the rates of translocation induction at the 6- and 12-week intervals are, respectively, $1.0\ 10^{-3}$ rad^{-1} and $1.9\ 10^{-3}$ rad^{-1}, with a mean of $1.45\ 10^{-3}$ rad^{-1} of the average *testis doses*. However, Green *et al.* (199) found that the alpha particle dose to spermatogonial stem cells was 2-2.5 times that to the testis as a whole in their experiments, after ^{239}Pu injection. Assuming a factor of 2.5 in the present experiments (with similar experimental conditions to those of Green *et al.*), one obtains a rate of induction of $0.58\ 10^{-3}$ rad^{-1} of spermatogonial alpha particle dose. This is very similar to that of $0.53\ 10^{-3}$ translocations per rad found after chronic exposures of mouse spermatogonia to fission neutrons of mean energy 0.7 MeV (518), which suggests that these two high-LET radiations have similar RBEs.

369. In the next set of experiments from the same laboratory (details of which were given in paragraph 363), Searle *et al.* (516) made a direct comparison of cytogenetic damage induced by chronic exposures to ^{239}Pu alpha particles and to gamma rays, with a reduction in the amount of plutonium injected and with longer exposure periods than in the previous study (33). As can be seen from an inspection of table 40, in the plutonium series, there were no significant differences in

frequencies of translocations between 21, 28 and 34 weeks of exposure. The estimated mean spermatogonial dose (not taking into account the inhomogeneous distribution of plutonium in the testis) was 15.5 rad and the corresponding mean frequency of translocations, 0.74 ± 0.18 per cent. With gamma rays (1055 rad to spermatogonia), the frequency was 1.7 ± 0.4 per cent. The induction rates, estimated by subtracting the mean control frequency (for both the plutonium and the gamma series), were $3.4\ 10^{-4}$ rad^{-1} of alpha particles and $1.4\ 10^{-5}$ rad^{-1} of gamma rays (linearity of response assumed). Thus it appears that irradiation with alpha particles from ^{239}Pu is about 24 times as effective as chronic gamma irradiation for translocation induction.

370. Other data reported in the paper of Searle *et al.* (516) pertain to induction of chromosome fragments, the rate for which was estimated as $1.2\ 10^{-2}$ rad^{-1}, which is over twice as high as the rate of $4.6\ 10^{-3}$ rad^{-1} which can be estimated from the results of Beechey *et al.* (33) with shorter exposures. Relative to chronic gamma irradiation, the ratio of effectiveness is about 24. In the same experiment, an alpha-gamma ratio of 22 was found for dominant lethal induction (see paragraph 365). Thus, three indices of cytogenetic damage gave very similar alpha-gamma ratios of 24, 24 and 22, from which a mean value of 23 can be derived. However, the frequencies of sperm-head abnormalities were not significantly different from that in controls in the plutonium series, whereas in the gamma series, they were significantly higher (17.1 per cent compared with 3.9 per cent).

371. The above estimates of relative effectiveness of alpha particles and gamma rays for the induction of cytogenetic damage are based on the average dose to the testis, which is likely to be different from the doses to the germ cells at risk because of the known inhomogeneity in plutonium distribution in the testis (199). The authors felt that it was unwise to try to correct for this because (a) no estimates of the magnitude of the inhomogeneity were available except for spermatogonial stem cells and (b) even for these stem cells, the 2-2.5 correction factor estimated by Green *et al.* (199) might not apply under the much more protracted exposure conditions of the present experiment. In particular, there were signs of aggregation of the plutonium deposit (198), which might decrease the effective alpha particle dose to the stem cells and thus could help to account for the much lower rate of translocation induction by alpha particles found in the present experiment ($3.4\ 10^{-4}$ rad^{-1}) than in the previous one of Beechey *et al.* (33), namely, $1.45\ 10^{-3}$ rad^{-1}. In any event, the present results confirm the high effectiveness of ^{239}Pu alpha particles in inducing translocations, even with very protracted exposures.

2. Tritium (^{3}H)

(a) *Induction of dominant lethals in mice*

372. Carsten and Commerford (81) and Carsten and Cronkite (80) have published the results of their studies on the induction of dominant lethals in mice (random-bred, Hale-Stoner-Brookhaven strain) fed with tritiated water (HTO). The HTO test animals were first-litter mice resulting from breeding of eight-week-old animals that had been maintained on HTO (3 μCi/ml) since weaning at four weeks of age. The control animals were first-litter mice taken from the colony and maintained on tap water. From the second generation animals, four experimental groups were established for dominant lethal tests. Group 1 consisted of animals where both the male and female were on HTO. Group 2 females received HTO, males, tap water. In group 3, the situation was the reverse of that in group 2, and group 4 received only tap water (both males and females). At eight weeks of age, in each group, each male was mated to five females for a 5-day period, and 15 days after the mid-point of this breeding period, the females were killed and their uterine contents examined for assessing dominant lethality.

373. The results, based on 366 pregnant females in the controls, 764 in group 1, 315 in group 2, and 316 in group 3, clearly demonstrated that dominant lethals are induced by HTO in both sexes. Significantly fewer viable embryos were found when either both mating partners or only the female was maintained on the tritium regimen. Similarly, when both the partners were on tritium, the incidence of early death (dark mole) is significantly higher than in the control group. Treatment of the males only gave similar effects, but these were not significant. When post-implantation mortality (early *plus* late deaths in the authors' terminology) is used as the basis for comparison, the increased mortality due to HTO in groups 2 and 3 is of the same magnitude in both sexes, and in group 1 (both sexes on HTO) the effect is nearly twice that in groups 2 or 3. Current experiments are directed at repeating these studies with a lower concentration of 1.0 μCi/ml.

(b) *Induction of specific-locus mutations in male mice*

374. Cumming *et al.* (128) have completed the first series of experiments on ^{3}H-induced specific-locus mutations in mice, providing the only data available on such gene mutations in any mammal. In view of possible levels of tritium release, not only from existing nuclear installations but also from contemplated controlled thermonuclear reactors, these data are of great relevance. A total of 14 groups of males was used. Two groups were injected with 0.75 mCi, and the 12 others with 0.50 mCi, of tritiated water per gram of body weight. The results demonstrate that beta radiation from the decay of tritium can induce specific-locus mutations in spermatogonia as well as in post-meiotic stages: 16 mutations have been recovered among a total of 20 626 offspring derived from germ cells irradiated as spermatogonia and 11 in 7943 offspring from irradiated post-meiotic stages. The mean absorbed dose to the spermatogonial cells has been estimated to be 700 rad and that to post-meiotic cells, 430 rad. These data thus permit mutation-rate estimates of $1.58\ 10^{-7}$ rad^{-1} per locus for spermatogonia and $4.60\ 10^{-7}$ rad^{-1} per locus for the other stages. These rates are within the statistical limits of what would have been expected from a comparable external dose of x or gamma irradiation. The point estimate of the RBE for post-spermatogonial stages is close to 1, with fairly wide confidence intervals;

that for spermatogonia is slightly above 2, with confidence intervals that include 1. There are some indications that the distribution of mutants among the seven loci may differ from that produced by gamma rays: noteworthy is the observation that only one of the mutations was at the *s* locus (the expectation would be about 5 or 6). In more recent studies, currently in progress at Oak Ridge, Cumming and W. L. Russell (129) are engaged in collecting more extensive data on tritium irradiation, focusing attention on the induction of mutations in spermatogonia.

(c) *Induction of chromosome aberrations in human lymphocytes by tritiated water (HTO)*

375. Hori and Nakai (233) and Bocian *et al.* (39) have reported on the induction of chromosome aberrations in human lymphocytes exposed to tritiated water *in vitro*. Exposures were carried out by the addition of whole blood to the culture medium containing tritiated water. In the work of Hori and Nakai, the concentration of tritium ranged from $1\ 10^{-6}$ μCi/ml to $1\ 10^{-2}$ μCi/ml, and the cells were exposed during their entire period in culture (48 h). Bocian *et al.*, used two regimens: in one ("acute exposures" in the authors' terminology), the lymphocytes were exposed for a 2-h period prior to PHA stimulation (range of concentrations, 1.71-14.36 mCi/ml), after which they were washed and cultured (53-h cultures); in the other ("protracted series") the cells were exposed during 53 h (concentration range, 0.063-0.51 mCi/ml).

376. The results indicate that with protracted exposures (48 or 53 h) the aberrations produced were mostly of the chromatid type, such as gaps, deletions and fragments, and there were relatively few chromatid exchanges. In the concentration range used by Hori and Nakai, the dose-effect curve for the number of breaks induced was quite complex at low concentrations. In the work of Bocian *et al.* and with the range of concentrations they used, the frequency of chromatid aberrations increased linearly with dose. A quantitative comparison of the frequencies between the two groups of authors is, however, not possible because each group used only one (but different) fixation time, and in addition, the ranges of concentration were different.

377. In the 2-hour exposure experiments of Bocian *et al.*, chromosome-type aberrations were found to be induced (dicentrics, centric rings, terminal and interstitial deletions). The data for dicentrics plus rings, as well as those on deletions, gave a good fit to a linear plus quadratic model. Using the data obtained in x irradiation experiments (acute doses of 50-300 rad), Bocian *et al.* have estimated that the RBE for the induction of dicentrics plus centric rings is about 1.2.

3. Summary and conclusions

378. During the past few years, there has been a growing interest in the study of the biological effects of radioisotopes, particularly of ^{239}Pu and ^{3}H. A number of genetic and cytogenetic studies that have so far been carried out in mice demonstrate that these isotopes are capable of inducing dominant lethals, chromosome aberrations and point mutations (for the last category, only the effects of ^{3}H have been studied).

379. Autoradiographic studies have shown that in mice, intravenously injected ^{239}Pu (as citrate solution) is inhomogeneously distributed in the testis and is largely localized in the interstitial tissue outside and between the seminiferous tubules. A consequence of this is that the alpha-irradiation dose rate to the spermatogonial stem cells is 2-2.5 times greater than the average for the testis as a whole.

380. When ^{239}Pu-injected males are mated to females, there is a significant excess of intra-uterine mortality relative to controls and the effect persists in matings up to five weeks after injection (post- and peri-meiotic stages sampled). In addition, the effect appears to be unrelated to the amount of ^{239}Pu injected (in the range 0.05-0.5 μCi per mouse).

381. Dominant lethal tests performed on F_1 males sired by fathers which received plutonium injection (and derived from matings during the ninth, fourteenth and sixteenth weeks) showed that here again there was an increase in intra-uterine mortality relative to controls.

382. Relative to chronic gamma irradiation, alpha particles from ^{239}Pu seem to be more than 20 times as effective in inducing dominant lethality (post-implantation) in meiotic and post-meiotic stages.

383. In male mice exposed to alpha particles from ^{239}Pu (intravenously injected citrate solution) for a duration of 6-34 weeks, reciprocal translocations (in spermatogonia) and chromosome fragments (in spermatocytes) are induced. Relative to chronic gamma irradiation, alpha-particle irradiation from ^{239}Pu is more than 20 times as efficient for the induction of these effects. This finding is similar to that recorded for the induction of dominant lethals in meiotic stages. These calculations do not take into account the inhomogeneous distribution of ^{239}Pu in the testis.

384. Male and female mice fed on tritiated water, show, in dominant lethal tests, an increased amount of intra-uterine death.

385. In specific-locus tests, mutations have been found to be induced in male mice fed with tritiated water. The data currently available suggest that the rate of induction per unit dose of irradiation with beta particles from ^{3}H is about the same as that of x irradiation. The estimates are $1.58\ 10^{-7}$ rad^{-1} per locus for spermatogonial mutations and $4.60\ 10^{-7}$ rad^{-1} per locus for post-spermatogonial stages. These estimates have wide confidence limits. There is some evidence that the distribution of mutants among the seven loci may be different from that after x irradiation.

386. In human lymphocytes exposed to tritiated water *in vitro*, both chromosome- and chromatid-type aberrations are induced, depending on the concentration of ^{3}H and the duration of exposure.

H. THE RADIATION RESPONSE OF SPERMATOGONIAL CELLS AND ITS RELEVANCE TO THE INTERPRETATION OF GENETIC EFFECTS OF RADIATION

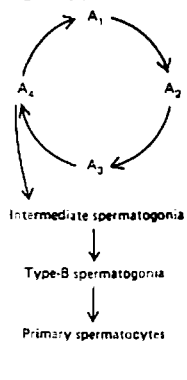
387. In the 1972 report, the model of stem cell renewal proposed by Oakberg (372) for the mouse and by Huckins (239) for the rat and the model of Clermont and Bustos-Obergon (113) for the rat were discussed. According to the Oakberg-Huckins model, stem-cell spermatogonia occur as single isolated cells in contrast to the groups of differentiating spermatogonia which form "chains" of cells connected by cytoplasmic bridges. Renewal of stem cells occurs by the division of some A_s cells; other divisions of A_s spermatogonia result in the formation of paired cells and constitute the initial step in differentiation. Further divisions of the pairs result in irregularly aligned spermatogonia which transform morphologically into the chains of A_1 spermatogonia. All A_1 cells divide into A_2 cells, then into A_3 cells, and so on. Division of A_4 cells results only in the formation of cells of the intermediate type. There is no evidence that the A-type spermatogonia of any type are formed from A_4 cells. The model can be diagrammatically shown as follows:

A_s – singles → A-paired (A_{pr}) → A-chains (aligned) (A_{al}) → A_1 → A_2 → A_3 → A_4 → intermediate spermatogonia → type-B spermatogonia → primary spermatocytes

388. The A_s spermatogonia are the most resistant of the spermatogonial types; they are the only survivors after x-ray exposures of 150 R or more and are responsible for the repopulation of the germinal epithelium. The studies of Huckins (237, 238, 239), Oakberg (372, 373) and de Rooij (439) have shown that some of the A_s cells have a long cell cycle (about 8.5 days in the mouse (372, 373)); it also seems that most have a much shorter cycle, only slightly longer than 26-28 h characteristic of differentiating spermatogonia (238, 374). The relationship between A_s cells having these two average cycle times has not been explained.

389. On the other hand, the "two-stem-cell" model of Clermont and Bustos-Obergon (113) assumes that there are two populations, one of which is the non-cycling A_0 (reserve stem cells, activated only if the more mature classes of cells become depleted) and the other, a renewing cycling population of A_1-A_4 spermatogonia. The A_4 cells were given the role of pivotal cells, forming either more differentiated *In* (intermediate spermatogonia) or less differentiated A_1 spermatogonia as in the following scheme:

(Activated A_0 in emergency)



390. In recent experiments, Oakberg and Huckins (377) used ^{3}H-thymidine labelling in conjunction with x irradiation to study further the problem of germ-cell repopulation in the testis of the mouse, more specifically, to examine whether the A_4 cells form A_1 cells and intermediate spermatogonia (as the model outlined in the preceding paragraph predicts), or whether confirmatory evidence can be obtained for their earlier findings that A_s cells are the active stem cells of the germinal epithelium. Both sectioned material (as in the earlier work of Oakberg) and whole mounts were used to compare the results of the two techniques. The activity of ^{3}H-thymidine used was 17.5 μCi/0.25 ml (intraperitoneal injections, either one or six at 12-h intervals), and the x-ray exposures were 150 R and 300 R (90 R/min).

391. The prediction was that, if the model of Clermont and Bustos-Obergon were valid, only A_1-A_4 cells should be labelled (and subsequently be killed by irradiation) and the A_0 cells should not be labelled. If the Huckins-Oakberg model were valid, since A_s cells are the only survivors after x-ray exposures of 100 R or more, only these should be labelled. It is worth pointing out that data demonstrating labelled A spermatogonia 5 days after an x-ray exposure as high as 1000 R had been available for some time (370) and preliminary results from long-term labelling studies in control mice revealed heavily labelled cells as long as 10 days (more than one cycle of the seminiferous epithelium) after ^{3}H-thymidine injection. On the basis of these results, it has been suggested that the A_0 spermatogonia are the active stem cells of the seminiferous epithelium (371).

392. The results obtained using both methods (sections and whole mounts) demonstrated the survival of A spermatogonia labelled with ^{3}H-thymidine prior to irradiation, and the survivors were almost exclusively A_s spermatogonia. The data are consistent with the hypothesis that the stem cells are indeed in continuous cycle, and that the total cycle time of some A_s cells is long. There was no evidence for a non-cycling reserve stem cell (A_0 population).

393. De Ruiter-Bootsma *et al.* (447) examined the survival of spermatogonial stem cells in the mouse after irradiation with 1-MeV fission neutrons. Groups of male mice (CBA strain) were irradiated with neutrons with acute doses of 200-410 rad (7 levels at 10 rad/min). For purposes of estimating the RBE, two other groups of mice were exposed to 900 and 1200 rad of 300-kVp x rays at 30 rad/min. The number of surviving cells after irradiation was estimated in histological preparations of the testes of the mice killed 11 weeks after irradiation by determining the fraction of repopulated seminiferous tubules in cross-sections. This fraction, called the "repopulation index" (RI)[17] was assumed to be directly proportional to the number of surviving stem cells.

394. It should be pointed out that the above method of estimating stem cell survival is different from the one

[17] The repopulation index after a given irradiation dose D, is defined as $RI(t) = 100\ Ng(t)/L$ (per cent), where N is the number of surviving stem cells, $g(t)$ represents the growth function (mean clone length as a function of time t), and L is the total length of all seminiferous tubules in a testis.

used by Oakberg and others. Subdividing the morphologically undifferentiated A-type spermatogonia into three classes, A-isolated, A-paired and A-aligned, Oakberg (372) observed that the isolated cells were the least sensitive, their numbers being reduced to about 58 per cent of control value when measured 72 h after irradiation with 100 R of x rays, while the numbers of the other undifferentiated types were drastically reduced. De Ruiter-Bootsma *et al.* point out that by counting the number of cells in cross-sections of the testis (as Oakberg has done), difficulties are encountered in distinguishing the isolated cells and the other spermatogonia. To avoid this complication, the authors use the colony-forming unit[18] as the stem cell and employ RI as a reliable measure of survival of A_s spermatogonia.

395. The results showed that the dose-response curve for stem cell survival had an exponential slope with a D_0 of 85 rad, indicating the rather low radiosensitivity of the stem cells. A comparison of the values of RI from the neutron and the x-ray experiments revealed that under the experimental conditions used, neutrons have an RBE of about 4.4. It also approximates the RBE of 6.5 for fission-neutron (1-2 MeV) doses of 18-101 rad and of 4.7 for 172-258 rad reported by Oakberg (370).

396. In a subsequent paper, de Ruiter-Bootsma *et al.* (448) have reported additional data on the radiation response of the spermatogonial stem cells in the mouse testis. Both neutron irradiation (1 MeV, 50-410 rad, 10 rad/min, single exposures) and x irradiation (200-1200 rad, 30 rad/min, single exposures) were used. The mice were killed at four different intervals after irradiation (3, 5, 8 and 11 weeks) and the numbers of surviving stem cells were determined using the colony method discussed earlier, as well as direct colony counts. The formula for calculating RI was slightly modified as follows: $RI(t, D) = 100\ Ng(t, D)/L(D)$ (per cent). According to this formula, at a given time t, RI is a linear function of N if either both the growth function $g(t)$ and the total tubular length L are independent of the degree of stem cell depletion or they vary in the same proportion.

397. The main results are the following: (a) for all post-irradiation intervals studied, RI is exponentially related to the neutron dose, except when its value exceeds 90 per cent; this has been explained by the authors by assuming that the clones which are distributed at random over the tubules, by growing in length, have an increased chance of meeting each other resulting in clonal growth inhibition; (b) the mean D_0 value of the stem cell survival curves in this period is 81 ± 2 rad, pointing to the existence of a highly radioresistant population of stem cells; (c) there is a good correspondence between the RI values and mean numbers of clones counted per testis; (d) the age of the animals does not influence stem cell sensitivity once the animal is adult, although clones grow at a slower rate in older animals; (e) the x-ray curve for stem cell survival is exponential from 400 rad onwards and the value of D_0 is 242 ± 7 rad; (f) the RBE of fission neutrons is dose-dependent and decreases from 5.5 at a surviving fraction of 0.3, to 4.1 at a fraction of 0.01; (g) their findings permit an estimate of about 1800 stem cells present in the normal unirradiated testis.[19]

[18] Commenting on the technique used by Ruiter-Bootsma *et al.* (447), Oakberg (367) has drawn attention to the possibility that the colony method can lead to errors if surviving stem cells are not randomly distributed, especially if longer intervals are used. His preliminary data suggest that survival at high doses is dependent upon the stage of the cell cycle of the seminiferous epithelium i.e., specific areas of the tubule) and, furthermore, that the number of tubules with more than one survivor per cross-section is greater than would be expected. This could lead to a change in the mechanics of repopulation along the inner wall of a cylinder.

1. Effects of dose fractionation

398. In the paper of de Ruiter-Bootsma *et al.* discussed in paragraph 393, results on the effects of neutron-dose fractionation on stem cell survival are also given. In these studies, male mice received 350 rad of neutrons delivered in two fractions of 150 and 200 rad, in that order, with intervals ranging from 4 to 48 h. The data show that fractionation decreases the number of surviving stem cells; the extent of such a decrease depends on the time interval between the fractions. The radiosensitivity of the stem cells increased sharply between 4 and 8 h after the first fraction. The authors surmise that, if this decrease in cell survival is due to a progressive decrease in D_0 values of the stem cells after irradiation, then the first dose apparently triggers the cells to pass into a very sensitive phase of their cell cycle within a period of 4-8 h. (The rise in translocation frequencies in the short-term fractionation experiments discussed in paragraphs 112-113 may thus be explained on the basis of the increased sensitivity of the stem cells to the induction of reciprocal translocations.)

399. Rudnicki and Trojczuk (445) and Rudnicki and Kochmánska-Twardowska (446) investigated the effects of x-ray dose fractionation (8 X 25 rad compared with 1 X 200 rad, 8 X 50 rad compared with 1 X 400 rad, 2 X 50 rad, 5 X 20 rad and 9 X 10.1 rad compared with 1 X 100 rad) on survival and repopulation kinetics of the different spermatogonial cell types. The interval between the dose fractions was 24, 72 or 96 h. The findings are that (a) the different cell types have differential sensitivity to killing, (b) dose fractionation leads to a detectable delay in the rate of repopulation of germinal epithelium and (c) the survival is approximately equal after single and fractionated irradiation and appears to be independent of the number of fractions and the interval between them.

2. Effects of dose rate

400. To evaluate the possible role of spermatogonial cell survival on mutation frequencies at different dose rates, Oakberg and Palatinus (378) irradiated male mice with 300 R of x rays (at 94 R/min) or with 300 R of ^{137}Cs gamma rays at rates of 0.0056 and 0.0007 R/min. One group of mice was killed immediately after

[19] From the relationship $\ln N_D = \ln N_0 - (D/D_0)$ where N_D is the number of clones after a dose D, N_0 is the number of cells in an unirradiated testis, and D_0 is the 37% survival dose.

removal from the gamma field; a second group was killed 24 h later in order to observe initiation of cell repopulation. Cell counts for these intervals were the same for gamma-irradiated mice, and the data were pooled. Mice exposed to x rays were killed five days later when cell survival is minimal. The testes were then processed for making histological preparations.

401. The results showed that (a) after 300 R of acute x rays, only 16 per cent of the stem cells (relative to controls) and only a few differentiating spermatogonia survived; (b) after gamma irradiation at 0.0056 R/min, the survival was 37 per cent for A_s and 24 per cent for A_1 cells; the remaining spermatogonial types showed a depletion to about 5 per cent of control, indicating a markedly higher radiosensitivity of these stages; and (c) at 0.0007 R/min, the number of stem cells was unaffected with survival values for A_1-A_4 spermatogonia ranging from 81 to 97 per cent.

402. On the basis of these data, the authors conclude that (a) the mutation frequency at 0.0007 R/min is measured on a cell population which is maintaining itself at normal levels; (b) after 300 R at 0.0056 R/min (which reduces the A_s spermatogonia to 37 per cent of control), the mutation frequency appears to be the same as after 0.0007 R/min (para. 284); and (c) after 300 R of x rays at 94 R/min (where cell survival is only 16 per cent), the mutation frequency is the highest of all (1972 report, Annex E, table 14); this result is the reverse of that expected if there is a positive correlation between sensitivity to cell killing and sensitivity to mutation induction under the radiation conditions investigated. Other mechanisms, such as repair, are indicated as the primary factors in the reduced frequency of mutations observed at low dose rates.

403. Hsu and Fabrikant (235) conducted a study to examine the cellular response and cell population kinetics during spermatogonial cell renewal in the mouse testis exposed to continuous gamma irradiation (^{137}Cs) at 1.8 rad/day (=0.00125 rad/min) and at 45 rad/day (=0.031 rad/min). Labelling with ^{3}H-thymidine was used for the analysis of cell-population kinetics. Mice were killed at different times during irradiation and their testes were processed for histological examination and autoradiography. In addition, the pattern of post-radiation recovery of the seminiferous epithelium was investigated in mice which were exposed to irradiation at 45 rad/day for two weeks (accumulated dose, 630 rad). The main results are given in the following paragraphs.

404. Depending on the dose rate, continuous irradiation alters the cell-population kinetics in the seminiferous epithelium and more damage occurs at the higher dose rate. At 1.8 rad/day, the type-A population considered as a whole (A_s and A_1-A_4) shows an initial decrease within the first two days of irradiation followed by a new level of steady-state growth at about 80 per cent of the control level. This is essentially a reflection of the decrease in the A_1-A_4 cells, since the A_s cells remain at near-control levels during the entire seven weeks of continuous irradiation. Among the A_1-A_4 spermatogonia there is a gradient in radiosensitivity, the reduction in cell numbers increasing from A_1 through A_4.

405. In the 45-rad/day group, there is a marked decrease in the numbers of type-A spermatogonia (to about 50 per cent) in the first three days (accumulated dose, 135 rad) followed by an increase to normal values by the second week, then a fall and a rise again (60-70 per cent) in about three to five weeks. The A_s cells alone undergo a reduction in numbers to nearly 50 per cent of controls during the first three days of continuous radiation; from day 4 up to about 10, this figure is about 80 per cent of controls and from then on, up to week 3 (when the studies were terminated) control levels are reached. The proliferating type-A cells, depending upon their individual radiosensitivities, reach steady-state levels at various levels below controls.

406. At the lower dose rate, in the *In* cell population, there is an initial (compensatory) rise in cell numbers on day 1, after which normal levels are attained for two weeks, followed by a slight decline to approximately 95 per cent of control values. At the higher dose rate, there is a steep decline in cell numbers and no cells are found in the seminiferous epithelium at the end of the first week of exposure.

407. At the lower dose rate, there is also a decrease in the type-B population, which reaches steady-state levels at about 80 per cent of controls by the third week of radiation exposure. At higher dose rates, the decline is steeper, so that by day 5 of exposure, this compartment is completely depleted.

408. Examination of the recovery pattern *after* irradiation (45 rad/day for two weeks; accumulated dose, 630 rad) shows that the repopulation of the seminiferous epithelium commences with increased cell proliferation in the A_s cells and is supported by the finding of an increase in the A_s mitotic index; the wave of renewed cell proliferation moves from A_s cells through to the A_4 cells. By day 14 after irradiation, *In* and type-B cells reappear, and their cell numbers reach a compensatory peak between 25 and 50 per cent above normal cell numbers, but subsequently stabilize at normal levels. By eight weeks, the curves showing the percentage of labelled mitoses for type-A, *In* and type-B cells show cell-cycle parameters similar to those for unirradiated controls.

409. All these findings of Hsu and Fabrikant (235) are in very good agreement with those of Oakberg (243, 370, 372), Oakberg and Clark (375), Oakberg and Palatinus (378), and Oakberg and Huckins (377). They demonstrate that at a dose rate of 0.00125 rad/min, which is twice the lowest rate employed by Oakberg and Palatinus, the A_s spermatogonia maintain themselves at control levels and that the temporal sequence of recovery commences with the A_s cells.

3. Stem-cell killing and sterile period

(a) *Irradiation of adult male mice*

410. It is known that when adult male mice are irradiated, a period of sterility develops several weeks after treatment and that it is a direct consequence of spermatogonial-cell killing. The length of the sterile

period therefore provides a good indirect measure of cell killing. A relationship between sterile period and dose was indicated in several studies carried out in the 1930s, but until the recent studies of Sheridan (533) with fractionated exposures, no precise measurements had been reported.

411. Sheridan irradiated male mice of the CBA strain with either single x-ray exposures of 600 or 800 R or with fractionated exposures of 300 + 300, 400 + 400 and 500 + 500 R, separated by time intervals of 24, 48, 72 or 144 h. he found that the mean number of days between irradiation and return of fertility was prolonged after fractionation (24, 48 and 72 h) relative to single treatments or with an interval of 144 h. He interpreted this observation as indicating that the shorter intervals used (24, 48 and 72 h) lead to a greater amount of cell killing.

412. Cattanach and Moseley (92) and Cattanach (90) made a thorough study using the length of the sterile period as a measure of spermatogonial killing by irradiating F_1 hybrid (C3H/HeH X 101H) mice with a wide range of single and fractionated x-ray exposures. It was found that the sterile periods were much shorter than those reported by Sheridan at equivalent exposures, even allowing for the fact that Sheridan reported his data in terms of the mean, rather than the median, as Cattanach did.

413. Cattanach (90) found (table 41) that after single x-ray exposures, the dose response curve for the recovery of fertility was irregular; the median day of return to fertility increased little from 300 to 400 R; there was then a slight increase to 500 R, but from 500 to 600 R, there was a dramatic increase in response. Beyond this level, there was little change up to 800 R, but the 900-R and 1000-R treatments gave rapidly increasing lengths of the sterile periods. Quite clearly, the exceptional point is that for the 600-R level: were it not for this, a simple exponential relationship would be obtained. However, five replicate experiments were carried out at this level, and all the results were consistent; consequently Cattanach feels that there is little doubt that the plateau is a true phenomenon. The fact that at 600-800 R, a plateau is obtained is not without significance: it is at these exposure levels that the yields of translocations and specific-locus mutations begin to decline and then fall giving humped dose-effect curves. The coincidence between the hump in the dose-effect curve for genetic damage and the plateau in the sterile period supports the conclusion that throughout the exposure range investigated, the sterile period is a direct consequence of the stem-cell killing.

414. Cattanach believes that the most readily acceptable explanation for the shape of the cell-killing curve is that it has two components, these representing two cell populations with different sensitivities to radiation killing. Since on the basis of Oakberg's data (372), all spermatogonial cells other than the stem cells should be eliminated by even the lowest dose (300 R) employed here, it may be concluded that the postulated sensitive and resistant cells must exist within the spermatogonial stem cell population itself. The two populations could represent two distinct stem cell types and this would find support in the histological observation that within the stem cell population, there are cells with quite different cell cycle times. Alternatively, the two populations could represent stages in the cycle of a single stem cell type. By either interpretation, the existence of two cell populations of different radiation sensitivities could provide the basis of the heterogeneity of the spermatogonial stem cell that has been proposed as an explanation for the humped dose-effect curves for genetic damage (190, 382, 470). Thus, if the genetic damage stems primarily from the population more sensitive to killing, then a drop in yield would be expected when killing increases beyond a certain point and at the highest exposures, genetic damage may only be recoverable from the more resistant cell population.

415. There is doubt on the extent to which the 600-800 R plateau in the length of the sterile period (para. 413) is really connected with stem-cell killing as Cattanach (90) has suggested. Oakberg's data (370) on survival of type-A spermatogonia gave a good fit to a simple exponential curve, as did the stem cell data of de Ruiter-Bootsma *et al.* in the 400-1200 rad range, as discussed earlier (paras. 396-397). Factors other than stem-cell killing, such as the mechanics of stem-cell repopulation, may well influence the shape of the dose-effect curve, for return to fertility, although it is difficult to see why they would modify the time recovery of fertility so specifically over a narrow range of doses.

416. The data obtained from the fractionation experiments (24-h interval between fractions) show that the effect on the sterile period varies according to the total exposure (table 41). Thus at the 400-R level, fractionation results in a sterile period not different from that with the single exposure, but at 600-R, fractionation reduces the sterile period irrespective of the relative magnitude of the two fractions. The opposite situation was then found at the 700-R level where fractionation enhanced the sterile period above that for the single exposure; at 1000 R, fractionation gave either the same response as the single exposure or caused some enhancement. The uncertainty about the effect of fractionation at the 1000-R level derives from the great variability in the response: while this may be characteristic only of high exposures, there is reason to suspect that the relative magnitude and the order of fractions may be important. When 100 R follows 900 R, the median day of return to fertility (108 days) is not very different from the 1000-R single exposure level (102 days) but when the fractions were given in the reverse order, this number is 135.

417. In spite of these complexities, two general conclusions can be made: (a) fractionation at high exposures causes more, rather than less, stem-cell killing than does single treatments. This demonstrates that the decline in yield of genetic damage with higher single doses does not derive from extensive cell killing *per se* and supports the idea that with this form of treatment, genetic damage and cell killing tend to occur in the same cells so that at higher doses, more cells with genetic damage are killed (382). The corollary of this is that, with fractionation, the cell killing brought about by the second of two fractions must tend to occur in different

cells from those in which the genetic damage had been induced by the first fraction: (b) the cell killing response with fractionated treatments rises regularly with increasing exposures, as does genetic damage, so that the irregularity of the single-exposure curve which indicated the existence of two cell populations is eliminated. This would again suggest that whether considering genetic damage or cell killing, the two fractions tend to hit different cells. Further interpretation of the data is not practicable, but it is probable that the diverse response obtained with fractionation, relative to that with the single treatments, stems from an alteration of the relative sensitivities of the two stem-cell populations. The results of Oakberg (372) show that differential cell survival occurs within the long-cycling A_s population.

418. In a subsequent paper, Cattanach and Moseley (92) explored the effects of 500 + 300 R, 500 + 500 R and 300 + 300 R separated by 2 h to 12 days (800-R series), 4 and 7 days (1000-R series), and 24 h, 3, 7 and 10 days (600-R series) between the two fractions (x irradiation). In some experiments, the yields of translocations and/or specific-locus mutations were also measured in addition to the determination of the lengths of the sterile periods.

419. In the 800-R series, with intervals of 16 h to 4 days, fractionation resulted in an increase in the sterile period, well beyond that of the acute exposure (from a median of 71 to one of 81 days); with longer intervals, there was a gradual decrease, reaching a minimum with a 10-day interval (median, about 55 days). In the 1000-R series, the 4-day interval gave a sterile period somewhat shorter (95 days) than that of the 1000-R acute (102 days); the 7-day interval led to a drop (about 82 days), but the results of the individual tests overlapped. In the 600-R series, fractionation reduced the sterile period from about 67 days (acute) to about 52 days (fractionated), and there was very little change with fractionation intervals longer than 24 h.

420. Although the translocation and specific-locus data collected in the fractionation experiments of Cattanach and Moseley (92) are discussed in other sections, it is worth pointing out here that there is no correlation between genetic damage and cell killing (as measured by the length of the sterile period) with different fractionation intervals. However, the translocation and specific-locus mutation experiments give, qualitatively if not quantitatively, a similar variation in response to variation in the treatments. Both indicate a peculiar state of cells surviving the first fraction, such that they may be particularly sensitive to genetic damage 24 h later. The translocation data suggest that this sensitive state may last up to two days and both types of experiment demonstrate that this state does not exist beyond this time.

(b) *Irradiation of young mice*

421. In a recent paper on x-ray induction of translocations in young male mice, Cattanach, Murray and Tracey (94) have presented some results on the incidence of sterile period. In the first two series involving whole-body exposures of 300 and 500 R (acute), 5-day-old, 10-day-old and adult mice were used. The younger age-groups were selected on the basis of Selby's results (527), which suggested a change from an immature to an adult response by the eighth day. In the third series, the exposure was 1000 R (part-body), and in this the response of 3-day-old mice was also studied. The results are summarized in table 41.

422. It can be seen that with 300- and 500-R treatments, the 5-day-old mice did not exhibit any obvious sterile period. As a group, they could be considered to become fertile as they reached maturity, and the fertility remained until the time of sacrifice; it was not of short duration. With adult mice irradiated with 300 and 500 R, the results are in good agreement with all previous tests (median day of return to fertility, 51 and 53, respectively). The response of 10-day-old mice is similar to that of adults.

423. After 1000 R, the response was different: in the 5-day-old group, 1 out of the 10 became fertile on reaching maturity, 5 showed some clear indication of a sterile period and the remaining 4 appeared to be permanently sterilized. The irradiation of 3-day-old mice gave similar results. Fertility in both groups, when regained, was highly variable; litter-size was often quite small, litter production was irregular and 4 of the 14 "fertile" males became sterile after producing only a few litters. All these findings contrast sharply with the response following adult irradiation. The response of animals treated with 1000 R when 10 days old tended to be intermediate between those of the younger and adult groups.

424. The lack of any clear sterile period following the irradiation of 3- or 5-day-old mice might suggest that their germ cells are perhaps more resistant to radiation killing than those of the adult. However, histological studies with rats irradiated when 4-5 days old have shown that the germ cells of the immature animal are highly sensitive to radiation killing (241, 287, 532). The difference from the adult lies in the fact that the surviving cells can still proceed directly into spermatogenesis and lead to the appearance of sperm at sexual maturity (241, 532). It is likely that a similar situation is obtained in the mouse, and this provides an explanation for the lack of clear sterile periods following irradiation of immature animals and points to oligospermia being the cause of the variable fertility observed with the most severe treatment.

(c) *Other species*

425. In studies on the induction of translocations in the spermatogonia of the golden hamster, guinea-pig and the rabbit, Lyon and Cox (308, 309) also examined the length of the sterile periods after different x-radiation doses delivered either singly or in two or more fractions with various time intervals between the fractions. A comparison of the results obtained with those collected by Cattanach (90) for the mouse clearly show that after single exposures the golden hamster, guinea-pig and rabbit took longer to return to fertility than the mouse; among the three, the golden hamsters were the most sensitive. After 600 rad. the guinea-pig appeared to have a somewhat shorter sterile period than the golden

hamster, but the confidence limits were wide. Since in the golden hamster the duration of spermatogenesis is 35 days, as in the mouse, and since the sterile period includes a component due to multiplication of surviving stem cell spermatogonia and another for the duration of spermatogenesis (after adequate spermatogonial repopulation has occurred) the longer sterile period in this species must indicate a longer period spent in spermatogonial repopulation. This might mean that either the spermatogonial killing is more severe in the golden hamster or the dynamics of their recovery is very different.

426. In the guinea-pig and rabbit, spermatogenesis lasts longer than in the mouse, durations of 49 days in the guinea-pig and 52-60 days in the rabbit being estimated for spermatogenesis plus epididymal transport. Therefore, for equal killing, longer sterile periods would be expected than in the mouse, but only 1-2 weeks longer (since spermatogenesis plus epididymal transport in the mouse takes about 42 days). In fact the sterile periods were more than 1-2 weeks longer and hence, again there is a suggestion either for more severe spermatogonial killing or for slower rates of recovery in the guinea-pig and hamster than in the mouse. Thus, although differences in recovery cannot be ruled out, it seems probable that spermatogonial killing is more severe in the guinea-pig and hamster than in the mouse and is most severe in the hamster.

427. In the golden hamster, with a 2 X 200 rad (24-h interval), the sterile period was longer by about a month relative to that after the acute dose (4.5 ± 0.5 months compared with 3.5 ± 0.5 months); in the guinea-pig treated with a 2 X 300 rad (24 h) the sterile period was much longer, and at the time cytological examinations were made, the testes were very small (one third normal size) and suggested that the animals were unlikely to recover fertility; in contrast, after a 600-rad single exposure, fertility was invariably recovered after 4.5 ± 1.5 months. Thus the increased length of the sterile periods in both the species indicate that spermatogonial killing was severe after the fractionated exposures. As will be recalled, in the mouse, at these dose levels, there was either no change in the length of the sterile period (relative to that after acute exposures) or a slight lowering with fractionation. The data with eight-week fractionation also suggest that in both the species, the spermatogonial population did not return to normal at the end of the second fraction. With multiple fractions, the sterile periods were slightly shorter than after single doses, but owing to repopulation of the testes during the course of the treatment, it is not possible to interpret this in terms of spermatogonial-cell killing.

4. A model for stem cell heterogeneity in the adult and immature mouse testis

428. The existence of heterogeneity in radiosensitivity among spermatogonial cells to the mutagenic and killing effects of ionizing radiation had long been inferred from genetic and cytongenetic studies and direct evidence had been provided by histological studies of the irradiated testis. It is also known that the A_s spermatogonia are the most resistant of the spermatogonial cell types (and the only survivors after x-ray exposures of 150 R or more) and are responsible for the repopulation of the germinal epithelium. Although the exact basis of stem cell heterogeneity is not fully resolved, two current ideas are the following: (1) two or more distinct stem cell types with differing radiosensitivities exist (90, 92, 93), and some basis for this is provided by the histological evidence from both rat and mouse that stem cells with different cell cycle times are present in the testis (see paragraph 388); (2) heterogeneity simply reflects cell stage sensitivity differences within a single cell type (90, 92, 93, 420). The model of Cattanach *et al.* (94), which in turn is based on the model of cell cycle devised by Smith and Martin (541) argues that the heterogeneity in radiosensitivity stems from variations in cell cycle times that normally occur in the stem-cell population (see also reference 96).

429. The model of Smith and Martin divides the cell cycle into two parts. One, termed the B phase, is regarded as a deterministic and highly co-ordinated process; it corresponds to S, G_2, M and part of G_1. The other part, contained within G_1 is called the A phase and is thought of as an indeterminate, static condition in which the cell is not actually progressing through the cell cycle. Cells may remain in the A phase for any length of time, but leave and enter the B phase exponentially with respect to the time they have spent in the A phase in much the same way as radioactive material will decay at a rate determined by its half-life. The model also predicts that the intermitotic times of sibling cells should also be exponentially distributed. It might be noted that a long A phase together with the deterministic part of G_1 constitutes the so-called G_0 period for slowly dividing or non-dividing cells.

430. Application of this model to the spermatogonial stem-cell populations of the adult mouse suggests that the existence of long (8.5-day) and short ($\approx$ 28-h) cycling cells (374) may perhaps be an over-simplification. A range of cell cycle times should be expected and these would not be characteristic of different cell types, but represent only cell-to-cell and generation-to-generation variations in the time a single cell type spends in the A phase. On the basis of this, the heterogeneity in radiosensitivity of the spermatogonial stem cells is a reflection of the existence of the A phase in addition to the stages of the B phase of the cell cycle. Cells in a long A phase might be most resistant to radiation damage since, like the non-dividing gonocytes (primordial cells) of the new-born mouse, they would have a great time available for mutational/lethal repair before the onset of S. Cells in a short A phase, leaving an A phase of any length or in the B phase might be more sensitive to radiation damage and yield higher levels of genetic damage at doses compatible with significant levels of survival. (However, this interpretation seems to be at variance with the observations of Huckins (237), which suggest that fast-cycling A_s spermatogonia are probably already differentiated.)

431. The above line of reasoning applies to spermatogonial stem-cell populations under normal conditions.

However, within a few days of germinal depletion by irradiation exposure, a quite different situation may exist. Genetic and sterile period data indicate that the surviving, formerly more resistant cells are stimulated into proliferating activity, this being maintained until stem-cell repopulation is essentially complete (90, 92, 93, 420). During this period, cell cycle times must be much shorter than under normal conditions and, on the model of Smith and Martin, this should be achieved by shortening or eliminating the A phase, and this might be expected to lead to a greater radiosensitivity. This may be true for cell killing (92, 93), but the yield of genetic damage from proliferating cells is actually reduced (92, 93, 420).

432. Evidence against the hypothesis of Cattanach *et al.* outlined in the preceding paragraphs has recently been presented by Oakberg (367a, 377a), and the relevant data are summarized in table 42. This shows no evidence for alterations in the cell-cycle properties of A_s spermatogonia labelled prior to irradiation with exposures of 100, 300, 500 and 600 R and scored 207 h after irradiation, even though survival was reduced to 9 per cent of control by 600 R. Differential cell survival was observed after a single 1000-R exposure and after two 500-R fractions given 24 h apart, yet no apparent effect on cycling properties occurred since relative positions of the different exposure groups (in per cent labelled cells) was maintained over the 207-414 h interval. (The lower value for controls at 414 h arises from differentiation into A_{pr} and A_{al} cell types.)

433. Turning now to the response of the testis of young mice, the observations of Cattanach *et al.* (94) are: (a) the lack of any clear sterile period following the irradiation of 3- or 5-day-old mice; (b) their reduced adult testis weight; (c) lower translocation yields than in adults with a decline in yield at the highest exposure of 1000 R, which is more pronounced than in adults (about 1 per cent in 3-day-old mice, 0.3 per cent in 5-day-old mice, and 4.2 per cent in adults). A consideration of the developmental processes that occur in the testis within the first few days of birth suggest an explanation for the different response of the immature mouse. Histological studies with rat and mouse testis (32, 240, 241, 341) have established that only non-dividing gonocytes are present at birth, but within the next 2-3 days, large division figures may be seen and the first generation of spermatogonia appear. These lie centrally within the sex-cords, but, at about 6.5-7.5 days in the rat (240) and evidently much earlier in the mouse (95), these move towards the limiting membrane, where proliferative activity is initiated. It is not known however, whether these mitotically active spermatogonia are stem cells or the more differentiated types that appear during spermatogenesis. Quite probably, both are represented.

434. Thus, it is clear that spermatogenesis must be underway in the 5-day-old mouse, for the animal is fertile by at most six weeks of age (the time taken for the duration of spermatogenesis, including sperm transport to the ejaculate). In addition, there may be a build-up of stem cell numbers over the first week or two of life. Proliferative activity by the stem cells could alone account for the low translocation yields. The situation may be considered analogous to that of the adult testis several days after an initial radiation exposure (92, 93, 420). In both situations, most spermatogonial stem cells may have a short cell cycle and yield low levels of genetic damage. It might also be expected that under these conditions, not all cells would be proliferating. Some would be longer cycling and thus, liable to be in the relatively radioresistant A phase. The presence of such cells in the generally proliferating stem-cell population of the immature testis would account for the heterogeneity in radiosensitivity indicated by the decline in yield of genetic damage at the highest exposure. Alternatively, this decline of genetic damage at the highest doses could be attributed to differential survival of stages in the mitotic cycle, just as in the adult.

435. Finally, it bears mentioning here that for the adult testis, the model of stem cell heterogeneity proposed by Cattanach *et al.* (94) is, in several conceptual aspects, strikingly similar to that independently advanced by Preston and Brewen (420) although the latter authors did not, at least explicitly, relate their model to that of Smith and Martin.

5. Summary and conclusions

436. Recent histological and labelling studies carried out with x-irradiated mouse testes have provided confirmatory evidence for the conclusion that the A_s spermatogonia are the active stem cells of the seminiferous epithelium and that they are in continuous cycle. There is no evidence for a non-cycling reserve stem cell.

437. After acute irradiation with fission neutrons, the dose-effect relationship for spermatogonial stem cell survival (50-410 rad) has an exponential character with a D_0 value of around 80 rad; after acute x-irradiation, the curve is also exponential from 400 to 1200 rad, with $D_0 = 242$ rad.

438. The RBE of fission neutrons relative to x rays for stem cell survival (acute irradiation) decreases from 5.5 at a surviving fraction of 0.3, to 4.1 at a fraction of 0.01.

439. Fractionation of a neutron dose of 350 rad into two fractions (150 + 200) with intervals ranging from 4 to 48 h leads to decreased survival of spermatogonial stem cells; the radiosensitivity of the latter increases sharply between 4 and 8 h after the first fraction.

440. After an x-ray exposure of 300 R delivered at a rate of 94 R/min, the survival of A_s spermatogonia is reduced to 16 per cent of that in controls; with gamma-ray exposures of 300 R delivered at rates of 0.0056 and 0.0007 R/min, the relative survival of the A_s spermatogonia was reduced to 37 per cent with the first régime and unaffected with the second. The mutation frequencies (specific-locus mutations) under the first régime (acute x rays) is higher than those under the latter two. These observations suggest that under these conditions, there is no correlation between spermatogonial stem-cell killing and mutation rate.

441. Under continuous gamma-irradiation conditions at a dose rate of 1.8 rad/day for seven days, the A_s spermatogonial cells show no reduction in number; when the dose rate is increased to 45 rad/day, the number of A_s cells is reduced to 50 per cent of that of controls during the first three days of continuous irradiation; from day 4 to 10, this figure is 80 per cent, and from then on, control levels are reached.

442. Examination of the recovery pattern after continuous irradiation with gamma rays at 45 rad/day for two weeks shows that the repopulation of the seminiferous epithelium commences with increased cell proliferation in the A_s cells and is supported by the finding of an increase in the A_s mitotic index.

443. The duration of the sterile period in irradiated male mice is a good but approximate measure of the amount of spermatogonial stem-cell killing. With acute x-ray exposures ranging from 300 to 1000 R, the relationship between exposure and the median day of return to fertility gives a good fit to an exponential relationship if the data obtained at levels of 600-800 R (where a plateau is observed) are excluded.

444. The length of the sterile period following fractionated x-ray exposures varies with the total exposure, the size and sequence of the fractions, and the time interval between the fractions. Thus, for instance, fractionation at high exposures (with 24-h intervals) causes more, rather than less, stem-cell killing than do single treatments. When 100 R follows 900 R, the median day of return to fertility (108 days) is not very different from the 1000-R single exposure (102 days), but when the fractions are given in the reverse order, this number is 135. In experiments where the fractionation interval varied from 2 h to 12 days, the length of the sterile period also varied; for instance, in the 800-R series (500 + 300 R), with intervals of 16 h to 4 days, fractionation led to an increase in the length of the sterile period (relative to that acute exposure), and with longer intervals there was a gradual decrease reaching a minimum with a 10-day interval.

445. X irradiation of 3- and 5-day-old male mice (300 and 500 R) did not lead to any clear sterile period; the adult testis weight of these mice was reduced and lower translocation yields were obtained (relative to adults); with a higher exposure of 1000 R, the response was variable: some mice became permanently sterilized, some showed clear indications of sterile period, and some became fertile (but in these, litter size, litter production etc., were quite variable). the translocation yields were also severely reduced.

446. After single x-ray exposures to males, the golden hamster, quinea-pig and rabbit took longer to return to fertility than the mouse; of the three, the golden hamsters were the most sensitive. With fractionated exposures, the sterile period in the golden hamster (2 X 200 rad, 24-h interval) was about a month longer than after acute exposure; in the guinea-pig (2 X 300 rad, 24 h interval), the situation was qualitatively the same. The data after multiple small fractions showed that the length of the sterile period was slightly shorter.

447. A model to account for spermatogonial stem-cell heterogeneity in the mouse has been proposed by Cattanach and co-workers, which in several respects is similar to that proposed by Preston and Brewen. The heterogeneity is attributed to a variation of cell cycle times within a single stem cell type. Those in the long G_1 (A phase) would be the most radioresistant, having greater time available for repair before the onset of S; those with a shorter A phase, leaving the A phase or in other stages of the cell cycle (S, G_2 and M) would be more radiosensitive and contribute most to the total yield of genetic damage at lower x-ray exposures (<600 R). Under normal conditions most cells will be in G_1, and after acute irradiation most of the genetic damage will be recovered from these stem cells. However, under fractionated irradiation conditions, for instance when cell proliferation takes place (depending on the interval), such cells must spend a much higher proportion of their time in S and G_2, and the recovery of both translocations and point mutations from these stages should approximate only one half of that from G_1 due to chromatid segregation. Likewise, yields from short-cycling cells such as those in the immature testis will be lower.

448. An alternative explanation has been proposed by Oakberg on the basis of the data of Huckins, which suggest that the short-cycling A_s spermatogonia are already differentiated. Furthermore, it appears that only the long-cycling A cells survive exposures of 300 R or more. As repopulation begins, short-cycling cells reappear, but they all will have been derived from survivors of the long-cycling A_s spermatogonia. The heterogeneity therefore arises from differences attributable to a stage in the mitotic cycle of the long-cycling stem cells.

I. TIMING OF OOCYTE DEVELOPMENT IN THE ADULT MOUSE

449. The timing of oocyte development in the adult mouse is an essential prerequisite to our understanding of the dramatic change in radiation-induced mutation rate; in addition, such knowledge is very important to relate specific oocyte (and follicular) stages to specific post-irradiation litters. With this objective in mind, Oakberg and Tyrell (379) have initiated an autoradiographic study in which adult eight-week-old female mice are given two injections of 50 μCi of N-(acetyl-^{3}H)-D-glucosamine 16 h apart (a total of 100 μCi per female). Mice are killed at intervals ranging from 1 h to 10 weeks after irradiation and the ovaries appropriately processed. The progressive appearance of unlabelled oocytes (unlabelled in the zona pellucida) and concurrently developing follicles was used to obtain an estimate of about 35 days for a follicle of 20-30 cells to reach maturity and be ovulated; this period of time is not long enough to account for the number of litters conceived after 50 R. However, more recent work (367) suggests that 45-46 days are required for all stage *3b* follicles to reach ovulation. Stages *2* and *3a* appear to grow quite slowly, and this may explain the fertility response after acute exposure of adult female mice to 50 R of x rays.

J. THE INDUCTION OF CHROMOSOME ABERRATIONS IN SOMATIC CELLS, THE ARM NUMBER HYPOTHESIS, AND ITS RELEVANCE TO THE EVALUATION OF HAZARDS FROM THE INDUCTION OF RECIPROCAL TRANSLOCATIONS

1. Introduction: the arm number hypothesis

450. The literature on the induction of chromosme aberrations in somatic cells, mainly in human peripheral blood lymphocytes, was last reviewed comprehensively in the Committee's 1969 report (588). In 1972, the Commitee had at its disposal some new data that had just become available from the comparative study of Brewen and colleagues[20] on the x-ray induction of asymmetrical interchanges (dicentrics) in lymphocytes of six different mammalian species (man, marmoset, wallaby, pig, Chinese hamster and mouse). The data showed that (a) in all the species except the wallaby, in the range of exposures up to 400 R, the exposure-frequency relationship for dicentric induction gave a good fit to the model

$$Y_j = b_j D + c_j D^2$$

where Y_j is the yield in the jth species, b_j and c_j, the linear and quadratic coefficients, and D, the radiation exposure. In the wallaby, the best fit was to the model $Y = cD^2$; (b) the combined dicentric data of all the species gave a satisfactory fit to the model

$$Y_j = (N_j - 1)(bD + cD^2)$$

where N_j is the effective chromosome arm number of the species and the other symbols are defined in (a); (c) the above models accounted for a large amount of variation in the frequencies among the species, but not all of it; (d) man, with an effective chromosome arm number of 81, was found to be twice as sensitive as the mouse, with an arm number of 40; and (e) with regard to the production of deletions, which was also studied, the arm number did not seem to influence the yields, and man and the mouse had approximately equal sensitivity.

451. Assuming that the probability of forming a reciprocal translocation is the same as that of forming a dicentric (as shown by Heddle's results in *Vicia faba* (224)), Brewen *et al.* concluded that "dicentric production in these organisms is, at best, a direct measure of reciprocal translocation production and that man is twice as sensitive as the mouse in the dose range measured". Both UNSCEAR and BEIR (34, 589) considered the above line of reasoning valid and assumed that human spermatogonia are twice as sensitive as those of the mouse for the induction of reciprocal translocations. Their risk estimates for this class of genetic damage were based on this assumption.

2. Relationships between the frequencies of dicentrics in lymphocytes, reciprocal translocations in spermatocytes, and heritable translocations in F_1 progeny

452. Subsequently, Brewen and Preston (52, 54) made a direct comparison of the yields of dicentrics after irradiation of lymphocytes and of reciprocal translocations in spermatocytes after spermatogonial irradiation in the mouse, Chinese hamster, marmoset and guinea-pig. The results showed that the model of a linear relationship between the dicentric yield and the effective chromosome arm number (which has come to be called the "arm number hypothesis") is applicable to translocation induction in spermatogonia as well; however, the absolute frequencies of reciprocal translocations in spermatocytes were roughly one fourth of those of dicentrics in lymphocytes.

453. The earlier published data of Ford *et al.* (170) had shown that, in mice, the frequencies of heritable translocations recovered in the F_1 progeny of irradiated fathers (spermatogonial irradiation) were about one eighth of those expected on the basis of direct counts in spermatocytes of the irradiated males themselves (also spermatogonial irradiation). Considering all these results together, Brewen and Preston (52, 54) proposed that (a) a method is now at hand to make at least a preliminary estimate of germ-cell radiosensitivity from an extrapolation of that of somatic cells and (b) the frequencies of heritable translocations after spermatogonial irradiation are predictable from those of dicentrics in lymphocytes (i.e., frequency in F_1 progeny = dicentric frequency in lymphocytes X 1/4 X 1/8 = 1/32).

3. Further work on the arm number hypothesis

454. Since the hypothesis looked plausible and, if valid, would permit a meaningful use of data collected with lymphocytes in the context of hazard evaluations, the work of Brewen and colleagues catalysed research. The work that has been carried out during the last few years in this area (see reference 494 for a recent review) bear on the different steps in the extrapolation sequence, dicentrics in somatic cells → reciprocal translocations in somatic cell → reciprocal translocations in spermatocytes → reciprocal translocations in the F_1 progeny. The evidence thus far accumulated suggests that the arm number hypothesis is now less strong than it was at the time it was formulated and the procedure of extrapolating from the sensitivity of somatic cells to that of germ cells in fraught with uncertainty.

(a) *The relationship between dicentrics and reciprocal translocations in lymphocytes*

455. Until recently, most of the data on the induction of aberrations in human peripheral blood lymphocytes were collected from experiments that were designed for purposes other than for testing whether dicentrics and reciprocal translocations are induced at equal frequencies (88, 231, 497, 504). There is a suggestion of an excess of dicentrics in these studies. The recent work of Buckton (66), in which she used G- and R-banding to identify the break-points in human lymphocyte chromosomes, shows, however, that after an x-ray dose of 200 rad, the frequencies of dicentrics are equal to that of reciprocal translocations involving two chromosomes (G-banding: 100 cells, 29 dicentrics and 31 trans-

[20] The results were published in 1973 (55).

locations: R banding: 100 cells, 26 dicentrics and 27 translocations: conventional staining: 100 cells, 33 dicentrics and 26 translocations).

(b) *Induction of dicentrics in lymphocytes of different mammalian species*

456. Extensive data that have recently become available on the radiation-induction of dicentrics in peripheral blood lymphocytes of species other than those investigated by Brewen and colleagues[21] have shown that the arm number hypothesis is by no means valid for all the species; exceptions have been found in several primate species and two carnivores (the beagle dog and the cat). In addition, the comparative study of de Boer *et al.* (41) involving, among others, mouse and human lymphocytes has shown that at x-ray dose levels of 100 and 200 rad (100 rad/min), the frequencies of dicentrics are equal in both species:

	Dose level (rad)			
	100		*200*	
	Mouse	*Man*	*Mouse*	*Man*
Cells scored	800	200	500	200
Dicentric frequency (%)	12.3	10	39.6	34

The major technical difference with respect to the mouse work is that de Boer *et al.* found that, 36 h after the initiation of the cultures, the irradiated-stimulated lymphocytes were in the first division and used this as their harvesting time. In the work of Brewen *et al.*, however, longer culture times (60-63 h) were used. The sensitivity of the lymphocytes of the tobacco mouse, which was also investigated in the study of de Boer *et al.* at the 100-rad level, was found to be the same as that of normal mouse lymphocytes.

457. In the rhesus monkey (*Macaca mulatta,* arm number 84), van Buul (70) noted that the frequencies were lower than those in man at x-ray dose levels of 100, 200 and 300 rad, although the difference reached statistical significance only at the highest dose (26.6 per cent in the monkey compared with 39.0 per cent in man). However, in this study, the absolute frequencies of dicentrics in man were much lower than those obtained in other work (see Brewen *et al.* (55), for example).

458. The results of Muramatsu and Matsuoka (352) with lymphocytes of the cynomolgus monkey (*Macaca fascicularis,* arm number 83) showed that their sensitivity relative to sensitivity of human lymphocytes was 0.79. Hirai and Nakai (229) noted that in the cynomolgus monkey, the squirrel monkey (*Saimiri sciureus,* arm number 77) and the slow loris (*Necticebus cougang,* arm number 99), the frequencies of dicentrics after 100, 200 and 300 rad of gamma rays were roughly similar. The lymphocytes of the two carnivorous species, the beagle dog (*Canis familiaris,* arm number 79) and the domestic cat (*Felix catus,* arm number 71), studied by Muramatsu and Matsuoka (352) manifested much lower sensitivities than human lymphocytes (16 and 22 per cent, respectively, of human lymphocytes). To this list may be added the work of Sasaki *et al.* (501) with human lymphocytes. These investigators found that, at a dose of 160 rad, approximately twice as many exchange aberrations (dicentrics plus rings) were induced in the lymphocytes of individuals who had trisomic constitutions (trisomy 21, trisomy 18, trisomy D etc.) as in those of normal individuals.

459. In contrast to the above findings, the work of Scott and Bigger (502) with potoroo lymphocytes (arm number 24) has shown that the frequencies of dicentrics observed were in agreement with the expectation based on the arm number hypothesis. The data of Léonard *et al.* (286) for the lymphocytes of the goat (*Capra hircus,* arm number 60), the sheep (*Ovis aries,* arm number 60) and the pig (*Sus scrofa,* arm number 64) showed that, up to 300 R (x rays), there were no striking differences between the dicentric frequencies of these three species. After 400 R however, higher yields were obtained with the pig and goat lymphocytes (76.3 ± 4.4 and 88.5 ± 4.5 per cent) than in those of sheep (57.5 ± 3.7 per cent). Although the sensitivity of the lymphocytes of the cow (*Bos taurus,* arm number 64) was also assessed in the work of Léonard *et al.*, the frequencies between replicates were so widely different that a firm conclusion cannot be made. The *average* frequencies recorded up to 300 R were not very different from those in the other three species, and at 400 R they were similar to those in sheep.

460. With rabbit lymphocytes, the reported results are contradictory: Scott and Bigger (502) found that after x- or neutron-irradiation, the observed frequencies of dicentrics were less than one half of those in human lymphocytes. The x-ray data of Muramatsu and Matsuoka (352) and the gamma-irradiation data of Sasaki (498) for the rabbit are in line with those of Scott and Bigger. In contrast, Bajerska and Liniecki (20) found that the frequencies of dicentrics in rabbit lymphocytes were similar to those recorded for human lymphocytes in an earlier study (291). There were several technical differences between the experiments of Bajerska and Liniecki and those of the others, so that here again, no firm conclusion can be reached.

(c) *Induction of dicentrics in mouse and human fibroblasts*

461. In assessing the radiosensitivity of another type of somatic cells, namely fibroblasts, Sasaki (499) found that (a) mouse embryonic fibroblasts irradiated *in vitro* at the fourth and sixth subculture generations manifested the same sensitivity to the induction of dicentrics as comparable human material irradiated under similar conditions. In addition, the frequency of dicentrics recorded were very similar to those in an earlier study of Sasaki and Tonomura (500) at 100-500 R with human lymphocytes; (b) fibroblasts from mice irradiated as embryos or as new-borns were less than one half as sensitive as those mentioned under (a), but the frequency increased to about 60 per cent for

[21] Brewen *et al.* had observed that in the marmoset, the dicentric yields were consistently higher than expected on the basis of relative arm numbers.

4-day-old mice and to 90 per cent for 11-day-old mice; and (c) human embryonic fibroblasts (from embryos 9-11 weeks old) had the same sensitivity as that of fibroblasts in advanced *in vitro* passages (see (a) above).

462. In other experiments briefly mentioned in his paper, Sasaki (499) noted that in the cultured fibroblasts of the rat (62 arms) and the African green monkey (*Cercopithecus aethiops*, arm number 120) similar yields of dicentrics were obtained, despite the wide difference in the chromosome arm numbers.

(d) *Induction of reciprocal translocations in spermatogonia of different mammalian species*

463. Work on translocation induction in spermatogonia of rats, guinea-pigs and rabbits have revealed no apparent correlation of the relative yields with arm numbers. Thus, after 300 R of x irradiation, the frequencies of translocations in the rat and the mouse were the same (191). The findings of Lyon and Cox (309) show that in the range of 100-300 rad of x rays, the mouse, with 40 chromosome arms, is the most sensitive, followed by the rabbit (80 arms), guinea-pig (64 arms) and golden hamster (80 arms). Essentially similar results were obtained with post-meiotic germ cells of the above four species. In the rhesus monkey, van Buul (70) and Lyon *et al.* (314) found that reciprocal translocations were induced at much lower frequencies than in the mouse.

(e) *Relationship between dicentrics (lymphocytes) and translocations (spermatogonia)*

464. It may be recalled (paras. 452-453) that the results of Brewen and Preston (54) in the Chinese hamster, mouse, marmoset and guinea-pig[22] suggested that there appeared to be a definite quantitative relationship between the frequencies of dicentrics in lymphocytes and those of reciprocal translocations in spermatocytes, namely, that the latter were about one fourth of the former. The complete data recorded in the paper of Brewen, Preston and Gengozian (57) for the marmoset and man[23] now raise questions about the validity of this relationship, as can be seen from an inspection of table 43. In this table data for the rhesus monkey and the rabbit are also given. It will be clear that the relationship between the dicentric frequencies (in lymphocytes) and reciprocal translocations (in spermatocytes) is dose- and species-dependent. Also worth noting is the finding that the radiosensitivity of human spermatogonia is more similar to that of the marmoset than to that of the rhesus monkey.

(f) *The relationship between the frequency of translocations observed in spermatocytes and in the* F_1 *progeny*

465. The new data of Generoso *et al.* (186) and of Brewen *et al.* (56) on the relationship between the frequency of translocations recorded in spermatocytes (after spermatogonial x irradiation) and that in the F_1 progeny have raised the possibility that the latter may be one fourth of the yield in spermatocytes at an exposure level of 150 R, one that is consistent with theoretical expectations. This is in contrast to the observations of the above authors at 300, 600 and 1200 R and the earlier ones of Ford *et al.* at 1200 R, where the ratio was one eighth. The limited data of Pomerantzeva *et al.* (416) (see paragraph 132) suggest that at a gamma-ray exposure level of 900 R (delivered in three equal fractions at 28-day intervals), the above ratio may be one fourth, although not significantly different from one eighth.

4. Problems, perspectives, summary and conclusions

466. The information presented in the preceding paragraphs supports the view that the arm number relationship is not adequately documented to be used at present to predict from lymphocyte data of one species the expected frequencies of dicentrics in lymphocytes of another, nor can it be reliably used to estimate the frequencies of translocations in spermatocytes of one species from those of another. Furthermore, the two-fold higher sensitivity of human lymphocytes to the induction of dicentrics (relative to the mouse) found by Brewen *et al.* could not be confirmed. The available human data (testicular irradiation), although consistent with a two-fold higher sensitivity of the human testis to translocation induction relative to mouse, do not rule out a difference as high as four-fold. Besides, the primate data considered as a whole show striking species differences.

467. The research interest generated by the work of Brewen and colleagues and the work that has followed have exposed several interesting facets of the problem of the induction of exchange-type aberrations, whether it be in somatic or germinal cells. Among these may be mentioned (a) the variations in aberration yields depending on fixation times arising as a consequence of the heterogeneity of the radiosensitivity of the lymphocytes even though they are at the same stage of the cell cycle; (b) differential spermatogonial killing in the different species, the nature and kinds of reciprocal translocations induced in spermatogonia and their differential effects (leading to different degrees of underscoring in spermatocytes, for instance); (c) differences in radiosensitivity between chromosomes and between parts of chromosomes and differences in the capacity for accurate DNA repair; and (d) the extent to which aberration induction is influenced by the amount and/or distribution of heterochromatin and the organization of the chromosomes and heterochromatin in the nuclei of cells or cell stages irradiated.

468. In their human lymphocyte experiments, Searbright (504), Holmberg and Jonasson (231), Caspersson *et al.* (88) and Aymé *et al.* (16) found that chromosome breakage was non-random and that the break-points were located preferentially in the so-called R bands (bands of weak fluorescence). In contrast, Buckton's results (66), while not contradicting the findings of non-random breakage of the chromosomes, show that chromosomes rich in R-band material are not preferentially damaged by irradiation at all and that

[22] The guinea-pig and marmoset results were incomplete at the time the paper (54) was published.

[23] Preliminary data on human testicular irradiation given in reference 51 were not inconsistent with a two-fold higher sensitivity of our species relative to the mouse for the induction of translocations.

about 30 per cent of the breaks that are induced occur neither in a G-positive nor in a negative band, but on the interface between them (which certainly does not constitute a third of the chromosome material). She argues that most of the investigators have used either G or Q bands for identification purposes and the majority of identifying features on the chromosomes is constituted by the positively stained bands (389). Because of this, if one positively stained band is determined to be present and the next positive band to be absent, there will tend to be a bias for locating the break-point in the associated negative band. Her technique in which the same cells are G-banded followed by R-banding appears to permit greater resolution of the location of break-points. In any case, the observations that breakage is non-random are valid, although the mechanism underlying it is not known. This non-randomness may have important implications for the formation of chromosome aberrations.

469. Conclusive cytogenetic evidence on the radiosensitivity of our species for translocation induction (at least in males) will have to come from irradiated human material. In the meantime, interspecific cytogenetic studies with several experimental mammals (including primate species) will continue to serve a useful purpose in providing us with insights into the kinds of problems that we are likely to encounter at the human level, so that the right questions can be asked.

III. NATURE OF RADIATION-INDUCED DAMAGE AND THE PHENOMENON OF REPAIR

1. Introduction

470. The 1972 report of the Committee considered in some detail the developments in the molecular and cellular radiobiology of damage to DNA induced by uv light and ionizing radiations and the processes of repair associated with it. The past few years have witnessed considerable progress in the study of uv damage in DNA and its repair in prokaryotic systems and an extension and application of this knowledge and know-how to eukaryotic systems and to damage induced by ionizing radiation and a number of chemicals. A comprehensive and up-to-date appraisal of the current state of the art in this area is given in the proceedings of the recent Squaw Valley Conference (343). Much of the progress made stems from the continued refinements of the existing methods and the development of more powerful and more sensitive ones; these have led to the isolation and characterization of a number of enzymes involved in the repair of DNA damage and the exploitation of the unique properties of such purified specific lesion-recognizing enzymes in further studies (392).

2. Progress in the enzymology of repair after uv irradiation

471. Ultraviolet and chemical treatment, particularly with prokaryotes, has led to the elucidation of major enzymatic reactions underlying both photoenzymatic and excision repair. An *E. coli* photoreactivating enzyme has been purified and characterized (551). A number of specific lesion-recognizing enzymes involved in excision repair (after uv or chemical treatment) have been purified and characterized including a further delineation of their roles (49, 101, 102, 103, 194, 207, 227, 392, 423, 590). Among these may be mentioned endonucleases specific for pyrimidine dimers, apurinic sites, uracil residues etc. (see references 207 and 392 for recent reviews). Advances in the study of post-replication repair in bacteria have demonstrated, among other things, that uv-induced pyrimidine dimers remain in high molecular weight DNA after DNA replication (181, 182, 449) and that they are transferred (by a process which may involve genetic exchange) into all daughter strands during post-replication repair (182). Evidence is rapidly accumulating for the existence of still another type of repair process in *E. coli*—called the "SOS repair"—which is induced or activated following damage to DNA, one which is "error-prone" ("mutation-prone") (424, 603, 615).

472. The continued efforts to elucidate repair pathways in *E. coli* and other prokaryotes have greatly aided in the search for similar ones in a number of eukaryotes. The existence of three repair mechanisms—photoenzymatic, excision and post-replication repair—is now documented in several higher organisms (213), including mammalian cells cultured *in vitro* (388). Attempts to isolate and characterize the photoreactivating enzyme from human leucocytes (550, 552) and from murine and human fibroblasts (553) have been fruitful. Sutherland *et al.* (554) have recently demonstrated that fibroblasts from patients with xeroderma pigmentosum contain low levels of the photoreactivating enzyme (0-50 per cent of normal in the four different strains tested). With the exception of *E. coli,* the excision repair process has perhaps been most extensively investigated in human diploid fibroblasts. The impetus came from the discovery of Cleaver in 1968 (110) that the molecular basis for one of the xeroderma pigmentosum syndromes (XP) in man is a defect in an early step in excision repair. Subsequent research revealed that XP is much more complicated than was originally imagined. (See reference 112 for a recent review.)

473. Employing somatic cell hybridization techniques, it has been possible to demonstrate the presence of five different complementation groups (A to E) associated with defects in excision repair in XP cells (43, 138, 139, 140, 258, 435). There is also evidence for the involvement of defects in post-replication repair in XP (276). Tanaka *et al.* (568a) found that when uv-irradiated XP cells of complementation groups A to E are incubated with endonuclease V of bacteriophage T4, the ability to perform unscheduled DNA synthesis was restored in all of them. These results suggest that those XP cells might have a common defect in the first step of excision repair. Motelmans *et al.* (347) recently showed that crude extracts of normal human diploid fibroblasts and of human peripheral blood lymphocytes excise thymine dimers from purified uv-irradiated *E. coli* DNA or from the DNA presumably present as chromatin in cell-free preparations of cells that has been labelled with ^{3}H-thymidine. Extracts of XP cells from complementation groups A, C and D also excise thymine dimers from

purified DNA, but extracts of group-A cells do not excise dimers from the DNA radioactively labelled, unfractionated cell-free preparations. These findings suggest a biochemical defect in cell-free extracts that mimics a defect known to exist in intact XP cells.

474. Buhl and Regan (67) reported the presence of sites sensitive to dimer-recognizing endonuclease from *Micrococcus luteus* in newly made DNA from uv-irradiated XP cells; this finding and one reported by Meneghini and Hanawalt (333) are similar to those recorded by Ganesan (182) in bacteria, suggest that DNA synthesis after uv-irradiation does not necessarily leave gaps opposite the dimers, raise the possibility of a recombination mechanism in which segments of dimers containing parental strands are inserted in daughter stands. However, in work with uv-irradiated XP cells, a Chinese hamster cell line, and chick embryonic cells (all of these are defective in the excision of dimers), using a protocol similar to that of Buhl and Regan (67), Paterson, Lohman and Sluyter (396) obtained no indication of endonuclease-susceptible sites in the daughter DNA. The technique employed by Paterson *et al.* would have detected the presence of as few as 15 per cent of the dimers initially induced in the parental DNA.

475. Work with XP prompted the search for similar repair defects in other human diseases but thus far has met only with limited success (see also paragraph 502). Thus, for example, in fibroblasts from a patient with Fanconi's anaemia (characterized by a progressive aplastic anaemia, increased frequencies of spontaneous and radiation-induced chromosome aberrations and a high incidence of cancer) normal amounts of unscheduled DNA synthesis were observed at early times after uv-irradiation; however, the excision of dimers assayed at 24 h was depressed compared to normal cells at doses over 15 J/m^2 (254-nm radiation). Excision seemed normal at early times and, at low doses, at late times (418). It may be that at high doses the basic defect is not in the repair system but in other cellular properties that result in the turn-off of the repair system at high doses and long times (530).

476. Some success has been achieved in showing the presence of putative dimer-specific endonuclease and a dimer-excising exonuclease in extracts of human cells (18, 142). Work in this area of enzymology of repair in mammalian cells has just begun.

477. Cell-fusion techniques have also been successfully used at the interspecific level: the experiments of Paterson *et al.* (397, 398, 399) and Paterson and Lohman (306) focused attention on a further characterization of repair mechanisms present in human and chick fibroblasts and an elucidation of the efficiency with which repair enzymes unique to each species can operate on uv-damaged foreign DNA in multinucleate human-chick heterokaryons artificially derived from both fibroblastic lines. Advantage was taken of the fact that primary human cells lack photoenzymatic repair but possess excision repair machinery, whereas chick fibroblasts possess photoenzymatic repair but not excision repair, to cope with uv-induced pyrimidine dimers. The results provide good evidence that "after artificial fusion of human and chick fibroblasts, DNA repair enzymes peculiar to each species not only remain functional in the resulting multinucleate heterokaryons, but are free to act on pyrimidine dimer-containing sites in foreign DNA contributed by the fusion partner ... with absolute impartiality" (393).

478. The use of uv-irradiated human viruses as a sensitive test to detect the various defects in DNA repair have already yielded interesting results (131, 425). For instance, uv-irradiated adenovirus-2 assay procedures have revealed that every xeroderma pigmentosum strain tested has a DNA repair defect, including those previously judged by other methods to have normal DNA repair.

3. Ionizing radiation: nature of the lesion produced and its repair

479. In contrast to the great strides made with the uv work, a brief overview of which was given in the preceding paragraphs, the progress in our understanding of the precise nature of the lesions induced by ionizing radiations and the repair processes operating on this damage must be considered modest. Ionizing radiations induce single- and double-strand breaks in the DNA, cross links, apyrimidinic and apurinic sites, as well as damage to the base and sugar moieties. The elucidation of the relationship between changes induced in the biological activity of DNA by ionizing radiation and specific structural modifications or lesions has therefore been difficult. Most of the available information is concerned with the production of single- and double-strand breaks, their yield, rejoining and biological significance; some of it was reviewed in the 1972 report of the Committee.

480. The physical reconstruction of radiation-induced single-strand breaks has been shown to occur in a number of organisms and systems investigated in this respect. In *E. coli*, this process of repair is mediated by at least two distinct mechanisms: rapid repair involving DNA polymerase I and a slower, presumable recombination, repair involving the *recA* gene product (574, 575). In the radioresistant bacterium *Micrococcus radiodurans*, radiation-induced double-strand breaks also are repaired (132, 257), and evidence for such repair is accumulating in other systems as well (116, 242, 269, 432). Recent studies on a radiosensitive mutant of *Micrococcus radiodurans* have shown that it was deficient in the initial fast-rejoining reaction and the second phase proceeded more slowly, concomitantly with greater degradation of the DNA (42). The work of Gentner (187) has provided evidence for the presence of a level of Mg-dependent DNA polymerase in the mutant that was only 2 per cent of normal. A good coverage of the efficiency of the production of double-strand breaks and the dynamics of repair of these lesions in *Micrococcus radiodurans* is given in Burrell and Dean (69).

481. It has been known that extracts of *Micrococcus luteus* (394, 610), *E. coli* (568) and human cells (50) contain endonuclease activity which selectively attacks defects other than strand breaks in gamma-irradiated DNA (the so-called "gamma lesions"). Using crude

protein extracts of 12-day-old chick embryos as the source of the test endonuclease in *in vitro* assays, Paterson and Smith (395) recently identified gamma lesions in the DNA of human diploid fibroblasts. Under anoxic conditions, the incidence of gamma lesions approximates 1.2 times that of single-strand breaks concomitantly produced. Substitution of the chick extract with a crude extract of *Micrococcus luteus* yields the same number of lesions, suggesting that the endonuclease activities involved have identical, or at least closely overlapping, substrate specificities. Although there is some indication that both the type of gamma lesions and the yield depend upon the irradiation conditions (563), the chemical identity of the gamma lesions is not known with certainty. Two possibilities exist, namely apurinic sites and ring-saturated radiolysis residues of pyrimidines (see below). Since neither the calf thymus endonuclease (Bacchetti and Benne, 17) nor *E. coli* extracts act on apurinic sites, ring-saturated pyrimidine residues are the more likely. In fact, the work of Hariharan, Cerutti and colleagues strongly supports this conclusion (reviewed by Cerutti (96)).

482. Early evidence for the contribution of DNA base damage to the lethal effects of ionizing radiation came from work with bacteriophages in which the formation of single- and double-strand breaks as a function of dose and radiation conditions could be accurately measured and related to the loss of infectivity. The involvement of some form of base damage in the inactivation process was inferred when less than one double-strand break was introduced per genome per biological hit (177, 178, 597). While a considerable amount of work has been done on the radiation chemistry of free nucleic acid bases, especially of thymine, not much is known as to whether or not the major reactions observed in these model systems under non-physiological conditions are representative of reactions occurring *in situ* in the living cell. The recent experimental demonstration in Cerutti's laboratory of the formation of thymine damage following irradiation with ionizing radiation (gamma rays) in both bacterial and mammalian systems and the progress made in the enzymology of repair of these lesions therefore represent a very significant forward step in molecular radiobiology with ionizing radiations. While the assay procedures used permit the identification only of damage to thymine, additional damage undoubtedly occurs at adenine, guanine and cytosine moieties, and consequently it has been concluded that base damage is a major type of damage induced by ionizing radiation in bacterial and mammalian cells (96).

483. Hariharan and Cerutti (214, 215) have developed two highly sensitive radiochemical procedures for the determination of gamma-ray-induced thymine damage in DNA both *in vitro* and *in vivo*. The first assay determines the radiochemical reactivity of the thymine methyl group and the second, ring-saturated radiation products of thymine of the 5-hydroxy-6-hydroperoxydihydrothymine type (the latter will hereafter be abbreviated to t′). In a series of papers, evidence was presented showing that (a) thymine damage is one of the major types of gamma-ray-induced damage in bacterial (214, 215, 556, 557) and mammalian cells *in situ* (219, 440); (b) excision repair of such products occurs in bacterial and mammalian cells (97, 215, 219); (c) crude concentrated extracts of *E. coli* (216, 218) and isolated mammalian nuclei (219, 326, 441) are able to selectively remove the t′ residue from gamma-irradiated poly [d(A-T)] or OsO_4-oxidized poly [d(A-T)] or bacteriophage PM2 DNA; (d) although the identity of the endonuclease recognizing t′ products in *E. coli* is not fully established, possible candidates appear to be endonuclease II (196) and the endonuclease recognizing depurinated DNA (598); (e) the second step in the excision repair of t′ (namely the exonucleolytic degradation of the damaged DNA region) is accomplished by $5' \rightarrow 3'$ exonuclease associated with the polymerase I of *E. coli* (247); (f) the last step in excision repair (strand resealing) is accomplished by ligase (216); and (g) the excision of gamma-ray-induced thymine damage in mammalian cells used (CHO, HeLa S3) is considerably faster—between 25 and 35 per cent of the t′ removed within 60 minutes of incubation at 37°C (219)—than that of cyclobutane-type photodimers, which has been shown to continue for several hours in human cells (see Cleaver (111) for a review of the latter).

484. In the context of the excision repair of gamma lesions discussed in the preceding paragraph, it is worth noting that Paterson *et al.* (400) observed a decreased ability of some ataxia telangiectasia (AT) strains to undergo repair replication following exposure to gamma rays delivered under anoxic conditions. This finding implicated defective DNA repair in the aetiology of radiosensitivity and predisposition to neoplastic transformation, two clinical features of the syndrome. In leucocytes from these patients, the radiation-induced chromosome aberrations were found to be enhanced (228, 426). In fibroblasts, the rates of rejoining of single and double-strand breaks appear to be similar to those in normal cells (571).

485. The results of Remsen and Cerutti (430), on the other hand, show no *in vitro* deficiencies for the excision of t′ products from exogenous DNA-chromatin substrates (from sonicates of three AT cell lines tested, including two studies by Paterson *et al.* (400)) which had been gamma irradiated under aerobic conditions. Remsen and Cerutti point out that differences in experimental design (in particular the irradiation conditions) between their work and that of Paterson *et al.* do not permit a straightforward comparison of the results. In addition, Remsen and Cerutti used unirradiated cell preparations as the enzyme source whereas supra-lethally irradiated cells were used by the other investigators. Different lesions are produced in DNA under aerobic and anoxic conditions, which may be processed by different repair pathways. Support for this notion comes from work with XP cells, where ionizing radiation induced normal levels of repair replication under aerobic but not anoxic conditions (386).

486. The role of DNA repair in the progeria syndrome (a human genetic disease characterized by accelerated ageing) is not clear and the reports that have appeared are contradictory. Epstein *et al.* (158) reported that progeroid fibroblasts seemed defective in strand-break repair, but Regan and Setlow (429) were unable to repeat this observation and suggested that the basic defect is not one of repair enzymes, but more likely one

of permeability or fragility of progeroid cells in culture. From the findings that several progeric strains manifest differing and unusual responses to ionizing radiation, a finite repair capacity in repair-deficient strains and that normal repair apparently returns after SV40 transformation, Little *et al.* (292) suggest that the control of the genetic expression of a repair system may be involved.

4. DNA repair in mouse germ cells

487. In spite of a number of DNA repair studies carried out with different mammalian somatic cell systems, not much similar work has been carried out with germ cells until recently. The report of Sega (522) in 1974 demonstrating unscheduled DNA synthesis in the germ cells of male mice exposed *in vivo* to alkylating chemical mutagen EMS,[24] therefore, is a very significant contribution. Using the well studied sequence of events occurring during spermatogenesis in particular and administering (by testicular injections) ^{3}H-dT, Sega obtained clear evidence for unscheduled DNA synthesis; the germ cell stages showing it ranged from early to middle meiotic prophase stages through early to middle spermatids. The initiation of this synthesis (taken to be evidence for repair of chemically-damaged DNA in these germ-cell stages) is rapid, beginning within one hour after injection of EMS. Unscheduled DNA synthesis was not detected in the most mature germ-cell stages, which are responsive to the induction of dominant lethals, nor was it found to occur in stages where protamine replaces the chromosomal proteins (during spermiogenesis).

488. Subsequently, Sega *et al.* (524) focused attention on early spermatids and extended the findings with EMS to three chemical analogues: MMS, PMS and IMS. The results indicate that (a) with all four there is a linear increase in DNA repair in early spermatids with increasing dose of the chemical; only at the highest dose of MMS (100 mg/kg) is the repair response observed higher than expected on linearity; and (b) with equimolar doses, the most effective chemical in inducing DNA repair is MMS followed by EMS, IMS, and PMS.

489. In a further study, Sega (523) has extended the finding of unscheduled DNA synthesis (with chemicals) to x-ray damage. The stages showing the repair of x-ray damage are the same as those found undergoing repair of EMS-induced damage except that the level of unscheduled incorporation of ^{3}H dT after x-ray treatment is much less, in spite of the fact that the EMS dose used (250 mg/kg) gives a roughly comparable yield of dominant lethals to that given by 600 R of x rays (185). Secondly, the level of DNA repair occurring in early spermatids has been found to increase linearly with increasing x-ray exposures from 50 to 600 R, and at 1200 R there is evidence for an elevated level of repair. Thirdly, unscheduled DNA synthesis (after 600 R) is highest immediately after irradiation and continually decreases during the subsequent 4 h although some repair is still measurable at this time.

[24] EMS = ethylmethane sulphonate, MMS = methylmethane sulphonate, PMS = propylmethane sulphonate, IMS = isopropylmethane sulphonate.

490. Ono and Okada (386) irradiated male mice 10-14 weeks old (gamma irradiation, 10-40 krad, 3300 rad/min) and used the testes from these animals to study single-strand breaks in the DNA and their rejoining using alkaline density-gradient centrifugation methods. Microscopic examination of cell suspensions from the testes revealed that the population was made up of about 3 per cent spermatogonia, 12 per cent spermatocytes, 70 per cent spermatids, 6 per cent spermatozoa and 9 per cent unknown. The conclusions drawn therefore apply primarily to DNA from spermatid-rich populations. It was found that the number of single-strand breaks was 0.22 per 10^{12} daltons of DNA per rad, one which was significantly lower than the rate of 0.6 to 0.7 per 10^{12} daltons per rad for mouse liver and thymus DNA found in an earlier investigation (385). The authors obtained evidence to show that this difference is primarily due to hypoxic conditions of the testicular cells. A majority of the breaks were found to rejoin quickly, the time necessary for rejoining of 50 per cent of the breaks being about 18 min at 10 krad and 50 min at 40 krad. The remainder of the breaks did not seem to rejoin until about 6 h after irradiation. Ono and Okada suggest that these latter breaks might be of the slow and/or non-reparable DNA scissions, since even under "low" dose-rate conditions (40 rad/min compared with 3300 rad/min) a similar situation was obtained.

491. In a subsequent study, Ono and Okada (387) refined their methods and were able to study single-strand breaks and their rejoining in spermatogonia-rich and spermatozoa-rich populations. In spermatogonia, single-strand breaks were induced at a rate of 0.42 10^{12} daltons of DNA per rad under oxic (aerated) conditions, decreasing to 0.24 per 10^{12} daltons per rad under hypoxic conditions. In spermatozoa, the break-efficiency was 0.22 breaks per 10^{12} daltons per rad under oxic conditions and changed little under anoxic conditions. The breaks were efficiently repaired in spermatogonia, 50 per cent of the breaks rejoining within about 10 min after 10 krad and within about 30 min after 40 krad. The slow or non-rejoining fraction for these doses was 40-60 per cent. In contrast, the breaks in spermatozoa were not rejoined at all even two days post-irradiation.

492. Masui and Pedersen (325) examined the repair capacity of full-grown mouse oocytes after exposure to uv-irradiation. Fully-grown oocytes were aseptically isolated from the ovaries of adult mice and cultured in chemically-defined medium. Irradiations were carried out 2-18 h after isolation and the oocytes were then immediately incubated with ^{3}H-dT. Many of the oocytes underwent germinal vesicle (GV) breakdown within 3 h after isolation and metaphase I (MI) was reached 4-8 h later. Oocytes cultured for 16-18 h reached metaphase II (MII) as evidenced by the appearance of the first polar body (PBI). Autoradiography showed that grain counts over the GVs or the chromosome set were significantly higher after uv irradiation than in controls, regardless of the stage of meiotic maturation at which they were irradiated. The grain count increased with dose from 30 to 60 J/m^{2}, but except for the MI oocytes, there was no further increase at 120 J/m^{2}. The numbers of grains over the GVs were approximately an order of magnitude higher than over the MI and MII chromosomes and those

over the PBI were much less (relative to MI and MII). It is thus clear that mouse oocytes can carry out unscheduled DNA synthesis after uv irradiation and thus seem capable of excision repair of DNA damage in these stages.

5. DNA repair in *Drosophila*

493. In recent years, an increasing interest has been manifest in studies on DNA repair in *Drosophila*. In 1969, Valencia and Plaut (594) demonstrated unscheduled DNA synthesis in the salivary glands of x-irradiated larvae. Trosko and Wilder (577) showed that thymine-containing dimers are excised from the DNA of uv-irradiated tissue culture cells. Boyd and Presley (47) showed that repair replication of DNA (in first instar larvae) was stimulated by treatment with uv, x rays, MMS and EMS; MMS was found to be ten times as potent as EMS. With uv, a dose of 20 J/m^2 largely saturates the level of repair replication; the latter falls off after x-ray exposures of 80 kR. The authors also studied photo repair (as a reduction in repair synthesis resulting from post-irradiation exposure to photo-reactivating light) and found that this occurs after uv irradiation but not after x irradiation.

494. Other lines of work have focused attention on the isolation of mutagen-sensitive mutants as experimental material for the systematic analysis of genetic controls of DNA replication, DNA repair and recombination (542, 543). A number of mutants which were selected on the basis of hypersensitivity to larval killing by MMS have now been assigned to seven complementation groups on the X-chromosome (48, 543), and mutants at one locus have been clearly identified as alleles of a previously described meiotic mutant *mei-41* (23), thereby confirming that mutagen sensitivity can be employed as an effective method for the selection of recombination-defective mutants in this organism. In addition, mutants belonging to certain complementation groups are sensitive to nitrogen mustard (HN_2) and current evidence (48) indicates that there is a correlation between sensitivity to HN_2, to 2-acetylaminofluorene and a deficiency in post-replication repair. Several of the mutants exhibit sensitivity to gamma rays, although only the *mei-41* mutants are hypersensitive to uv irradiation. Nguyen and Boyd (362), who studied the *mei-9*^{b} mutant (mutant alleles at the *mei-9* locus which reduce meiotic recombination in homozygous females (77)) using the technique employed previously by Boyd and Presley (47), found that it was deficient in repair replication after uv or x irradiation. This result is complementary to their observations that homozygous larvae of *mei-9* alleles are hypersensitive to killing by x-rays as well as uv irradiation.

6. Relationships between the radiation-induced lesion in DNA, its repair, and the production of mutations and chromosome aberrations

495. Turning now to the question of how the nature of the uv- or x-ray-induced lesions in the DNA and the mechanisms by which they are repaired can account for the production of mutations or chromosome aberrations, it can be stated that we have relatively more information available for uv damage. In prokaryotes where this problem has been intensively studied, there is no doubt that pyrimidine dimers are an important source of mutations, although the role of other photoproducts is less clear. In the yeast *Saccharomyces cerevisiae*, there is evidence that pyrimidine dimers are responsible for most of the revertants of *cyc1-9* in *rad+*, *rad 1* and *rad 6* strains (271) (see also paragraph 498). If pyrimidine dimers or the other photoproducts were the direct cause of mutations, every kind of repair that eliminates these products should reduce the frequency of mutations. This however is not the case. Convincing evidence for the possibility that under certain circumstances repair may produce mutations rather than erase them was provided in bacteria by Witkin (613). Her distinction between error-proof (mutation-proof) and error-prone (mutation-prone) repair has been generally accepted. Both types of repair remove lethal lesions and increase survival, but while the former restores the original nucleotide sequence and thus removes potential mutations, the latter tends to insert a wrong base sequence and thus produces mutations.

496. Photoenzymatic repair is error-proof; the bulk of excision repair, too, is error-proof and reduces lethality as well as mutation frequency. Only a small fraction of mutations induced by uv arise from errors in pre-replicative repair while the bulk are produced by an error-prone post-replicative process. Recently, Witkin and others (188, 614, 616) have adduced evidence that in bacteria the error-prone mechanism requires an inducible enzyme for its action.

497. There is much less information on the relationship between uv damage and chromosome aberrations. Griggs and Bender (202) demonstrated that all the lesions which lead to uv-induced chromosome aberrations in *Xenopus* cells disappear on photoreactivation. This is perhaps the only experiment which directly demonstrates a relationship between DNA repair and chromosome aberrations. Following uv irradiation of XP cells, Parrington *et al.* (391) demonstrated that there was a six- to seven-fold increase in the frequency of chromosome aberrations (relative to normal cells). However, the data are only preliminary, with only one fixation time, namely 30 h, and the increase could be due to other factors as well (357).

498. The possible role of single-strand breaks and base changes in generating x-ray-induced mutations was considered in the 1972 report of the Committee (Annex E, paras. 516-525). The recent experimental demonstration that base damage is a predominant component of x-ray damage in the DNA (*in vivo* and *in vitro*) and that it is repairable will undoubtedly intensify the search for correlations between this and mutational damage in prokaryotic and eukaryotic systems. Whatever the nature of the primary lesion, its final fate depends largely on the type of repair to which it is exposed. It is clear that repair mechanisms—some of them identical with those acting on uv lesions—enter in similar ways into x-ray mutagenesis. In bacteria, the functions of two repair genes (*recA* and *exrA*) that are essential for uv

mutagenesis also play a major role in the production of mutations by x rays (234). A similar situation is obtained in the yeast *Saccharomyces cerevisiae:* Lawrence *et al.* (271) have shown that the highly specific uv-inducible reversion of *cyc1-9* (an ochre mutant (UAA codon) of the structural gene for iso-1-cytochrome c) depends largely on the action of the *rad6* locus, which appears to be involved in the repair of damage induced by uv gamma rays and all chemicals tested. *Rad18,* a gene concerned in the same pathway as *rad6,* also has some influence on the specificity, though the evidence is less decisive in this case. *Rad1,* a gene that functions in ecxision repair, has no effect on this specificity.

499. In a subsequent paper (271a), Lawrence and Christensen have presented data which suggest that in *Saccharomyces cerevisiae* there is a single error-prone repair pathway involving the function of at least seven genes (*rad6, rad9, rad18, rev1, rev3* and possibly *rev2* and *rad8*). The function of two of these (*rad6, rev3*) would seem to be essential for uv mutagenesis at all sites and of all types, while the others appear to act principally or exclusively during the production of certain mutational events. In contrast, all mutations blocking excision repair exhibit enhanced mutability per unit dose, a result compatible with the idea that this process is largely error-free.

500. Double-strand breaks in the DNA are presumably responsible for the production of chromosome aberrations. The possibility of single-strand breaks being converted into double-strand breaks during repair by a single-strand nuclease has been proposed by Bender *et al.* (35) in their general model for chromosome aberration production by diverse agents. Currently available information on the sensitivity of cells from patients with different inherited disorders to the induction of chromosome aberrations by different mutagens (including x rays) and the known defects in DNA repair mechanisms in these cells has been summarized by Natarajan (357). In the case of AT cells discussed earlier (para. 484) there is evidence for an increased sensitivity to chromosome aberration induction by x rays in leucocytes, and as may be recalled, these cells may be deficient in excision repair of base damage under certain conditions. XP cells and cells from patients with Fanconi's anaemia and progeria do not appear to show any increased sensitivity to x-ray induction of aberrations although they are known to be deficient in one or another step in DNA repair.

501. Scott, Fox and Fox (503) studied the relationship between chromosomal aberrations, survival and DNA repair in tumour cell lines of differential sensitivity to sulphur mustard (SM) and x rays. In the first comparison with a pair of rat lymphosarcoma cell lines (Yoshida) with a pronounced differential sensitivity to killing by SM (but with the same sensitivity to x rays), the resistant line suffered much less chromosome damage after SM treatment than the sensitive cells in spite of equal alkylation of DNA, RNA and protein in both; the amount of x-ray-induced chromosomal damage was similar in both. In the second comparison with a pair of mouse lymphoma cells (one resistant and the other sensitive to killing by x rays), much less chromosomal damage was observed in the resistant line, although there were no differences between the two lines in their capacities for repair replication either after SM or x-ray treatment. As Natarajan (357) has pointed out, the type of measurement used for repair replication, i.e. unscheduled DNA synthesis, gives information only about the whole repair process which may not all be related to the induction of chromosome aberrations.

7. Conventional (non-molecular approach) repair studies in *Drosophila*

502. Several aspects of radiosensitivity and repair phenomena studied in *Drosophila* germ-cell stages were reviewed in the 1972 report of the Committee. A comprehensive treatment of the subject has since appeared (496), besides others which focus attention on the radiosensitivity of embryonic stages (623) and on aberration induction and segregation in female germ-cell stages (390). In what follows, some of the more recent work on repair of genetic radiation damage in *Drosophila* and that which has a bearing on the restitution of chromosome breaks induced in mature spermatozoa will be considered.

503. It has long been known that chromosome breaks induced in *Drosophila* spermatozoa do not rejoin before fertilization (256, 350). More recently, Leigh and Sobels (277) showed that compound chromosomes (autosomes) homozygous for markers on one or the other of the chromosome arms could be recovered after x irradiation of post-meiotic male germ-cell stages. The interpretation of this finding was that these chromosomes originate by a chromatid type of exchange occurring after the post-zygotic chromosome replication, the implication being that the chromosome breaks induced in these germ-cell stages stay open until this time. Further evidence substantiating this thesis came from exposure fractionation studies which showed interaction of breaks produced in spermatids in male flies (544) (or in male pupae, 48 h old (545)) with those produced in mature spermatozoa (in inseminated females). There are other findings which strongly suggest that the repair machinery in the oocytes plays a vital role in the formation of induced chromosome aberrations in male germ-cell stages (see paras. 504-505). It should therefore be possible, by suitably modifying the genotype of the females and/or physiological environment of the oocytes to influence the magnitude of the genetic damage induced in the male germ cells. The work that has been carried out during the past few years in the laboratories of Sobels and of Würgler adequately support this line of reasoning.

504. In a series of studies, Würgler and his collaborators (68, 622, 625) have collected data which indicate that (a) the rate of recoverable ring-X chromosome losses in mature sperm is dependent on the genotype of the females used; (b) such "maternal effects" are demonstrable for radiation-induced dominant lethals, loss of rod-X chromosomes and translocations; and (c) for all the female stocks, the rate of recoverable XO males falls drastically to nearly one-half after the first day. The authors concluded that (a) some factors which are under the control of the maternal genome influence the

x-ray-induced lesions in the sperm chromosomes after insemination of the egg, (b) a change in the lesions in the stored sperm occurs during the first 24 h of storage in the females, and (c) sperm inseminating old, stored stage-14 oocytes (present in aged virgin females) are influenced by a maternal factor in a different way or to a different degree than sperm inseminating newly produced non-stored oocytes. The observation of Würgler and Maier (622) that the frequency of sex-chromosome losses induced in spermatozoa is dependent on the genotype of the females used for the matings and that of Würgler, Bürki and Bürki (624) and Bürki (68) that it is differentially affected in stored and non-stored oocytes in the females have been extended by Clark (109).

505. Following the earlier work of Proust (421) and of Proust, Sankaranarayanan and Sobels (422), which showed that mating of irradiated males to females injected with actinomycin D led to an increase in the frequencies of dominant lethals and a decrease in those of translocations and recessive lethals, Mendelson (330, 331) and Mendelson and Sobels (332) extended this line of inquiry to the effects of caffeine treatment of females. It was found that (a) caffeine treatment of females led to an increase in the frequencies of dominant lethals and sex-chromosome losses and a decrease in those of translocations induced by x irradiation of mature sperm; (b) different strains of females used manifested different levels of repair of radiation-induced breaks in males, with one strain very deficient in this repair machinery; and (c) the repair system specific for the repair of chromosome damage induced in the paternal genome is susceptible to blocking by metabolic inhibitors such as caffeine.

506. In a very recent study, Maddern and Leigh (320) have obtained convincing evidence for the thesis that a high proportion (as much as 75 per cent) of the "total" and "partial" sex-chromosome loss induced by x irradiation of mature *Drosophila* sperm is a consequence of chromatid rearrangements arising from chromosome breaks which stay open until they are replicated. This finding provides a fresh insight into our thinking on the mechanism of chromosome loss.

8. Summary and conclusions

507. The past few years have witnessed the accumulation of a substantial amount of information on DNA damage induced by mutagenic agents and on repair processes in both prokaryotic and eukaryotic systems.

508. A number of specific lesion-recognizing enzymes involved in excision repair have been purified and characterized. Evidence for the presence of photoreactivating enzymes in human leucocytes, human and murine fibroblasts have also been adduced.

509. With the exception of *E. coli*, the excision repair process is perhaps most extensively investigated in human fibroblasts. There is evidence that there are at least five complementation groups associated with defects in excision repair in xeroderma pigmentosum cells. Search for similar repair defects in other human diseases has met with only limited success.

510. By means of cell-fusion techniques (human and chick fibroblasts) it has been possible to show that the repair enzymes peculiar to each species remain functional in the resulting multinucleate heterokaryons and act on pyrimidine dimer-containing sites in foreign DNA contributed by the fusion partner.

511. The most significant advance in ionizing radiation studies is the identification of base (thymine) damage and the development of sensitive procedures (radiochemical) for detecting it in microorganisms as well as in mammalian cells. These gamma lesions (as they are called) are subject to excision repair and an endonuclease acting specifically on such lesions has been found.

512. Some ataxia telangiectasia cell strains appear to be defective in the excision repair of gamma lesions following gamma-ray exposures under anoxic conditions; after irradiation and under aerobic conditions, they are excision-repair proficient.

513. The induction of single-strand breaks in mouse germ cells has been investigated. The results show that they are induced at rates of 0.42 per 10^{12} daltons of DNA per rad in spermatogonia, 0.22 per 10^{12} per rad in spermatids, and 0.22 per 10^{12} per rad in spermatozoa (under aerated conditions). A majority of the single-strand breaks induced in spermatogonia and spermatids undergo rapid rejoining (50 per cent of the breaks rejoining in 10-18 minutes after 10 krad), while the remainder were of the slow or non-rejoining type. In contrast, in spermatozoa, the breaks induced do not undergo rejoining even two days post-irradiation.

514. Unscheduled DNA synthesis has been demonstrated to occur following treatment with alkylating agents and with x rays in meiotic prophase stages and in spermatids in the mouse; such synthesis also takes place in full-grown mouse oocytes after uv irradiation.

515. There is evidence for the occurrence of unscheduled DNA synthesis in the salivary glands of x-irradiated *Drosophila* larvae and for the excision of thymine-containing dimers in tissue culture cells. In first instar larvae, repair replication is stimulated by treatment with uv, x rays, MMS and EMS.

516. In *Drosophila* as in prokaryotes, sensitivity to mutagens can be employed as an effective method for the selection of recombination-deficient mutants. Mutants selected on the basis of hypersensitivity to larval killing by MMS have been assigned to seven complementation groups. Mutants belonging to certain complementation groups are also sensitive to nitrogen mustard, 2-acetylaminofluorene and appear to be deficient in post-replication repair.

517. The relationships between lesions induced in DNA, repair processes and mutations have been worked out in prokaryotes and some simple eukaryotes; after uv irradiation, there is no doubt that pyrimidine dimers are an important source of mutations, but there is evidence that certain repair processes may be error-prone. Photoenzymatic repair is error-proof; most

excision repair is also error-proof. The bulk of mutations are produced by an error-prone post-replicative repair process (after uv irradiation).

518. In higher eukaryotic systems (mammalian cells, for instance) there is no direct evidence on the relationship between uv lesions and mutation induction. In *Xenopus*, there is some evidence for the involvement of photoreactivable uv damage in chromosome aberrations.

519. The recent experimental demonstration that base damage is a major component of damage induced by ionizing radiation in prokaryotic as well as eukaryotic systems and that it is subject to excision repair will intensify the search for correlations between these and mutational events.

520. Double-strand breaks induced in DNA are presumably responsible for the production of chromosome aberrations, but the exact relationship between these and the known DNA repair processes is not clear.

521. Studies on the repair of x-ray-induced genetic damage in male germ-cell stages of *Drosophila* (non-molecular approach) have shown that chromosome breaks induced in spermatids of pupae 48 h old remain open and are available for interaction with breaks produced in spermatozoa.

522. A considerable amount of evidence has been obtained in *Drosophila* which strongly suggests that the repair machinery in females plays a vital role in the formation of induced chromosome aberrations in male germ-cell stages. This has been demonstrated by suitably modifying the genotype of the females and by physiological alteration of the oocyte environment with metabolic inhibitors.

523. In *Drosophila*, recent results indicate that a high proportion of the total and partial sex-chromosome losses induced by x rays in spermatozoa is a consequence of chromatid rearrangement arising from breaks which stay open until they are replicated (after sperm entry into the egg).

IV. INTERSPECIFIC COMPARISON OF MUTATION RATE ESTIMATES

1. Introduction

524. Recently, Abrahamson *et al.* (4) re-examined the available data on forward mutations at specific loci induced by acute, low-LET irradiation for a wide variety of organisms from bacteria to mammals and noted that the rates per locus per rad varied over three orders of magnitude; however, when these rates were adjusted for the amount of DNA per nucleus, the mutation rates obtained were all essentially the same, varying by a mere factor of 3 instead of 1000. The authors speculated that "the consistency that obtains when the data are adjusted for the amount of DNA per nucleus for each species indicates either that it is the nucleus and not the locus that determines the target size or that, on the average, the size of a (radiation-mutable) locus is proportional to the total genome (DNA content) for the species . . . it suggests that extrapolation directly from experimental organisms to man can be done with confidence."

525. In a subsequent paper, Conger (118) compiled and analysed the data on the amount of chromosomal proteins and RNA in relation to the amount of DNA in different species. He found that the total mass of chromatin per unit mass of DNA is not very different over the span from prokaryotes to higher eukaryotes, i.e., the total chromosomal mass and expected target size is proportional to DNA content over this span of species. That permitted him to conclude that "the correlation of induced mutation rate with DNA content per cell over a wide range of species cannot be used to establish that DNA alone is the target for induction of mutations by ionizing radiation. The target could be DNA alone; but equally well, it could be total chromatin mass." The *Ad Hoc* Panel on Research Needs for Estimating the Biological Hazards of Low Doses of Ionizing Radiations of the United States National Research Council–National Academy of Sciences (431) expressed this opinion: "We believe this normalizing of mutation rates by the amounts of DNA per nucleus is a valid genetic bridge between lower organisms and man" (see also Wolff (617)).

526. Kohn (265) made estimates of gene sizes in different species based on target theory considerations and found that (a) in the mouse, the estimates from the data on the seven-specific-loci tests (300 R, acute x irradiation, spermatogonia) are consistent with expectations, whereas those from the histocompatibility loci are not; and (b) most of the genes (or groups of genes) tested in different organisms for forward mutation with low-LET irradiation tend to behave more like the histocompatibility loci than the seven loci in the mouse (see also paragraph 275).

527. If the hypothesis of Abrahamson *et al.* (4) is valid, it will have far-reaching implications, especially for the evaluation of mutational radiation hazards in man. Schalet and Sankaranarayanan (562), who made a critical analysis of the data used by Abrahamson *et al.* (and of others not cited by these authors but which bear on the issue in question), concluded that (a) the notion of simple proportionality between DNA content and mutation rate cannot be substantiated and (b) the generalization that we can now extrapolate from lower organisms to man with greater confidence must be viewed with extreme reservations. Since all the arguments have been given in detail in the above paper, the following paragraphs will be devoted to summarizing the main points only. The papers of Conger (118) and of Kohn (265) will not be further considered in this review since, for the former, the basic premise (the existence of a linear relationship between mutation rate and DNA content) is weakened (562) and, for the latter, the estimates of gene size based on target theory considerations are likely to be incorrect.

2. General considerations

528. One very important consideration that should be borne in mind in normalizing mutation rates in different species to DNA content is whether the mutation rates

themselves relate to a common base line, namely, to changes within a "locus" or gene to the extent to which we can define them with precision at present. Furthermore, for most of the organisms, owing to the lack of biochemical and genetic analysis, there is the uncertainty as to whether a locus consists of one gene or more than one gene, although the terms "locus" and gene are used interchangeably in the absence of a better alternative.

529. A second important consideration is whether, with the array of mutation screening techniques used in different organisms, the same proportion of all the induced mutations is detected. The question itself is not a new one and has been raised earlier (see, for example, reference 358). In fact, the particular technique used for detecting mutations can be a major determinant of the mutation rate estimate. Two examples will suffice to illustrate this point. First, in *Drosophila, rosy* locus mutants are detected as brownish eye-colour variants by conventional tests; in addition to eye-colour variants, there are, at this locus, several classes of mutations which present a normal eye colour and that can be detected by other techniques (105). Secondly, there are other findings, such as those in *Saccharomyces cerevisiae,* which show that, at the molecular level, different forward mutation systems vary widely in their ability to detect the broad spectrum of intragenic mutational events (539) and consequently, the comparison of mutation rates even in one and the same organism is complex, not to mention interspecific comparisons.

530. Thirdly, and this is a relatively minor point, some of the DNA values cited in the paper of Abrahamson *et al.* refer to total cellular DNA. Therefore, these values include different, but for the present purpose generally insignificant, proportions of non-nuclear DNA. However, it is clear that Abrahamson *et al.* erred in using a DNA content for *E. coli* which is about three times the widely accepted value (0.004 pg) (75, 119). Furthermore, a very recent estimate of the nuclear DNA content for *Saccharomyces cerevisiae* has raised the distinct possibility that the value used by Abrahamson *et al.* may also be overestimated by a factor of three (270).

3. Examination of the data used by Abrahamson *et al.*

531. The data used by Abrahamson *et al.* are derived from experiments and with test systems which differ widely in their ability to discriminate between changes within genes as opposed to those involving several genes or loci and those which can include gross chromosomal aberrations, such as losses of chromosome arms or even entire chromosomes. That means that the effective radiation-mutable target is not necessarily the same in the different organisms whose mutational response is compared, making the grounds for comparison insecure, if not totally invalid.

532. The rate for the induction of *waxy* mutations given by Abrahamson *et al.* is not a forward mutation rate but a back mutation rate, does not pertain to three loci but to a single locus, and does not relate to acute irradiation but to chronic irradiation with ^{90}Sr. Arguments have been presented in the literature (159, 290) for believing that radiation-induced *waxy* mutations are in fact chromosomal aberrations. Likewise, the data for tomato used by Abrahamson *et al.* pertain to chromosomal deletions (60, 61, 434) and some of the mutations may represent loss of chromosome arms or even whole chromosomes.

533. The *E. coli* data of Demerec and Latarjet (137) on the resistance to T1 phage used by Abrahamson *et al.* were collected at a time when much was not known about the nature of changes involved in phage resistance in *E. coli.* Several lines of evidence accumulated since then testify to the complexity of this phenomenon. Phage resistance in *E. coli* can originate in two unlinked regions designated as *tonA* and *tonB*, the latter of which is a classical deletion system: *E. coli* can tolerate extensive deletions of *tonB* including the neighbouring tryptophan operon, and such deletions exhibit the *tonB* phenotype. Mutations to T1 resistance having an additional auxotrophic phenotype of many types other than tryptophan have been reported (64, 65). Some of these may have been deficiencies involving the *tonA* region while others seem to involve nutritional deficiencies that are not linked to either *tonA* or *tonB*. *TonB* mutants and deletions require exogenous iron for their growth and are inhibited by chromium (210); surprisingly high concentrations of chromium have been found in commercial agar preparations commonly used to prepare solid media (120). Consequently, the recovery of phage-resistant mutants on solid media containing chromium in sufficient quantity to inhibit growth of resistant (but not of sensitive) cells may well have contributed to the low mutation rate reported by Demerec and Latarjet (137).

534. In the other organisms–*Neurospora, Drosophila,* and the mouse–(the data for which were used by Abrahamson *et al.*), the level of genetic analysis used to detect and characterize the events scored as specific-locus mutations varies a great deal. Only in *Neurospora* can one be certain that the data pertain to intragenic changes, since here the distinction between intragenic and extragenic changes has been made by intensive and rigorous complementation tests. In *Drosophila,* this distinction is made on the basis of cytological analysis of the mutants (salivary gland chromosomes), and the absence of a detectable aberration (within the limits of resolution possible) is considered presumptive evidence that one is most likely dealing with a change at the level of the gene. While the viability of homozygotes for the mutation (or of hemizygotes in the case of sex-linked ones) can be considered good evidence for intragenic change, its lack does not necessarily demonstrate the presence of an aberration, since lethal intralocus changes are well documented in *Drosophila* (604). In the mouse, transmission tests (to determine whether one is dealing with a mutation) and homozygous viability tests are used to characterize the nature of changes. Here again, while homozygous viability can be construed as good evidence for an intralocus change, its lack does not necessarily demonstrate the presence of an aberration. For instance, most of the *d* locus mutations recovered from irradiated (x or gamma) spermatogonia have been found to be homozygous lethal, but the evidence from complementation tests suggests that a majority of these involve intragenic lethal changes at the *d* locus (453).

535. The estimate of $1.28\ 10^{-8}$ rad^{-1} per locus of Alexander (9) used by Abrahamson *et al.* represents the best presumptive intralocus mutation rate for *Drosophila* spermatogonia. For mouse spermatogonia, the rate of $1.7\ 10^{-7}$ rad^{-1} per locus (used in the 1972 report of the Committee) has been estimated from the results obtained in experiments involving two sets of loci (seven and six respectively, with one locus being common to both sets) giving equal weight to each locus. It should be remembered that the overall response of the two sets of loci differ by a factor of three and within the seven loci (for which the data are extensive) the difference between the lowest rate (*a* and *se* loci) and the highest rate (*s* locus) is more than 30-fold (488). Schalet and Sankaranarayanan (562) used the data presented by W. L. Russell and L. B. Russell (488) and L. B. Russell and W. L. Russell (459), in conjunction with those given by L. B. Russell (453) to estimate a probable intralocus rate for mouse spermatogonial specific-locus mutations. The assumptions here are that (a) all homozygous viable mutations are intralocus changes and (b) most of the *d* locus lethals are intralocus events. From these they concluded that for the seven loci, about 37 per cent of all spermatogonial mutations are likely to be intralocus changes. This gives a figure of $0.81\ 10^{-7}$ rad^{-1} per locus (i.e., 37 per cent of $2.2\ 10^{-7}$).

4. Other relevant data

536. An examination of other relevant mutation rate data published in the literature suggests, not unexpectedly, that the average mutation rate is a function of a given cell stage, a given set of loci, or a given set of experimental conditions; there is therefore no sound reason to use one or the other alone as typical of the response of the species under consideration. This point can be illustrated by the following examples.

537. In *Neurospora*, de Serres *et al.* (529) reported an intralocus rate of (5-6) 10^{-9} rad^{-1} per locus (*ad-3A* and *ad-3B* loci) under slightly different experimental conditions than the ones used in the work of Webber and de Serres (602). (In the latter work, the rate was estimated as $2.7\ 10^{-9}$ rad^{-1} per locus.) Again in *Neurospora*, Hoffmann and Malling (230) found that the rate of x-ray induction of forward mutations at the *aza* locus was higher than in the *ad-3* system, being $3.1\ 10^{-8}$ rad^{-1}. Although the isolated mutants were tested for transmissibility, no analysis was made to discriminate between intralocus and extralocus events. If the *aza-3* locus were to show a proportion of intralocus mutations similar to that in the *ad-3* system (in the latter, at 10 kR, roughly two thirds were intralocus events), then the mutation rate becomes $2.0\ 10^{-8}$ rad^{-1}. The above data plus those for the *ad-3* loci permit an overall estimate of $8.7\ 10^{-9}$ or $1.0\ 10^{-8}$ rad^{-1} per locus, depending on whether the *ad-3* data used are those of Webber and de Serres or those of de Serres *et al.* (See also the arguments presented in Hoffmann and Malling (230) for believing that the *aza-3* frequency and possibly even the *ad-3* frequencies were obtained under conditions of suboptimal mutant expression.) At face value, either of the two rates above is not far removed from the rate for *Drosophila* spermatogonia ($1.28\ 10^{-8}$ R^{-1} per locus). The *Drosophila* haploid DNA content is about 4.5 times higher than that of *Neurospora*.

538. In *Saccharomyces cerevisiae*, Skobkin (540) studied the gamma-ray induction of canavanine resistance and noted that the maximal recovery rate was $1.0\ 10^{-10}$ rad^{-1} per locus or about one fifteenth of that given by Abrahamson *et al.* Skobkin found that the selection of mutants, among other things, was so strongly dependent on the initial number of cells inoculated into the medium and the concentration of canavanine used that, under certain conditions, no mutants were recovered. (For details of other complexities encountered in this system, see also references 201 and 637.) Schwaier (564) who studied the x-ray induction of forward mutations at the adenine loci in the same organism, reported a rate of $6.0\ 10^{-9}$ rad^{-1} per locus. In a similar system studied in *Schizosaccharomyces pombe*, the data of Nasim (356) and of Loprieno *et al.* (293) permit estimates ranging from $0.4\ 10^{-9}$ to $1.1\ 10^{-9}$ rad^{-1} per locus per haploid genome.

539. In barley, the available data for the x- or gamma-ray induction of eceriferum, erectoides and chloroplast mutations show that there is no discernible relationship between the mutation rates and DNA content; in *Arabidopsis thaliana* the mutation rate to thiamine auxotrophy is $(1.1\text{-}1.5)\ 10^{-9}$ rad^{-1} per locus per haploid genome, which is an order of magnitude *lower* than that for *Drosophila* spermatogonia, although the haploid content of *Arabidopsis* is 1.5 times that in *Drosophila*.

540. Data collected by W. L. Russell (475, 478, 480) in female mice (see reference 506 for a recent review) show that the mutation rate at the seven specific loci (acute x irradiation) for maturing oocytes varies with the dose; in immature oocytes virtually no mutations have been recovered. These observations are out of line with the predictions of Abrahamson *et al.* on the relationship between DNA content and mutation rate. The near absence of x-ray-induction of mutations at the histocompatibility loci (paras. 272-274) in the mouse provides an additional case in point.

541. Table 44 summarizes the data (some of which were discussed in the preceding paragraphs) that are worth examining in the context of interspecific comparisons, although it should be realized that here, too, there are several uncertainties that stem from the lack of detailed genetic analysis, resolution power of the system and the paucity of loci examined for some organisms. Inspection of the table will reveal that an increase in DNA content is not always accompanied by a proportional increase in mutation rate (compare, for example, the entries for barley with those for *Arabidopsis* or *Neurospora*). Thus the data do not bear out the reasoning that higher DNA content and higher mutation rates go hand in hand; it is true of some cases, but by no means all, and consequently no unifying interpretation is possible.

542. To explain the "uniformity" of mutation rates among different species that they observed, Abrahamson *et al.* suggested as one possibility that, on the average,

the size of a radiation-mutable locus is proportional to the total genome (DNA content) for the species. A simpler way of stating this is that bacteria and higher organisms contain the same number of genes, but in the latter they are larger, with the implication that the larger the gene, the higher the mutation rate. As the authors themselves point out, although the inference of larger genes "is contrary to the usual genetic expectation that the structural gene should be of the same size in bacteria as in man, we note that the functional genetic unit in *Drosophila* corresponds to a band in the salivary gland polytene chromosomes. This indicates that complementation groups in higher forms contain much more DNA than is necessary for the specification of a protein. It has been postulated that the extra DNA has a regulatory function and that mutations in any one of the components of the functional genetic unit would fail to complement mutations in any of the other components."

543. Recent studies of DNA organization in higher organisms indicate that *Drosophila* DNA exhibits a quite different pattern of sequence organization as compared with many other eukaryotes including the rat, which have higher DNA contents (130, 323). Thus, for *Drosophila*, there appears to be much greater average length for the single copy sequence DNA (about 13 000 nucleotides compared with 800 to several thousand nucleotides), which is interspersed with relatively larger middle repetitive sequences (5600 nucleotides average length compared with about 300 nucleotides). It would therefore appear that the *Drosophila* pattern may not serve as the best model to speculate about the size of the radiation-mutable target.

544. In *Drosophila* there are some data that permit one to examine whether there is a positive correlation between salivary band size and mutation rate as might be expected if the total amount of DNA associated with a particular band played a major role in determining the mutation rate. The basic premise here is that a functional genetic unit corresponds to a salivary chromosome band (252). Inspection of table 45, in which the data that bear on this point are summarized, will reveal that there is no simple correlation between band size and mutation rate. For example, loci associated with bands of the smallest size (*g, ct* and *ras*) span the greater-than-one-order-of-magnitude range of mutation rates indicated by the loci listed in the table; when the male-lethal *ct* and *ras* mutations are included as "gene mutations", the rates for these loci are among the highest.

545. The inability to detect a predictable relationship between band size and mutation rates is not surprising in view of the detailed cytological analysis of the *white (w)* locus, which indicates that, for this locus at least, the radiation-mutable part occupies at most only a small fraction of the DNA present in the band with which it has been thought to be associated (546). Evidence from yet another *Drosophila* system documents a similar conclusion: Mutations at the *rosy (ry)* locus in chromosome III can be detected as eye-colour mutants. The cytological position of the locus has only been delimited to a region containing no more than five bands (*86D8-12*). In Lefevre's view (272), whichever of the bands *ry* is associated with, it would be of below average dimensions. (Gelbart *et al.* (183) believe that the bands are of average dimensions.) Although the kind of cytogenetic analysis performed at the *w* locus has not been done here, the *ry* locus has the advantage in that it is known to code for the structural gene of the enzyme xanthine dehydrogenase (XDH). Of primary importance is the fact that spontaneously occurring electrophoretic variants of the enzyme are known, and the mutant sites responsible for electrophoretic differences in XDH have been located on the known genetic map of x-ray-induced null-enzyme eye-colour mutants.

546. Gelbert *et al.* (184), in a very recent paper, have presented more decisive evidence than that presented earlier (183) and have concluded that "every rosy eye-colour mutant (null XDH) is now included within the structural element" and that there are "no mutant sites, either radiation- or EMS-induced, which fall outside of this region". From the work of Rudkin (443, 444), it is known that the amount of DNA in the average band, $3.5\ 10^4$ base pairs, is sufficient to code for approximately 30 average-size proteins. The XDH polypeptide requires a coding sequence of (3-4) 10^3 base pairs (183). The available mutation rate data for intralocus null-enzyme *ry* mutants (23 mutants in 170 000 flies after about 4700 R exposure of spermatozoa) give a rate of $2.9\ 10^{-8}\ R^{-1}$ (526, 561), which falls close to the upper limit of the range of mutation rates given in table 45. One is thus left with the firm conclusion that, at the *ry* locus, an average or above-average mutation rate has been elicited from changes restricted to the structural portion of the locus, i.e., the DNA which codes for XDH and represents a target size of about one tenth of the amount of DNA in the average size salivary gland chromosome band.

547. In summary, an examination of mutation rates for a number of loci associated with bands of different dimensions reveals that the relative size of the bands is *not* quantitatively correlated with the intralocus mutation rate. There are therefore *no* firm grounds for believing that the higher average mutation rate in *Drosophila* as compared with some lower forms may be due to the fact that on the average, the amount of DNA associated with complementation groups in *Drosophila* is far in excess of that required to code for single average-size proteins.

5. Summary and conclusions

548. On the basis of an examination of some data on forward mutations at specific loci induced by acute low-LET irradiation in different organisms, Abrahamson *et al.* proposed that there is a linear relationship between DNA content and mutation rate and that this relationship could be used to extrapolate directly from lower organisms to man with confidence and to predict the mutational response of human genes to irradiation.

549. The data used by Abrahamson *et al.* come from experiments and with test systems which differ widely in their ability to discriminate between changes within genes as opposed to changes involving several genes or loci and those which can include gross chromosomal

aberrations such as losses of whole chromosome arms or even entire chromosomes. The effective radiation-mutable target is therefore not the same in the different organisms, and consequently the grounds for comparison are insecure, if not invalid.

550. A consideration of data other than those cited by Abrahamson *et al.* does not lend credence to the line of reasoning pursued by them. There are several notable exceptions, such as the response of the immature oocytes of the mouse and that of the histocompatibility loci.

551. In *Drosophila*, the available evidence indicates that there is no simple quantitative correlation between the size of the band in the salivary gland chromosome and the mutation rates of loci located in them. For instance, at the *rosy* locus which codes for the enzyme xanthine dehydrogenase, every null-enzyme mutant (whether x-ray or EMS-induced) is located within the structural portion of the gene, which is no more than half (and perhaps as low as 10 per cent) of the DNA in the band with which *rosy* is associated. Yet, the intralocus mutation rate for null-enzyme mutants at this locus (after x irradiation) is close to the upper limit of intralocus mutation rates in this organism.

552. In conclusion, the reanalysis of the data on mutation rates has made it clear that the hypothesis of a simple linear relationship between DNA content and the radiation-induced forward mutation rate in living organisms as a whole cannot be substantiated. Even within the different germ-cell stages of a single species such as the mouse, there is extreme variation in radiosensitivity with no variation in DNA content. In view of this, the belief that DNA content can be used as a valid genetic bridge to extrapolate from micro-organisms through higher species to man is unwarranted. The diverse processes, including repair, which intervene in mammals between the induction of mutation and its expression would, in any event, preclude such an extrapolation.

V. SOMATIC CELL GENETICS[25]

A. INTRODUCTION

553. The 1972 report of the Committee (589) considered the data then available from studies on mutation induction in mammalian somatic cells. The events studied are biochemical ones capable of expression at the cellular level under appropriate conditions. Most of the investigations reviewed in the report had been carried out with an aneuploid (near-diploid) Chinese hamster cell line (V 79) and studies with human diploid fibroblasts were just beginning. During the last few years, the scope of somatic cell genetics has expanded: new cell systems and selection schemes have come into use. While the roles of some of the factors that affect the recovery of the "mutants" are now better understood, several new ones have been uncovered and their effects are actively pursued at present.

[25] In this section, the terms "mutant" and "variant" will be used interchangeably in view of the fact that although there is good evidence for mutational origin of the events studied, it is not unequivocally proven.

B. HYPOXANTHINE-GUANINE PHOSPHORIBOSYL TRANSFERASE (HG-PRT)

1. Gene localization

554. The discovery of a severe deficiency of hypoxanthine-guanine phosphoribosyl transferase (HG-PRT) (521) in patients affected with the Lesch-Nyhan syndrome (288) catalysed interest in studies on purine metabolism in man. The Lesch-Nyhan syndrome is characterized clinically by symptoms of excessive production of uric acid and certain neurological abnormalities, including mental retardation. Studies of pedigrees affected with this syndrome indicated that the locus for HG-PRT is on the X-chromosome and that the mode of transmission is X-linked recessive (63, 226, 366, 629). With *in vitro* methods (somatic cell hybridization) it was demonstrated that in human fibroblasts, the loci for HG-PRT, G-6-PD and 3-phosphoglycerate kinase (PKG) are linked (329); current evidence indicates that HG-PRT and G-6-PD genes are localized on the distal half of the long arm of the X-chromosome and with the following sequence: centromere, PGK, HG-PRT and G-6-PD (433, 533). A major review article on HG-PRT deficiency in man has recently been published (62).

555. Chu (106, 107) advanced the hypothesis that in Chinese hamsters and perhaps in other mammals as well, the gene controlling HG-PRT activity is also X-linked. This hypothesis has now been confirmed for the Chinese hamster by Westerveld *et al.* (606), who demonstrated linkage of loci for PGK, HG-PRT and G-6-PD, and for the mouse by Epstein (156, 157), Shows, Brown and Chapman (536), and Hashmi and Miller (223).

2. Screening methods and origin of HG-PRT deficiency

556. Normal substrates for HG-PRT are hypoxanthine and guanine which are converted to inosine 5′-monophosphate and guanosine 5′-monophosphate, respectively. Cells having HG-PRT activity can also convert purine analogues such as 8-azaguanine (8-AG), 6-mercaptopurine and 6-thioguanine to their respective nucleotides, the incorporation of which results in growth inhibition or death, indicating that normal cells are sensitive to these metabolites. The screening systems employed to detect the HG-PRT variants therefore use resistance to these purine analogues as markers. It has been found that some cell variants that are resistant to 8-AG have either a defective HG-PRT protein, caused by a mutation in the structural genes (31), or a variant enzyme with altered kinetic constants and heat sensitivity (531).

557. In his review, De Mars (135) considered in detail the general question of resistance of cultured human fibroblasts and other cells to purine and pyrimidine analogues in relation to mutagenesis; he pointed out that

(a) genetic changes have been, and may still be, regarded as reasonable explanations for the origin of base-analogue-resistant variants although definitive proof for the mutational origin of these is lacking; (b) arguments favouring explanations invoking epigenetic mechanisms of resistance to base-analogues (such as those of Harris (220, 221) and of Mezger-Freed, (336)) are based on inconclusive evidence; and (c) emphasis must be placed on rigorous studies aimed at examining the nature of events scored for which several possibilities can be envisaged (mutations in genes determining the structure of the enzyme, mutations in genes regulating the expression of the structural genes, mutations in genes that have epistatic functions modifying the expression of the enzyme phenotypes, karyotype changes, mitotic recombination, extra-nuclear genetic changes, etc.).

3. Factors affecting the recovery of spontaneous and induced mutants

558. Several factors, such as the analogue used, its concentration, cell-seeding density, time of addition of the analogue to the mutagen-treated cells (expression time), the source of serum used in the selective medium, interclone metabolic co-operation etc., have been found to influence the recovery and type of mutants obtained (2, 7, 86, 87, 105, 135, 173, 380, 407, 538, 575, 630, 633, 634, 635). Table 46 summarizes the role of some of these factors in the different cell systems currently in use. While most of the studies referred to above have employed 8-AG as the selective agent, in recent years, a preference for the use of 6-thioguanine (6-TG) has been expressed (125, 126, 175, 259, 632). Human HG-PRT has a much greater affinity for 6-TG than for 8-AG (267).

559. Nikaido and Fox (364), who compared the relative effectiveness of both these selective agents in two V 79 Chinese hamster cell lines, (V 79A and V 79S) found that in both cell lines (a) the frequency of surviving colonies exposed to either agent was dependent on the initial plating density; (b) different degrees of metabolic co-operation were manifest and the loss of both spontaneous and added mutants (the latter in reconstruction experiments) occurred at lower cell-density with 6-TG; (c) both analogues were degraded on the incubation in medium plus serum in the absence of added cells; and (d) variations in serum batch had little effect on the rate of degradation or on the frequency of colonies recovered after treatment with 8-AG. They concluded that, at least in V 79 cell lines, (a) cell killing by 8-AG is less dependent on cell density than that by 6-TC, (b) 6-TG is apparently not more efficient in selecting for HG-PRT-mutants (although 6-TG is effective in cell killing at much lower doses), and (c) since 6-TG has been shown to be incorporated into DNA (155) (in contrast to 8-AG which is incorporated into RNA (342), 6-TG itself may be mutagenic, and therefore 8-AG is preferable.

560. Thacker *et al.* (573) however, found that the use of 8-AG as the selective agent yielded highly variable results with the Chinese hamster cell line V-79-4 and that different batches of sera in the growth medium could affect the response considerably. Although dialysis of the serum eliminated some of the variation, it also reduced the plating efficiency of the cells. More consistent results were obtained with 6-TG, although, the "mutation fraction" was not completely resistant to the analogue. The authors noted that the mutants fell into two classes: one class is HG-PRT$^-$ (less than 2 per cent wild-type activity), resistant to 5 μg/ml of thioguanine and sensitive to azaserine[26] while the other shows about 15 per cent of wild-type HG-PRT activity, resistance to 1 μg/ml of thioguanine and some growth in azaserine medium. The two classes of mutants differed little in ability to withstand suppression of their growth on dishes by wild-type cells and performed similarly in competition experiments where mixtures of mutant and wild-type cells were kept in exponential growth over several population doublings. Only one of these types (HG-PRT$^-$) increased in frequency with radiation dose. The authors suggested that these results can account for many of the discrepancies encountered in previous studies and stressed that characterization of the mutants is essential to establish the true frequency of resistant mutants. The work of Cox and Masson (125) provides additional evidence that in human diploid fibroblasts, too, 6-TG is a better selective agent.

561. Van Zeeland and Simons (631) studied the problem of the x-ray induction of 8-AG mutants in two sets of diploid and tetraploid Chinese hamster cells (DON and V 79) and found that the induced mutation frequencies in both kinds of cells were of the same order of magnitude and that all mutants showed an almost complete loss of HG-PRT activity, except that in the tetraploid V 79 cells, 50-100 per cent activity was retained. Measurements of G-6-PD activity in these cells revealed that the spontaneous and induced mutants from the diploid V 79 and DON, as well as the tetraploid DON cells, retained the G-6-PD activity of the parental cells whereas the induced mutants from the tetraploid V 79 cells had about 35 per cent of the parental G-6-PD activity. Using 6-TG as a selective agent, the authors found that the induced "mutant" frequencies in diploid and tetraploid DON cells and in diploid V 79 cells were in the same order of magnitude, but no mutants could be recovered from tetraploid V 79 cells in a single step. Thioguanine-resistant tetraploid V 79 cells could only be obtained from the AG-resistant mutants and some of them showed an increase in G-6-PD activity. All these results taken together led the authors to conclude that the induction of HG-PRT deficiency may not be a single-step event and that it may be the result of a two-step process, as has been suggested by them for the human diploid fibroblasts (635) and by Freed and Mezger-Freed (176) for BUdR resistance in haploid frog cells.

562. Van Zeeland *et al.* (635) tested the validity of the assumption implicit in selecting for purine-analogue-resistant variants in somatic cells (AG-resistance in this case), namely, that their origin is independent of the selective agent. Should this be true, then the proportion of mutants with no or very little HG-PRT activity will be

[26] Azaserine is known to inhibit *de novo* synthesis of purines in cultured human cells and cells dependent for growth on *de novo* purine synthesis (as a result of defective purine salvage enzymes). Impaired growth in azaserine medium might be expected (180).

the same at different selective AG concentrations. DeMars and Held (136) reported that in diploid human fibroblasts, 90 per cent of the variants selected at 1.2 μg/ml AG concentration had residual enzyme activities; in contrast, the experiments of van Zeeland and colleagues showed that mutants selected at 5 or 10 μg/ml AG were totally deficient in HG-PRT activity. Further experiments were therefore aimed at resolving this contradiction.

563. Using human fibroblasts, van Zeeland *et al.* (635) selected for spontaneous mutants at 1.2 and 5 μg/ml AG concentrations. It was found that the total mutation frequencies were the same at both concentrations; however, the mutants selected at the low concentration (the A mutants) were qualitatively different from those selected at the high concentration (the B mutants): among the A mutants, the proportion that had very little or zero enzyme activity was small (3 out of 28) whereas in the other group, a vast majority fell in this class (20 out of 25). This finding strengthened the results obtained from the direct HG-PRT assays of the mutants and suggested that AG is not acting merely as a selective agent. To test this, mutants recovered from both groups were examined for their stability in the presence or absence of AG (1.2μg/ml). It was found that 5 mutants without residual HG-PRT activity (4 A and 1 B) remained stable over a period of 30-50 days; 7 with residual activity (5 As and 2 Bs) showed varying degrees of *increase* of activity indicating that stability of the mutant phenotype in these was dependent on the presence of AG. On the basis of this and other lines of evidence collected, the authors proposed that AG resistance may occur through a two-step process; the first step, which is rare and occurs at random, is AG-independent. In it wild-type cells are predisposed to mutation in a second step, which is AG-dependent. While the validity of this theoretical model remains to be proved, it nonetheless suggests that the property of AG-resistance may not have a simple basis.

564. Until recently, in most of the mutation experiments, the induction of and selection for AG-resistant phenotypes had been carried out within the same dish of cultured cells, as described by Chu and Malling (108). With this technique, as the expression time is increased, the number of presumptive mutant colonies characteristically rises to an optimum and then sharply falls. Thus, for instance, Chu and Malling observed a maximum frequency of AG-resistant colonies at 42 h expression time following treatment of V 79 cells with 10^{-2} M EMS. The usual explanation for the sharp decline in mutant colony frequencies is the metabolic co-operation between wild-type and mutant colonies, causing a shift to the HG-PRT$^+$ phenotype (547, 634). This process limits the time available for expression of the HG-PRT$^-$ phenotype and may in fact cause a spurious reduction in the maximum observable mutation frequency. Myhr and DiPaolo (355), who investigated the reliability of this assay procedure demonstrated this to be true and showed, with three different chemical mutagens, that it is necessary to respread the cells after a suitable expression time before adding the selection medium to obtain maximum frequency of colonies resistant to 8-AG. (The maximum frequencies following MMS or MNNG[27] treatments were about 10-fold greater than those obtained when induction and selection of AG-resistant mutants were performed in the same culture dish.)

565. Fox (173) compared the efficiency of the two assay procedures (*in situ* and replating techniques) for the selection of 8-AG mutants in V 79 Chinese hamster cells (after x-ray, MMS, EMS and uv treatment) and showed that a significantly higher frequency of mutants was obtained in replated experiments as compared with the *in situ* situation. The experiments of Abbondandolo *et al.* (2) adduce further evidence that the identification of a plateau in expression time by the replating techniques is important for an accurate quantitative evaluation of mutation rates. Similar conclusions were reached by Carver *et al.* (86).

4. Dose-effect relationships

566. In the 1972 report, it was pointed out that in V 79 Chinese hamster cells, the dose-effect relationship for the induction of AG-resistant mutations was non-linear and that there were dose-rate and dose-fractionation effects (100-1200 R) (12, 59, 107). The concentration of AG used for selection varied from 7.5 μg/ml in the experiments of Bridges and Huckle (59) and those of Arlett and Potter (12) to 30 μg/ml in those of Chu (107). The results of Albertini and De Mars with diploid human fibroblasts (unpublished at that time) also showed that the dose-effect relationship for AG-resistant mutants was non-linear. Albertini and De Mars (7) have now published their complete results, which show that (a) the average spontaneous rate is about $4.5\ 10^{-6}$ per cell generation ($1.9\ 10^{-6}$ if one large-yield experiment is excluded) and (b) the minimum estimates of the induced rates at different dose levels are

Induced rate (R^{-1} per cell)	*Exposure (R)*
$1.13\ 10^{-9}$	75
$7.14\ 10^{-8}$	125
$6.85\ 10^{-8}$	150
$2.16\ 10^{-7}$	250

indicating, as in Chinese hamster cells, a dose dependence of the mutation rate.

567. Van Zeeland and Simons (632) used the replating method for selecting for induced 6-TG mutants in V 79 cells and showed that the optimal expression time is about 7 days, beyond which the induced mutant frequency stays constant (in contrast to a dropping-off of the yield in earlier studies). The exposure-frequency relationship for x-ray-induced mutants is consistent with linearity in the range up to 800 R, the mutation rate being $1.35\ 10^{-7}\ R^{-1}$ per cell. Thus, with the improved method, there appears to be no dose dependence of the mutation rate.

568. Cox and Masson (126) investigated the x-ray induction of 6-TG mutations in human diploid fibroblasts. They found that the maximum yield was observed when the cells surviving the irradiation had completed 3-4 doublings (6-7 days growth) in a

[27] MNNG = N-methyl-N'-nitro-N-nitrosoguanidine.

non-selective medium and that under these conditions, in the range 50-200 rad, the mutation frequency was linearly related to dose, the rate being 3.1 10^{-7} rad^{-1} per cell.

569. Knaap and Simons (259) have succeeded in developing the mouse lymphoma cell system (L5178Y) as a useful and reliable test system for studying induction of mutations to HG-PRT deficiency (this system differs from others, such as the fibroblasts, in that the growth of the cells takes place in suspension culture). The selective agent used was 6-TG. The results show that (a) the selection of the mutants is not influenced by the concentration of the selective agent (1 or 5 μg/ml); (b) all of the mutants selected (spontaneous as well as induced ones) show a complete loss of HG-PRT activity; (c) the optimal expression time for the mutants is 6-7 days and appears to be dose-independent; and (d) over the range of exposures from 200 to 400 R, the dose-response curve is approximately linear with a rate of (1-1.8) 10^{-7} R^{-1} per cell. After 500 and 600 R, the induction rate is slightly higher. In agreement with the results of Clive *et al.* (114), Knaap and Simons (259) also found that 8-AG was unsuitable as a selective agent in the mouse lymphoma system, owing to inactivation of 8-AG by a serum factor (630).

C. THYMIDINE KINASE (TK)

570. Another locus that is currently used in mutation studies is the thymidine kinase locus (TK) in mouse lymphoma cells. It is known that in man, the gene coding for this enzyme is located on an autosome (chromosome 17) (337, 339, 442), and it is presumed that the situation is similar in the mouse. Like HG-PRT, TK provides a "salvage pathway" which can circumvent a folate-dependent step, i.e., thymidylate synthetase in this particular case. Thus the same principle employed in the HG-PRT system applies to the use of selective media in the TK system. Forward mutations at the TK locus are detected through resistance to BUdR, IUdR or TdR, depending on the cell strain used.

571. In the earlier work, Fox (171) used P388 cells (a mouse lymphoma cell line) and studied IUdR resistance after x irradiation. The selective concentrations of IUdR used in experiments on dose-effect relationships ranged from 10 μg/ml to 100 μg/ml. Surviving colonies, both in control and irradiated populations (scored after 10 days of incubation) were tested for heritable resistance to IUdR. The results showed that (a) after selective doses of 10 μg/ml or less, no heritable resistance could be demonstrated; when higher selective concentrations (20 μg/ml and 100 μg/ml) were used, the number of variant colonies increased, although there appeared to be no consistent increase in efficiency of mutation induction with increasing x-ray dose; and (b) there was a linear relationship between inoculum size and the frequency of IUdR-resistant variants and greater numbers of resistant colonies were recovered when cells were incubated for 24 h before plating on the selective medium.

572. Fox and Anderson (174) isolated IUdR-resistant and TdR-resistant clones from x-irradiation and chemical-treatment experiments with the P388 cell line and conducted TK assays on them. All were found to show significantly reduced enzyme activity relative to wild-type levels, but none showed zero levels. Fourteen of these clones were tested for thymidine uptake and all showed a marked reduction in the rate of ^{3}H-TdR incorporation into acid-soluble fractions and into DNA. Measurements of TK activity in 8 TdR-resistant clones showed that the initial rate of thymidine phosphorylation was not significantly altered in 5 of them; however, significantly lower amounts of phosphorylated products were observed in 6 of the 8 clones. Incorporation of ^{3}H-dTR was reduced in 9 of the 12 clones tested, and 2 of them showed no corresponding reduction in TK activity.

573. In another set of experiments, Fox (172) compared the x-ray induction of IUdR-resistant and TdR-resistant variants in P388 cells and found that the dose-response curves for both of these showed linear and quadratic terms and were roughly similar. In the same study, Fox also compared the x-ray induction of TdR-resistant variants in four L5178Y cell lines, LS (the most sensitive), AII, AIII and AIV, which differed in radiosensitivity to killing. When induction frequencies were compared, either at the same dose or at the same survival levels, the most radiosensitive line (LS) was more mutable than the others, including P388. It may be pointed out that the expression times for both IUdR- and TdR-resistant variants were similar, the maximum frequencies being reached at 48 h followed by a slight falling-off at the longest expression time (96 h) tested.

574. In limited radiation studies with L5178Y, Clive *et al.* (114) recorded an induced mutation rate of 5.0 10^{-7} R^{-1} using BUdR as the selective agent (600-R level). Clive *et al.* as well as Fox and Anderson (174) have discussed the possible genotypic constitution of the respective cell strains used in their mutation assay systems. The former authors showed that the original L5178 Y cell strain is TK^+/TK^+ with spontaneous mutation rate to BUdR-resistance of 5 10^{-11} per generation (based on one recovered mutant); they recovered revertant cell lines from the single TK^-/TK^- originally isolated, and a study of their enzyme levels and mutability indicated that some of these were TK^+/TK^-. One such line was used for determining the x-ray mutation rate given earlier.

575. Fox and Anderson (174) favour the view that the P388 and L5178 cells that they used are TK^+/TK^- and TK^+/TK^+, respectively. The reasoning is based on the following: (a) L5178YS cells have much higher TK levels, possibly a reflection of a gene-dosage effect, as demonstrated by Clive *et al.* (114); (b) L5178YS cells have a very low frequency of IUdR-resistant colonies (no mutants recovered from 10^8 plated cells), which also suggests that they may be TK^+/TK^+; (c) if P388 cells are TK^+/TK^+, it is difficult to explain the large difference in the frequency of spontaneously occurring IUdR-resistant colonies in the two cell lines; this is not the case when other mutagens (chemicals) are used (172, 174).

576. The nature of the events involved in IUdR resistance in the P388 line was examined by Fox and Anderson (174) in revertability tests; it was found that five out of the seven tested reverted at measurable rates

either spontaneously or after mutagenic treatment (HN_2, MNU, MMS etc.), suggesting that the IUdR resistant mutants tested could have been the result of gene mutations at the TK locus rather than deletion-type events.

D. OUABAIN RESISTANCE

577. Arlett *et al.* (13) have recently compared the mutagenic effects of gamma rays, uv light and several chemical mutagens using AG-resistance and systems in Chinese hamster cells resistant to ouabain (Oua). Resistance to Oua is different from that to AG and is probably the result of an alteration of the membrane ATP-ase involved in Na^+/K^+ transport such that it is no longer sensitive to Oua (322). The resistance alleles behave codominantly in somatic hybridization experiments (24). The results of Arlett *et al.* showed that there was a broad agreement between the AG and Oua systems for each mutagen tested, EMS being the most effective mutagen. Surprisingly however, Oua-resistance could not be induced by gamma rays, and the authors have as yet no ready explanation for this negative result.

E. FRUCTOSE UTILIZATION

578. Cox and Masson (124) reported the development of another selective system for mutation studies in human fibroblasts: this is concerned with the utilization of fructose instead of glucose as the major energy and carbon source. HF 10 diploid human fibroblast cultures were initiated from a male embryonic limb, and cells from early passage (6-25 generations in culture) were utilized for the x-ray experiments. Cells were irradiated in suspension and immediately afterwards plated on fructose medium. It was found that the frequency of Fruct clones (uncorrected for cloning efficiency) increased approximately exponentially with radiation dose, the rates per survivor being $4\ 10^{-8}$ (0-100 rad range), $1.24\ 10^{-7}$ (0-200 rad), and $2.10\ 10^{-7}$ (0-343 rad). The genetic basis of $Fruc^+$ variants observed is however, not yet worked out.

F. BACK MUTATIONS

579. Susuki and Okada (549) studied the reversion from alanine auxotrophy to prototrophy in mouse lymphoma cells (L5178Y) both *in vitro* and *in vivo*, following gamma irradiation (100-800 rad). (In the *in vivo* experiments, the alanine-requiring cells were injected into mice (intraperitoneal injections); the mice were irradiated on the eleventh day after inoculation, following which the irradiated cells were removed and assayed for reverse mutations.) The expression time was chosen to be two days for cells grown *in vitro* and five days for those grown *in vivo*. It was found that (a) the cells grown *in vitro* were more sensitive, both to killing and to mutation induction and (b) the dose-effect relationship was linear for cells irradiated *in vivo* and appeared faster than linear for the other. The rate of induction under *in vivo* conditions was approximately $1\ 10^{-7}$ rad^{-1}, for the *in vitro* irradiation, it was higher by factors of 2.5 to about 4.

580. Morrow *et al.* (346) studied the effect of EMS, NG and quinacrine hydrochloride on the induction of reverse mutations from asparagine auxotrophy to prototrophy in rat sarcoma cells; EMS was most effective. No x-irradiation experiments have so far been carried out.

G. GENE TRANSFER THROUGH PURIFIED METAPHASE CHROMOSOMES

581. Following the initial demonstration by McBride and Ozer (327) that incubation of $HG\text{-}PRT^-$ mouse cells with purified metaphase chromosomes from $HG\text{-}PRT^+$ Chinese hamster cells resulted in the appearance of $HG\text{-}PRT^+$ mouse cells in which the Chinese hamster enzyme was expressed, a number of investigators have carried out similar experiments. Willecke and Ruddle (611) extended this work by successfully transferring the human HG-PRT gene (via isolated metaphase chromosomes from He La S3 cells) into murine A9 cells which lacked functional murine HG-PRT activity. Twenty human isozymes other than HG-PRT, whose genes have been assigned to 14 human chromosomes, were found to be absent in the transformed clones. In addition, the human isozymes of G-6-PD and PGK (whose genes are linked to that of HG-PRT) were also absent. In subsequent work, Willecke *et al.* (612) succeeded in transferring two linked human genes which code for the expression of cytosol thymidine kinase and galactokinase to mouse L cells.

582. Wullems *et al.* (619, 620) and Degnen *et al.* (134) published the results of experiments in which both intraspecific and interspecific gene transfers have been accomplished. In the experiments of Wullems *et al.* (619) for instance, the mutant cell line Wg 3-h (derived from the Chinese hamster DON cell line by stepwise selection with increasing concentration of 8-AG and propagated in the presence of 6 μg/ml AG) with HG-PRT activity of about 2 per cent (compared to the DON cells) served as the recipient in all experiments; the donor chromosomes were from the DON line (intraspecies) or from the human He La S3 cell line and the human T cell line (interspecies).

583. The results show that (a) incubation of $HG\text{-}PRT^-$ Chinese hamster cells with chromosomes isolated from $HG\text{-}PRT^+$ Chinese hamster or human cells resulted in the appearance of $HG\text{-}PRT^+$ cells; (b) in the hamster-hamster situation, the frequency of $HG\text{-}PRT^+$ clones was found to be dependent on the number of chromosomes added ($5\ 10^{-5}$ and $16.6\ 10^{-5}$ following incubation with 10^7 and 10^8 chromosomes, respectively). In the hamster-human situation (after incubation with 10^7 human chromosomes) the frequency of $HG\text{-}PRT^+$ cells was $6\ 10^{-6}$, showing that intraspecies transfer may be more effective. Furthermore, in the first situation, the HG-PRT activity of the cells approached the level found in DON cells whereas treatment with human chromosomes resulted in 20-40 per cent of the activity in the Chinese hamster and 15-25 per cent of that in human T cell line; and (c) two clones isolated after incubation of Chinese hamster cells with human chromosomes, which were tested electrophoretically, showed the pattern of the human HG-PRT. However, the human X-linked

genes codes for G-6-PD, phosphoglycerate kinase and α-galactosidase) were not expressed in those clones, suggesting, as in the work of Willecke and Ruddle (611), that perhaps only a small fragment of the X-chromosome was incorporated into the Chinese hamster cells, a finding similar to that of Willecke and Ruddle (611).

584. In their very recent paper, Wullems *et al.* (621) presented evidence for the uptake of the human X-chromosome by human-Chinese hamster cell hybrids, which lack HG-PRT activity, following incubation with isolated human chromosomes from He La S3 cells. The activity of X-linked genes other than that for HG-PRT, such as PGK, alpha-Gal A, G-6-PD, was also found to be present, as determined by electrophoresis (the recipient cells gave no evidence of containing human X-chromosomes). These results therefore suggest that incorporation and expression of He La X-chromosome is accomplished in human-Chinese hamster cell hybrids which lack X-chromosomes. This is in marked contrast to the results obtained with other experimental systems discussed earlier.

H. SUMMARY AND CONCLUSIONS

585. Since the publication of the 1972 report of the Committee, substantial progress has been made in the field of somatic cell genetics. A number of selection systems have come into general use and the role of several factors affecting the recovery of mutants is now better understood.

586. Most of the data have come from the work on the induction of forward mutations leading to a deficiency of hypoxanthine-guanine phosphoribosyl transferase ($HG\text{-}PRT^-$) in Chinese hamster cells, mouse lymphoma cells and human fibroblasts. While the purine analogue 8-azaguanine (8AG) continues to be used as the selective agent, in recent years, there has been a preference to use 6-thioguanine (6-TG) instead; the use of the latter has provided more reproducible results.

587. One of the major technical advances concerns the delineation of the "expression time", the time needed for the mutants to fully express themselves following their induction, in contrast to earlier studies with Chinese hamster and human cell lines where the induction of and selection for mutant phenotypes were carried out in the same culture dishes, under which conditions the frequency of mutant colonies rose to a maximum and then fell. The current use of the replating technique (where the treated cells are respread on to new plates for optimal mutant expression) has facilitated the recovery of mutants. With the replating technique, it has been found, for instance, that the optimal expression time for $HG\text{-}PRT^-$ mutants x-ray or EMS-induced in V 79 Chinese hamster cells is about 7 days, beyond which the induced mutant frequency stays constant. The same is true for the induction of such mutants in human fibroblasts.

588. Using the replating technique, it has been shown that the dose-effect relationship for the x-ray induction of $HG\text{-}PRT^-$ mutants is linear in Chinese hamster cells as well as in human fibroblasts. The rates are, respectively, $1.35\ 10^{-7}\ R^{-1}$ per cell and $3.1\ 10^{-7}\ rad^{-1}$ per cell.

589. In mouse lymphoma cells (L5178Y), 6-TG-resistant mutants have an expression time of 6-7 days, and here too, the exposure frequency relationship is approximately linear, being $(1\text{-}1.8)\ 10^{-7}\ R^{-1}$ (200-400 R); at higher exposures (500 and 600 R) the rate tends to be slightly higher.

590. Another locus at which mutation induction in somatic cells is being studied is the thymidine kinase locus (TK); all the studies so far have been carried out with mouse lymphoma cells. Forward mutations at this locus are detected through resistance to BUdR, IUdR or TdR, depending on the cell strain used. For BUdR resistance in L5178Y cells, the x-ray induction rate is $5.0\ 10^{-7}\ R^{-1}$ per cell (600-R level).

591. Resistance to ouabain (result of alteration of the membrane ATP-ase) is another potentially useful forward mutation system in Chinese hamster cells; x rays have been found to be ineffective in inducing ouabain-resistant mutants, although several chemical mutagens are capable of inducing such mutants.

592. Attempts to induce back mutations from alanine auxotrophy to prototrophy in mouse lymphoma cells and from asparagine requirement to prototrophy in rat sarcoma cells have met with success.

593. Techniques are now available for effecting gene transfer in somatic cells using purified preparations of metaphase chromosomes. Both intraspecific transfer (Chinese hamster) and interspecific transfer (mouse-Chinese hamster, human-mouse, human-Chinese hamster) of HG-PRT genes have been demonstrated. Donor genes can be selected for in the recipient cell population by independent electrophoretic, chromatographic or immunological criteria. The frequency of chromosomal gene transfer is about an order of magnitude higher than the rate of reversion of recipient cells but can also lie within the same range. Evidence for the presence of donor chromosomes was negative in these studies, suggesting that the transferred chromosomal segment must be very small.

594. In contrast, in more recent experiments success has been obtained in transferring a presumably whole human X-chromosome using metaphase chromosomes, from human He La cells as the donor to human-Chinese hamster cell hybrids as the recipient. These studies offer interesting possibilities for examining the problem of gene regulation in somatic cells.

VI. EVALUATION OF GENETIC RADIATION HAZARDS IN MAN

A. A COMPARISON OF THE MAIN CONCLUSIONS OF THE UNSCEAR AND BEIR REPORTS

595. The UNSCEAR (589) and BEIR (34) reports brought into focus the status of knowledge in the area of radiation genetics and, using this knowledge as a basis, made quantitative evaluations of genetic radiation hazards to man. Tables 47 and 48, which are reproduced

from these reports, summarize these estimates. Some of the major conclusions reached in these reports have since been reviewed and compared (360, 383, 495, 508, 509).

596. The general approach to the problem of hazard evaluation has been essentially the same in both the reports; they have the following aspects in common:

(a) The germ cell stages most relevant are spermatogonia in males and oocytes in females;

(b) Due to the paucity of direct human data, the results obtained with experimental mammals, primarily the mouse, form the main basis for hazard evaluations;

(c) Since most of the genetically significant radiation dose received by the human population is delivered either as small doses at high dose rates or as greatly protracted exposures, these are the radiation conditions under which the response of the human germ cells have been assessed;

(d) The rates of induction of different kinds of genetic damage used for hazard evaluation purposes are all based on the response of the mouse germ cells under the radiation conditions stated in (c) above. Appropriate corrections, if any, are made to apply them to man. The rates of induction are assumed to be linear with dose. For the induction of one kind of chromosomal damage, namely that of reciprocal translocations, human germ cells were assumed to be twice as sensitive as those of the mouse.

597. The two reports differ from one another in certain respects. The UNSCEAR report predominantly used the direct method to express risks, namely in terms of the amount of damage expected per gamete per unit dose of radiation; however, some limited attention was paid to quantify risks in relation to the natural incidence of hereditary diseases in man (the doubling dose method). The BEIR report mainly used the doubling dose method to quantify risks, although it stressed the fact that "there are so many facets to the problem that several ways of estimating the risk are more useful than any single one in arriving at the best policy decisions".

598. Although in both reports the increases in the amount of hereditary diseases in man (with the doubling dose method) were estimated using the spontaneous incidence figures as given in the 1962 and 1966 UNSCEAR reports (587, 596) (which in turn were modified from the original ones given by Stevenson (566)), the actual doubling doses were arrived at in different ways. The 100-rad doubling dose used by UNSCEAR was based on those estimated by Lüning and Searle (302). These authors showed that, for different kinds of genetic damage induced in mouse spermatogonia by high acute x-ray doses, the point estimates for the doubling doses ranged from 16 to 51 rad, averaging about 30 rad; with chronic exposures or with acute x irradiation at very low doses, it was inferred (based on different lines of evidence) that the rate of induction will be reduced by a factor of 3-4 and hence the doubling dose under these conditions was estimated as approximately 100 rad for males. Lüning and Searle (302) gave no doubling dose estimates for oocytes since very little information on spontaneous rates in females has been obtained.

599. BEIR, on the other hand, used a range of 20-200 rad as the doubling dose, calculated in the following way: the average rate of induction of recessive specific-locus mutations in the mouse (unweighted average of the rates for mouse spermatogonia and oocytes) under conditions of low-dose, low dose-rate irradiation was taken as $0.25\ 10^{-7}\ rad^{-1}$ per locus. The spontaneous rate of mutations for human recessive genes was taken to be in the range of $(0.5\text{-}5)\ 10^{-6}$ per locus. Dividing the spontaneous rate by the rate of induction, one gets a doubling dose range of 20-200 rad. This range, which, as just mentioned was estimated from spontaneous rates of human recessive gene mutations and induced rates of recessive specific-locus mutations in the mouse was assumed to be applicable to the different categories of genetic disease in man. BEIR considered that (a) the mouse induced mutation rate used above might be on the high side because these loci were to some extent preselected for mutability; (b) the rate of induction of dominant visible mutations in the mouse was at least an order of magnitude lower than that for recessive specific locus mutations; and (c) the mortality data pertaining to the children of Hiroshima and Nagasaki offered strong evidence for believing that the doubling dose is unlikely to be as low as 20 rad of chronic irradiation.

600. The UNSCEAR report gave two estimates for the risk of induction of recessive point mutations per genome using the direct method, namely, one based on the specific-locus mutation rate in mouse spermatogonia ($0.5\ 10^{-7}\ rad^{-1}$ per locus) multiplied by the assumed number of "genes" that make up the human genome (30 000), and another based on data on the induction of autosomal recessive lethals in mouse spermatogonia (since a majority of specific-locus mutations behave as recessive lethals). There was roughly a 40-fold difference between the two estimates (1500 mutations per 10^6 gametes following 1 rad of paternal irradiation (specific-locus data used) versus 36 recessive lethals per 10^6 gametes per rad (recessive lethal data used)).

601. The estimated size of the human genome (30 000 genes) was based on that of the mouse genome (25 000 genes); the latter figure was indirectly derived from results on complementation analysis of a very short segment of the mouse genome (*d-se* region, 0.16 map unit, 1/7500 of the mouse genome) and in fact referred to "functional units" rather than genes or loci. Since there is evidence from complementation tests that some of the events scored as specific-locus mutations involve more than one functional unit, and since specific-locus mutations are scored after birth at weaning age and autosomal recessive lethals, pre-natally, it was thought that these factors could explain the discrepancy between the two estimates (1500 point mutations per 10^6 gametes per rad versus 36 recessive lethals per 10^6 gametes per rad).

602. The UNSCEAR report used, again, a multiplicative method to estimate the rate of dominant mutations per genome (the assumed per-locus rate times the assumed number of loci that determine dominant traits in man). The BEIR report used, as mentioned earlier, the doubling dose method (20-200 rad) to estimate the expected increases in both recessive and dominant genetic diseases.

603. The UNSCEAR report gave no quantitiative estimates for expected increases in congenital anomalies, constitutional and degenerative diseases due to radiation exposures. The reason was that with the direct method employed (where mouse rates were used), such calculations are not possible. Although the calculations can be done with the doubling dose method, the Committee refrained from giving quantitative estimates because of uncertainties regarding the genetic basis of such diseases. The BEIR report, on the other hand, did provide such figures and stressed the uncertainties involved.

604. The UNSCEAR report gave separate estimates of risk for irradiation of males and females and pointed out that in females, because of inadequate or no information, no estimates could be given for recessive lethals, dominant visibles and skeletal mutations. The BEIR report estimates are for irradiation of both sexes; the rates used (in conjunction with the doubling dose range of 20-200 rad) were either unweighted averages of the rates in males and females (when known, as in the case of specific-locus mutation and X-chromosome losses) or were based on the conservative assumption that the rate in females is the same as in males (as is the case with translocations).

605. Estimates of hazards given in the UNSCEAR report related to the induction of the different kinds of genetic damage per rad of parental exposure, and the expected effects in F_1 per 10^6 conceptions. The BEIR report figures relate to the estimated increase among 10^6 live-born individuals whose ancestors had received radiation at the rate of 0.17 rad/year (5 rad per 30-year reproductive generation). The first-generation effects were arbitrarily estimated as one fifth of that expected at equilibrium (for dominant diseases) or as one tenth of that at equilibrium (for congenital anomalies etc.). For chromosomal and recessive diseases the effects were found to be negligible.

B. CURRENT STATUS

1. Introduction

606. The new human and mammalian data reviewed in the preceding sections permit a revision of some of the estimates of hazards arrived at by the Committee in its 1972 report (589). Lüning (295) has drawn attention to some of the main problems in risk assessment that still exist, and Lüning and Eiche (303), Oftedal (383), Newcombe (360), Sankaranarayanan (494, 495), Schalet and Sankaranarayanan (562), Searle (508, 509, 510), and Selby and Selby (528) have considered the extent to which some of the new data bear relevance to human hazard evaluations. In addition, a task group of the ICRP is currently engaged in preparing a document on the impact of a radiation-induced increase in mutation rate on the frequency of serious genetic disease in man (381). In what follows, an attempt will be made first to summarize the pertinent new information and then inquire whether (or not) and how it can be used to make genetic risk estimates. As in the 1972 report, such evaluations will be made using both the direct and the doubling dose methods.

2. Direct method

(a) *Recessive mutations*

607. It may be recalled that from a reanalysis of dose-rate data (gamma irradiation) for the induction of specific-locus mutations in mouse spermatogonia (paras. 276-280), Lyon *et al.* (318) suggested that at very low dose rates, the risk of induction of these mutational events may be higher than hitherto assumed and that this might be due to very low or no spermatogonial cell killing (relative to that which occurs at rates such as 0.009 R/min or higher). However, the available data also fit the concept of no change in mutation rate at exposure rates below 0.8 R/min, and besides, there are now two new lines of evidence. Firstly, the data currently available from the continuing work of W. L. Russell and Kelly (486, 487) (paras. 282-286) show that when a 300-R gamma-ray exposure is delivered to mouse spermatogonia at rates of 0.0056 R/min and 0.0007 R/min, the mutation frequencies are practically identical but significantly above controls. Secondly, in parallel experiments, also at 300 R, Oakberg and Palatinus (378) (paras. 285, 400-402) have demonstrated that the survival of stem-cell spermatogonia under x irradiation is unaffected at a rate of 0.0007 R/min, reduced to 37 per cent of controls at a rate of 0.0056 R/min, and to 16 per cent of controls after 94 R/min. Yet, the mutation rates obtained at the two low rates are identical and highest after high exposure-rate x-irradiation, showing no correlation between sensitivity to cell killing and to mutation induction. It therefore does not seem justified to alter the earlier premise used in hazard evaluations, namely that at low doses and dose rates, the rates of induction of point mutations in spermatogonia is about one third of that observed at high doses and dose rates.

608. As was fully discussed in the 1972 report, the two major uncertainties in the estimate by the multiplicative method of the rate of induction per genome of recessive point mutations (i.e., specific-locus rate multiplied by the assumed number of loci that make up the genome) relate to (a) whether the average specific-locus rate based on the 12 loci is representative of the mutational sensitivity of the genome in general and (b) the number of loci in the genome capable of mutating to recessive visibles. For spontaneous recessive mutations, it is known that the forward mutation rate at unselected loci is at least an order of magnitude lower than that at specific loci. The situation with respect to the radiation-induced rate for recessive visibles at unselected loci is not entirely known, although such data on dominant visibles indicate a very much lower rate relative to that for recessive specific loci (506, 589). Thus, the problem of selected versus unselected loci and the differences in their mutational potentialities will always remain. Since there is no easy way to get a precise estimate of the number of loci in the genome, the reliability of the genome estimate arrived at by the multiplicative method will continue to remain questionable.

609. Autosomal recessive lethals which represent mutations at unselected loci have been found to be induced at a much lower rate per gamete than would have been expected on the basis of the specific-locus

experiments. If for the sake of argument; one divides the per gamete induction rate for recessive lethals ($0.9\ 10^{-4}$ rad^{-1}) by the per-locus specific-locus rate ($1.7\ 10^{-7}$ rad^{-1}), one gets an improbably low figure of about 500 as the total number of loci capable of mutating to recessive lethals.

610. In view of these considerations, it would appear preferable to use the direct estimate based on recessive lethals in hazard evaluations. The value of the specific-locus data in this context lies in the information they provide on the effects of various physical and biological variables on mutation induction. If this basic conceptual change is accepted as a more reliable way to express risks, then the rate of induction of recessive lethals can be used as a meaningful starting point.

611. As was pointed out earlier, the estimated rate of $0.9\ 10^{-4}$ rad^{-1} per gamete (high dose, high dose-rate irradiation) is for autosomal recessive lethals acting *in utero*. The unpublished observations of W. L. Russell referred to in the 1972 report have shown that the proportion of pre-natal lethals averaged over the loci (at specific loci) is less than one half of the total number of mutations. If true in general, then the rate of induction of recessive mutations is likely to be at least $2 \times 0.9\ 10^{-4} = 1.8\ 10^{-4}$ rad^{-1} per gamete. Dividing this by 3 (to correct for expected effects at low dose-rate, low-dose conditions applicable to man) one gets a figure of $0.6\ 10^{-4}$ rad^{-1} per gamete for spermatogonial irradiation.

612. In making these calculations, it has been assumed that the rate of induction of recessive lethals reflects the genome rate for the induction of point mutations in general. This assumption derives support from the fact that recessive lethals represent events as unselected loci and from the fact that a majority of radiation-induced specific-locus mutations studied in the mice behave as recessive lethals in the homozygous condition.

613. There are no data on the induction of recessive lethals in mouse females. Since, under radiation conditions applicable to man, maturing mouse oocytes show a very low level of mutational sensitivity and immature oocytes are virtually insensitive to the induction of specific-locus mutations, it may be presumed that the risk in females will be low, but no quantitative estimates can be given.

(b) *Dominant mutations*

614. There are two sets of data in mice which allow a rough estimate to be made of the risk of inducing mutations with dominant effects. These data refer to (a) dominant visible mutations and (b) skeletal mutations appearing in the F_1 generation after x or gamma irradiation. For chronic gamma irradiation, the mean rate of induction of dominant visible mutations is $1.0\ 10^{-7}$ rad^{-1} per gamete (506). This can be converted into a per-locus rate by dividing it by the number of loci in the mouse (approximately 75) at which dominant visible mutations have occurred. Assuming an equal mutation rate in man, this figure ($1.3\ 10^{-9}$) can then be multiplied by the assumed number of loci (1000) which determine dominant traits in man to get an overall rate for dominant mutations. This procedure was used in the 1972 report. The Committee was, however, aware of the uncertainties and limitations of this approach and have not used it in the present document.

615. As far as skeletal mutations are concerned, there are new data on heritability and rate of induction. The new data of Selby and Selby (528) (paras. 335-339) confirm that abnormalities classified as presumed mutations on the basis of Ehling's criteria (paras. 332-333) are probably mostly heritable. The data of Selby and Selby, when appropriately corrected for dose-fractionation and dose-rate effect, [28] give the same rate of induction as that which could be derived from Ehling's data (namely, a rate of $4\ 10^{-6}$ rad^{-1} per gamete). In both the investigations, the authors recognized that this may be an underestimate of the true rate (paras. 336, 338).

(c) *The relationship between rates of induction of recessive and dominant mutations and the effects of these mutations in the progeny*

616. In its 1972 report, the Committee arrived at estimates of the effects of recessive and dominant mutations in the generation following paternal irradiation (see table 47) in the following way: for recessives, the induction rate (1500 per 10^6 gametes per rad or 36 per 10^6 gametes per rad) was multiplied by 2-5 per cent (this range of figures being based on the average semi-dominant effects of recessive lethals in *Drosophila*) and the resultant figures (30-75 per 10^6 or 1-2 per 10^6) were considered as representing the "expression" of mutations in the F_1 generation. In fact, what these figures imply is that the mean Darwinian fitness of heterozygotes for these mutations will be reduced by 2-5 per cent relative to those not carrying the mutations and that, on the average, these mutant genes will persist in the population for 20 (5% semi-dominance) or 50 (2% semi-dominance) generations subsequent to their induction. In other words, the impact of natural selection on mutant genes is through their heterozygous effects and the duration of persistence of the mutant genes will vary, depending on, among other things, their semi-dominant effect in heterozygotes, i.e., the smaller their semi-dominant effects, the longer will they persist in the population.

617. For dominant visibles, the procedure was simple: the induction rate and the expression in the F_1 were considered the same (2 per 10^6). Based on the limited information then available, mutations causing dominant skeletal defects were considered together with recessive mutations, since it was thought that they might represent heterozygous manifestations of recessive mutations.

618. In the light of new data on mutations causing dominant skeletal defects in the mouse, the finding that

[28] The frequency of $1.4\ 10^{-2}$ is divided by 600 (dose in rad) and further divided by 1.9 (to correct for the enhancement in mutation frequency due to the fractionation régime employed, based on findings in specific-locus work) and by 3 (to get a rate at low dose-rates, again based on specific-locus work) $(1.4\ 10^{-2})/(1.9)\ (3)\ (600) \approx 4\ 10^{-6}$.

four out of four such mutations tested thus far (525) behaved as recessive lethals when made homozygous, other evidence (para. 625), and the premise that dominance and recessivity are attributes of the phenotype and not of genes, the Committee feels that it is now possible to improve the estimates given in 1972 along the following lines: (a) by considering dominant and recessive mutations together to estimate effects in the F_1 and (b) by attempting to express these effects in socially meaningful terms, i.e., in terms of handicaps or disabilities that are expected.

619. An overall estimate of the risk from the induction of mutations causing dominant effects in the progeny (and this includes recessives with semi-dominant effects as well as dominants) can be derived using the data on the rate of induction of skeletal abnormalities in the mouse. The main argument for this rests on the premise that many of the skeletal abnormalities recovered in the mouse experiments are similar to rare dominants and rare irregularly inherited dominant conditions in man, which together constitute a sizeable portion of human genetic diseases. However, to convert the rate of induction of mutations causing skeletal abnormalities in the mouse to an overall rate for all dominant mutations with serious effects in man, one needs information on (a) the proportion of dominant conditions in man whose main effect is in the skeleton and (b) the proportion of skeletal abnormalities studied in the mouse which, at the human level, is likely to cause a serious handicap.

620. Firstly, a perusal of McKusick's latest tabulation of monogenic disorders in man (328) will reveal that out of the 583 "proved" autosomal dominants, 328 are clinically important; in the latter group, 74 (or roughly 20 per cent) involve one or more parts of the skeleton to a varying extent. However, this figure is undoubtedly a reflection of the ease of diagnosis of such abnormalities by phenotypic inspection and/or radiography. The true figure is therefore likely to be lower and, in the opinion of Carter (82) and McKusick (328a), is of the order of 10 per cent.

621. Secondly, not all of the skeletal abnormalities of mutational origin studied in the mouse will impose a serious handicap in humans. Selby (525) suggests that this proportion of abnormalities (leading to serious handicaps) may range from 25 to 75 per cent; in Carter's opinion, a figure of 50 per cent may be accepted as a tentative estimate and this has been confirmed in a detailed discussion of the mutants by Selby (525) and McKusick (328a).

622. It follows that, if the estimated rate of induction of mutations causing skeletal abnormalities in the mouse ($4\ 10^{-6}$ rad^{-1} per gamete under low-LET, low-dose or low dose-rate irradiation; spermatogonia) is multiplied by 10 and then divided by 2, the resultant rate, $20\ 10^{-6}$ rad^{-1} per gamete, is one of induction of mutation having dominant effects on any of the bodily systems in man. In other words, following 1 rad of paternal (spermatogonial) irradiation, 20 out of every million progeny will be expected to carry mutations which cause one or another kind of dominant genetic disease, in the first generation.

623. It is well known in both man and mouse that dominant mutations may show pleiotropism and thus may affect both the skeleton and non-skeletal systems (such as the spleen and stomach in the case of mouse dominant hemimelia). Similar skeletal anomalies may also turn up in different genetic syndromes in both man and mouse. However, in making the calculations referred to above, allowance was made for such pleiotropism.

624. Since in man skeletal abnormalities are frequently observed in association with chromosomal aberrations, such as complete trisomies and partial monosomies and trisomies (208a), it is important to establish to what extent the skeletal conditions described by the Selbys could have been chromosomal rather than genic in origin. Nine mutant lines (mainly involving sterile and semi-sterile individuals) have been tested cytologically and three contained translocation heterozygotes. Two of these three seemed to be associated with the skeletal effects. It should be noted that (a) no unbalanced forms, such as trisomies, were found; (b) the possibility that some rare human apparent dominants are associated with chromosome anomalies cannot be ruled out; and (c) effects of balanced translocations have not been included in any other category in the risk assessments. For these reasons and those given in paragraph 340 the amount of overlap with the chromosomal aberration risk category is likely to be very small, although it cannot be estimated in the absence of detailed refined chromosome analysis.

625. On the other hand, a substantial fraction of these dominant conditions are likely to be lethal in the homozygote and can therefore also be placed in the recessive lethals category. Of 164 dominant mutations in the mouse (apart from those concerned with enzyme polymorphisms and immunological traits) at least 45, or 27 per cent, appear to be lethal in the homozygote. It is quite clear, however, that the dominant manifestation is the important one from the point of view of risk estimation. Homozygotes for human deleterious dominants have rarely been observed, but if so, are lethal.

626. Although the many uncertainties involved in extrapolating from mutations causing dominant skeletal effects in the mouse to the overall number of harmful dominants in man are realized, it is felt that the induction rate of 20 per progeny per rad of paternal irradiation (to spermatogonia), as calculated in paragraph 622, is the best estimate which can be obtained in our present state of knowledge. It is therefore the rate given in table 49.

(d) *Reciprocal translocations*

627. For the induction of reciprocal translocations, more information, including some limited human data, is now available (paras. 131, 184-187). The combined human and marmoset spermatogonial data (at doses of 100 rad and below, acute x-irradiation) indicate a translocation rate of $6.94\ 10^{-4}$ rad^{-1} per cell, on the assumption of linearity (para. 185). A much lower rate could be estimated from the two sets of data now available for the rhesus monkey (paras. 182, 183), but for reasons discussed earlier (paras. 186, 187), it has been decided to base estimates of risk on the human and marmoset data in this report.

628. For estimating the rate at low doses or after chronic exposures, the following lines of evidence from mouse work are pertinent. When a total dose of 300 rad of x rays is administered in 30 or 60 equal fractions, the frequencies of translocations observed in the spermatocytes are reduced by a factor of 4 relative to acute doses (315). At the lowest x-ray dose rate of 0.09 rad/min (300-rad level), the reduction in frequency is by a factor of 2 (512). The efficiency of chronic gamma irradiation at 0.02 rad/min (600-rad level) is lower by a factor of about 10 relative to acute irradiation (517); at a lower dose rate of 0.007 rad/min, over a range of up to 1200 rad, the dose-effect relationship is linear and here too, there is a dose-rate reduction factor of at least 10 (Pomerantzeva *et al.*; refs. 415 and 417). Finally, in the experiments of Searle *et al.* (516) with a gamma-ray dose of 1128 rad delivered over a period of 28 weeks at a rate of 0.004 rad/min, the rate of induction was $1.40\ 10^{-5}$ rad^{-1} per cell, which is lower by a factor of about 20 relative to that after acute irradiation. (In the work of Pomerantzeva *et al.* (417), however, a lowering of the rate from 0.007 to 0.003 rad/min did not lead to any sizeable reduction in the efficiency of gamma irradiation.)

629. If these results are considered applicable to translocation induction in human spermatogonia, the use of reduction factors of, respectively 4, 2 and 10 (to correct the rate of $6.94\ 10^{-4}$ rad^{-1}) for low-dose x rays, low dose-rate x rays, and chronic gamma irradiation, would appear to be reasonable. The corresponding figures then are (rad^{-1} per cell): $1.74\ 10^{-4}$ (low-dose x rays), $3.47\ 10^{-4}$ (low dose-rate x rays), and $0.694\ 10^{-4}$ (chronic gamma irradiation).

630. The induction rate of importance for hazard evaluations is the one that relates to recoverable translocations in the F_1 progeny. Although in its 1972 report the Committee used a reduction factor of 8 to get the above from spermatocyte data (based on the work of Ford *et al.* (170)), it would appear prudent (on the basis of new evidence reported in paragraphs 131 and 132) to assume that the rate of recovery in the F_1 will be one fourth of that in spermatocytes. This means the rates will be (rad^{-1} per gamete): $0.44\ 10^{-4}$ (low-dose x rays), $0.87\ 10^{-4}$ (low dose-rate x rays), and $0.174\ 10^{-4}$ (chronic gamma irradiation).

631. It follows that if males are exposed to low-dose x rays, low dose-rate x rays, or chronic gamma irradiation, the expected number of balanced and unbalanced translocation-carrying zygotes in the F_1 will be, respectively, 44 and 88, 87 and 174, or 17 and 34 per million conceptions per rad of exposure. Assuming further (as the Committee did in its 1972 report) that only about 6 per cent of the unbalanced zygotes will result in children with multiple congenital anomalies, there will be about 5, 10 or 2 such children per million conceptions after one rad of paternal (spermatogonial) exposure. One third of the remaining unbalanced zygotes ($83 \times 1/3 = 28$, $164 \times 1/3 = 55$, $32 \times 1/3 = 11$) would fall into the recognized abortion category, and the remaining two thirds would die so early as to go undetected.

632. It bears reiterating here that the rates of translocation induction used above are based on human and marmoset cytogenetic data with corrections for transmission and expected effects at low doses and dose rates being based on mouse data. Should it turn out that the rate of induction in human spermatogonia is more similar to that in the rhesus monkey, the estimates may need revision, and consequently the quantitative figures arrived at must be considered provisional at present. In the 1972 report, the rate used for human spermatogonia was based on that in the mouse ($\approx 0.3\ 10^{-4}$ rad^{-1} per gamete, acute x irradiation, semi-sterility data), multiplied by 2 to take into account the two-fold difference between man and mouse in effective chromosome arm number and divided by factors of 4 or 9 to get the rates under low dose or chronic exposure conditions, respectively. The change in approach was dictated in part by the lack of validity of the arm number hypothesis (paras. 450-465) for interspecific extrapolations and in part by the availability of new data in man, the marmoset and the mouse on the transmission of translocations to the F_1 progeny.

633. The rate of translocation induction in human females is not known. The data for mouse females discussed earlier (para. 166) show that in maturing oocytes exposed to acute x irradiation, the rate is $0.16\ 10^{-4}$ rad^{-1} per gamete (semi-sterility data). Although there is no direct evidence on the response of immature oocyte stages to the induction of translocations at low doses and dose rates, the data on specific locus mutations and on X-chromosome losses (see paras. 230-231 for the latter) strongly support the view that the rate for translocations is also likely to be low, but no quantitative estimate can be given.

(e) *Other structural aberrations*

634. It seems likely that the risk from the induction of structural aberrations other than reciprocal translocations will be very small. In the mouse, "dominant lethals, due to isochromatid exchange etc., with resultant chromosomal breakage, can be transmitted after oocyte irradiation, though apparently not after spermatogonial irradiation because of germinal selection. It seems likely that most of them act too early to constitute a real hazard. Deficiencies are also induced at comparatively high frequency after oocyte irradiation; however not enough is known yet about their probable overall rate of induction or deleterious effects (especially in the heterozygote) to make any estimate of the genetic damage they may cause" (508).

(f) *Sex-chromosome losses*

635. The complete data on the x-ray induction of sex-chromosome losses in male mice (para. 229) support the conclusion reached by the Committee in 1972, namely that the risk from this class of genetic damage after spermatogonial irradiation is very low or nil. The new data for female mice (table 32 and para. 231) show that the frequencies of sex-chromosome losses are low and not significantly above the controls both after acute x irradiation with 50 R and after chronic gamma ray exposures (400 R) delivered at a rate of 0.006 R/min. These findings therefore suggest that if the human

oocytes respond like those of the mouse, the risk is probably very low, but no quantitative estimates can be given.

636. The risk from the induction of other chromosomal aberrations cannot be reliably estimated at present. As far as chromosome gains are concerned, there is no clear evidence in the mouse, for their induction after spermatogonial irradiation (450, 506). In oocytes however, Yamamoto *et al.* (627) obtained some presumptive evidence for the x-ray induction of non-disjunction in older mice (para. 237), but these data do not lend themselves to risk estimation because of some statistical problems (para. 238). The work of Uchida and Lee (582) (paras. 239-241) also provides evidence for the induction of non-disjunction in oocytes, but the total number of non-disjunctional events is too scanty to define the form of the dose-effect relationship. The results in humans are conflicting (paras. 33-37) and furthermore, there is a large maternal-age component. In view of these, it seems judicious to refrain from predicting the overall extra risk of trisomy in the offspring of women exposed to irradiation until some more information becomes available.

3. Doubling dose method

637. Turning now to the method of expressing risks in relation to the natural incidence of genetic diseases in man (i.e., the doubling dose method), it should be stressed that this method has certain advantages as well as limitations: these were dealt with in the 1972 report of the Committee. Suffice to point out that its chief advantage lies in the fact that it expresses risks in more comprehensible terms than the direct method, although one of the main assumptions, namely, that there is proportionality between spontaneous and induced rates, still remains an unproved one. To employ the doubling dose method, one needs, in addition to other information, the following kinds of data: (a) the natural incidence of the different classes of genetic disease in man; (b) the relationship between incidence and mutation rate; (c) the doubling dose; (d) the radiation dose to which the population is exposed.

638. The data of Trimble and Doughty (576), with the substantial modifications suggested for regular dominant diseases (para. 11) and those summarized by Nielsen and Sillesen (363) on the incidence of chromosome anomalies (see last column in table 9), provide the requisite information on point (a). Of the total frequency of 0.6 per cent chromosomal anomalies recorded in new-born surveys (table 11), roughly two thirds (0.4 per cent) is constituted by numerical sex-chromosomal and autosomal anomalies plus aneuploid structural abnormalities. This 0.4 per cent can be considered as the rate of incidence of chromosomal diseases, although this figure (which does not include balanced reciprocal translocations) may be an underestimate since there is evidence that heterozygosity for balanced reciprocal translocations in some cases, especially in those involving the sex-chromosomes, can result in a handicap to carriers (143, 144). The evidence of Jacobs *et al.* (250) from new-born surveys that aneuploid structural rearrangements of the chromosomes detectable with non-banding techniques may be a rare cause of congenital malformations needs to be viewed with some caution since such malformations may still be recognized later in life.

639. As far as point (b) is concerned, it is safe to assume that the incidence of autosomal dominants and X-linked diseases is essentially proportional to the mutation rate, i.e., their incidence will increase after radiation exposures. The incidence of recessive diseases is only very indirectly related to mutation rate. The incidence of numerical chromosomal disorders and unbalanced structural anomalies will be directly proportional to mutation rate.

640. For diseases of complex aetiology, such as irregularly inherited dominant diseases, multifactorial diseases and congenital malformations (together consisting about 9 per cent in the British Columbia Survey), as was mentioned earlier (para. 15), we shall assume that the mutational component (i.e., the proportion of these diseases that will respond to radiation exposures in a manner similar to that of simple monogenic dominant diseases) is of the order of 5 per cent (para. 15). In terms of absolute effects expected at equilibrium, this is equivalent to assuming that 0.45 per cent diseases of complex aetiology (i.e., 5 per cent of 9 per cent) are irregularly-inherited dominants, and these will behave like simple dominants in their response to irradiation. The reason for not lumping these two classes is that under the radiation conditions assumed for the estimation of risks (see below) the expected effects in the first generation are different for these two classes.

641. Coming now to the doubling dose, as was discussed earlier, the BEIR report used a range of 20-200 rad; the 1972 UNSCEAR report used the figure of 100 rad for males. The examination of available evidence in the mouse suggests that the use of a 100-rad doubling dose (for both sexes) will not underestimate the risk (495, 510). The ICRP Task Group (381) has also used this figure in its calculations. Further justification for the use of this figure derives from the recent Hiroshima and Nagasaki data (para. 39), which suggest that for normal radiation conditions applicable to the human population (low LET, low dose or low dose rate), the minimal doubling dose for the type of damage resulting in death during the first 17 years of life is at least 138 rad for males and over 1000 rad for females. We shall therefore use 100 rad as the doubling dose in this report.

642. To facilitate comparisons with the estimates given in table 49, we shall assume that the population is exposed at a rate of 1 rad per generation (low-LET, low dose rate). The resultant estimates are given in table 50 (top half). It can be seen that (a) the expected increment in the first generation is estimated to be one fifth of that at equilibrium for simple dominant and X-linked diseases and one tenth of that at equilibrium for diseases of complex aetiology (based on the assumptions used in the BEIR report); (b) for chromosomal diseases, the first generation incidence is nearly the same as at equilibrium; and (c) the total increment expected in the first

generation is 63 new cases of genetic disease per 10^6 (0.06 per cent of current incidence) and 185 cases per 10^6 at equilibrium (0.17 per cent of current incidence).

643. A comparison of the present estimates with those of the BEIR report (bottom half of table 50) will show that there are some discrepancies between the two sets of estimates. The differences in certain numerical estimates derive from the use of (a) different current incidence figures (10.7 per cent in the present report, 6 per cent in the BEIR report); (b) a single doubling dose of 100 rad rather than a range of doubling doses from 20 to 200 rad; (c) a single figure instead of a range of figures to quantify the mutational component in diseases of complex aetiology (5 per cent instead of 5-50 per cent); and (d) a numerical estimate for the effects of radiation on the increment in chromosomal diseases (based on data from new-born surveys) in the present report.

644. It is worth pointing out here that the first-generation effects for simple dominant diseases (20 per 10^6) and for irregularly inherited dominants (5 per 10^6—a total of 25 per 10^6 live-born—is quite similar to the figure of 20 per 10^6 arrived at using the direct method.

4. Summary and conclusions

645. This chapter has been devoted to (a) a comparison of the main conclusions reached by UNSCEAR and BEIR in their 1972 reports; (b) summarizing the major new findings that are pertinent for the evaluation of genetic radiation hazards (details of which were discussed in the different chapters of this annex); and (c) presenting revised estimates of risk on the basis of the information currently available. The estimates arrived at are given in table 49 (direct method) and in table 50 (doubling dose method); these effects are those expected following low-LET irradiation of the germ-cell stages most at risk (spermatogonia in males and oocytes in females) and are for conditions of radiation exposure most relevant, namely, low doses and chronic exposures.

646. The rate of induction of recessive mutations has been estimated to be $0.6\ 10^{-4}$ rad^{-1} per gamete. This figure is derived from the rate of induction of autosomal recessive lethals in male mice following acute x irradiation of spermatogonia ($0.9\ 10^{-4}$ rad^{-1} per gamete), corrected for (a) low dose-rate irradiation conditions (i.e., the use of a reduction factor of 3 which gives $0.9\ 10^{-4} \div 3 = 0.3\ 10^{-4}$) and (b) assuming that the proportion of recessive lethals scored by the pre-natal method represents about one half of all recessive mutations (i.e., multiplying $0.3\ 10^{-4}$ by 2, we obtain $0.6\ 10^{-4}$).

647. The Committee examined the possibility that, at very low dose rates, the mutation-rate reduction factor of 3 (correction (a) above) may not be applicable because of the lack of cell killing in the context of (a) new data on specific locus mutations at low dose rates and (b) new data on the survival of stem-cell spermatogonia at different dose rates and concluded that, at the dose rates studied (one high and two low), there was no correlation between cell killing and the mutation rate. In view of this, the reduction factor of 3 to estimate effects at low dose rates has been retained.

648. Since there are no data on the induction of recessive lethals in female mice, no estimates are possible for this kind of damage in human females. However, the evidence from specific-locus experiments strongly support the view that the risk in females is low.

649. The overall dominant effects from the induction of mutations in man (including recessives with semi-dominant effects and dominants), estimated as $20\ 10^{-6}$ rad^{-1} per gamete, has been arrived at using the expected rate of induction of mutations affecting the skeleton in mice (following spermatogonial irradiation at low dose rates) as the starting point ($4\ 10^{-6}$ rad^{-1} per gamete). This figure was multiplied by 10 to take into account the fact that approximately 10 per cent of dominant mutations recorded in man are associated with skeletal abnormalities and divided by 2 to take into account the possibility that about 50 per cent of the skeletal mutations found in the mouse, if induced in humans, could cause serious handicap.

650. There are no data on the induction of skeletal mutations in female mice, and consequently no attempt has been made to make a quantitative estimate of risk for the induction of dominant mutations in human females. The risk is expected to be low, however, if the results of specific-locus tests in female mice are considered applicable to human females.

651. The rate of induction of reciprocal translocations have been estimated to be $0.44\ 10^{-4}$, $0.87\ 10^{-4}$, and $0.174\ 10^{-4}$ rad^{-1} per gamete for low-dose x rays, low dose-rate x rays, and chronic gamma irradiation, respectively. With these rates of induction, the consequences following 1 rad of paternal exposure are 2-10 congenitally malformed children, 11-55 recognized abortions and 22-109 early embryonic losses per 10^6 conceptions. The rates of induction have been derived using the limited human and marmoset cytogenetic data (spermatogonial irradiation) obtained in experiments involving acute x irradiation and making corrections for expected effects at low doses and dose rates and for transmission to the F_1 progeny using mouse results as a guide. The Committee wishes to stress that the risk from the induction of translocations as given above is subject to uncertainty in view of the limited nature of the primary data and the fact that within primates there is considerable heterogeneity; in fact, the data from Rhesus monkeys suggest that the rates may be much lower than in both the marmoset and the mouse, and should this suggestion be confirmed in subsequent experiments with primates, especially the monkey and/or man, there may be grounds for revision of the estimates.

652. The reason for using human and marmoset data for hazard evaluation (and not the rate of induction in mice with a multiplication factor of 2 to apply to man, as was done in the 1972 report) is that the basic premise for the use of the multiplication factor of 2 (namely, the hypothesis of linear relationship between effective

chromosome arm number and the relative sensitivity to the induction of dicentrics or translocations) now appears invalid.

653. There are no data which will permit an evaluation of the risk from the induction of translocations in human females. Again, on the basis of mouse results with another end-point of genetic damage, namely the loss of X-chromosomes, it would appear that the risks are low, but no quantitative estimates can be given.

654. The risk from the induction of other kinds of structural aberrations is likely to be small by analogy with the mouse, but no estimate can be made at present.

655. For the induction of sex-chromosome losses, the available mouse data suggest that in both males and females (at low doses or after chronic gamma irradiation) the risk is low or negligible. The lack of a significant difference in X-loss frequencies (between controls and the irradiated groups of mice), viewed in conjunction with the fact that in humans, a predominant majority of the XO conceptions are inviable, would suggest that in humans, too, the risk is likely to be quite low.

656. Although in mouse experiments, presumptive evidence for the induction of non-disjunction has been obtained at low doses, in view of some uncertainties (lack of information on dose-effect relationship, statistical problems and complications due to maternal-age effects), it is not possible to make a realistic quantitative estimate for this kind of damage.

657. Estimates of doubling doses arrived at in the mouse for various end-points of genetic damage, as well as the data on the mortality of children born to A-bomb survivors in Hiroshima and Nagasaki, suggest that the doubling dose in man (both sexes) is unlikely to be lower than 100 rad.

658. The doubling dose of 100 rad has been used in conjunction with the frequencies of spontaneous incidence of genetic disease in man to compute, the expected increments. The spontaneous incidence figures used are (per cent): dominant and X-linked diseases, 1; recessive diseases, 0.1; chromosomal diseases, 0.4; diseases with complex aetiology, 9.0. Under the assumption that the population is exposed to low-LET, low dose-rate irradiation at the rate of 1 rad per generation, it was estimated that in the first generation there will be, per million live-born, 20 additional cases suffering from dominant and X-linked diseases, 38 from chromosomal diseases, and 5 cases from diseases of complex aetiology. The total, 63, represents 0.06 per cent of the current incidence (10.5 per cent). At equilibrium (which will be reached after different numbers of generations depending on the kinds of disease), this total increment will be 185 cases per million live-born, or 0.17 per cent of current incidence.

659. The overall increment due to the induction of dominant mutations (simple dominants plus those with irregular penetrance), estimated by the doubling dose method is 25 cases per million (20 + 5; see preceding paragraph) in the first generation and is about the same as that estimated using the direct method (20 per million live-born; see paragraph 649).

VII. SUGGESTIONS FOR FUTURE RESEARCH

660. In this annex, the progress that has been made in mammalian and human genetics, cytogenetics, molecular radiobiology and somatic cell genetics since the publication of the 1972 report has been reviewed, and revised estimates of genetic risks to man from exposure to ionizing radiation have been presented. These estimates reflect our current state of knowledge; as will be evident from the Committee's consecutive reports on this subject, the process of risk assessment is a continuous one: new advances help us to view old problems with a new perspective, to examine the validity of assumptions and extrapolation procedures used, and to identify areas of research which are likely to contribute to a better understanding of the genetic radiosensitivity of human beings. The Committee feels that, in order to increase our precision in risk assessment, more research effort along the following main lines will be useful (the order in which these are listed do not reflect the order of importance):

(a) Additional surveys on the prevalence of hereditary defects and disease in human populations (similar to that carried out in British Columbia), including an ascertainment of chromosomal diseases and diseases of late onset;

(b) Mutation monitoring in man by biochemical techniques;

(c) Continuation of studies on non-disjunction and the effects of radiation thereupon;

(d) Continuation of genetic and cytogenetic studies on Hiroshima and Nagasaki populations;

(e) Continuation of comparative radiation studies in different mammalian species;

(f) Further studies on the relationship between the frequencies of reciprocal translocations scored cytogenetically in spermatocytes and those observed in genetic tests, especially at low doses and after low dose-rate irradiation;

(g) Collection of more cytogenetic data on the induction of reciprocal translocations in primate species using when possible, human testes which happen to have been irradiated for medical reasons;

(h) Continuation of studies on the radiation induction of structural chromosomal aberrations (including translocations) in mammalian oocytes;

(i) Further studies on the role of factors influencing the induction of structural aberrations in somatic as well as germinal cells, such as the amount and distribution of heterochromatin in the chromosomes, the basis for differential sensitivity to radiation-induced breakage observed between chromosomes or chromosome regions;

(j) Further studies on the repair of radiation-induced chromosome breaks;

(k) Continuation of studies aimed at the characterization of the radiation-induced mutational events at biochemically-defined loci in mammals and other organisms such as *Drosophila;*

(l) Continuation of studies on the nature of radiation-induced specific-locus and dominant mutations;

(m) Studies on the induction of autosomal recessive lethals in female mice;

(n) Continuation of studies on the induction and characterization of mutations affecting the skeleton and other apropriate bodily systems in the mouse;

(o) Studies on the induction of mutations in germ cells and somatic cells at very low doses and dose rates and the development of techniques to facilitate such studies;

(p) Continuation of genetic and cytogenetic studies with mice on the effects of incorporated radioisotopes;

(q) Continuation of studies on the factors that modify radiation-induced genetic damage;

(r) Development and exploitation of more mutational assay systems in somatic cells *in vitro* and *in vivo;*

(s) Studies on the nature of radiation-induced damage at the DNA level and its relationship to mutations and chromosome aberrations;

(t) Validation of the assumptions involved in the use of the doubling dose approach for hazard evaluation;

(u) Continuation of studies on the interaction of radiation and chemical mutagens.

TABLE 1. SINGLE GENE DOMINANT DISORDERS BY ICDA CODE

ICDA code[a]	*Number of persons affected*[b]	*ICDA title*[c]
282.0	17	Familial acholuric jaundice
286.3	4	Vascular haemophilia
312.9	1	Moderate idiopathic mental retardation
313.9	1	Severe idiopathic mental retardation
314.9	1	Profound idiopathic mental retardation
330.0	6	Neuropathic muscular atrophy
330.4	4	Myotonia atrophica
330.9	3	Unspecified neuromuscular disorder
331.0	2	Hereditary chorea
350.0	1	Facial paralysis
354.0	2	Polyneuritis and polyradiculitis
358.0	2	Horner's syndrome
377.9	4	Unspecified disease of retina and optic nerve
389.9	3	Impairment of hearing, one or both ears
520.5	3	Hereditary disturbances in tooth structure
733.2	3	Myositis ossificans
743.4	29	Neurofibromatosis
744.2	1	Buphthalmos
744.3	27	Congenital cataract
744.5	8	Aniridia
744.7	3	Congenital blepharoptosis
744.8	24	Anomalies of eye
752.2	2	Hypospadias
753.1	1	Cystic kidney disease
755.0	21	Polydactyly
755.2	2	Reduction deformity of upper limb
755.3	1	Reduction deformity of lower limb
755.5	5	Anomaly of upper limb (including shoulder girdle)
755.8	2	Generalized flexion contracture of limb joints
756.0	16	Anomalies of skull and face bones
756.6	57	Chondrodystrophy
756.6	30	Osteogenesis imperfecta
756.7	1	Generalized anomalies of skeleton
757.0	1	Hereditary oedema of legs
757.2	15	Anomalies of skin
757.9	3	Unspecified anomalies of skin, hair and nails
759.6	12	Tuberous sclerosis
759.8	34	Congenital syndrome, affecting multiple systems
	Total 352	

Source: Based on the British Columbia Survey (576).

[a] ICDA = International Classification of Diseases Adapted, 8th revision (244).

[b] Since ascertainment for many conditions, especially congenital malformations, is not routinely good for all birth cohorts, and since these numerators are not broken down by birth period, valid estimates of rates of individual conditions cannot be calculated from these numbers.

[c] These titles do not describe single disease entities but rather the nature of the groups of conditions to which the ICDA rubrics apply. Detailed diagnostic lists for each ICDA code are given in the ICDA, 8th revision (244).

TABLE 2. SINGLE GENE RECESSIVE DISORDERS BY ICDA CODE

ICDA code	*Number of persons affected*	*ICDA title*
243.0	3	Cretinism of congenital origin
253.1	1	Anterior pituitary hypofunction
253.9	1	Unspecified disease of pituitary gland
270.0	41	Phenylketonuria
270.7[a]	28	Albinism
270.8	11	Congenital disorders of amino acid metabolism
271.0	5	Von Gierke's disease
271.1	8	Unspecified glycogen storage disease
271.2	5	Galactosaemia
272.2	4	Lipid storage disorders
273.0	151	Cystic fibrosis
273.3	1	Hepatolenticular degeneration
273.4	6	Disorders involving metabolism of minerals
273.6	22	Disorders of steroid metabolism
273.8	16	Congenital disorders of metabolism
275.0	7	Agammaglobulinaemia
275.1	5	Hypogammaglobulinaemia
279.0	5	Unspecified metabolic diseases
282.4	10	Mediterranean anaemia
284.0	2	Aplastic anaemia
311.9	1	Mild idiopathic mental retardation
315.9	1	Unspecified idiopathic mental retardation
330.0	3	Neuropathic muscular atrophy
330.1	19	Familial progressive spinal muscular atrophy
330.2	24	Amyotonia congenita
330.3	28	Progressive muscular dystrophy
332.0	5	Hereditary spinal ataxia
333.0	10	Amaurotic family idiocy
333.1	4	Progressive cerebral leukodystrophy
333.9	2	Unspecified hereditary diseases of nervous system
377.9	1	Unspecified diseases of retina and optic nerve
389.0	13	Deafness, both ears
389.9	20	Impairment of hearing, one or both ears
583.0	1	Nephritis, unqualified
742.0	1	Congenital hydrocephalus
743.1	6	Microcephalus
743.8	1	Congenital anomalies of nervous system
744.1	2	Micropthalmos
744.2	16	Buphthalmos
744.3	1	Congenital cataract
747.2	1	Anomaly of aorta
747.9	1	Unspecified anomaly of circulatory system
751.5	1	Atresia of biliary ducts
752.7	5	Pseudohermaphroditism
753.1	19	Cystic kidney disease
756.5	3	Chondrodystrophy
756.7	3	Generalized anomalies of skeleton
757.2	17	Anomalies of skin
759.8	9	Syndromes affecting multiple systems
Total	550	

Source: Based on the British Columbia Survey (576).

Note: See notes to table 1.

[a]Special registry code.

TABLE 3. SINGLE GENE X-LINKED DISORDERS BY ICDA CODE

ICDA code	*Number of persons affected*	*ICDA title*
257.9	1	Unspecified ovarian dysfunction
265.1	2	Rickets, late effect
270.7[a]	4	Albinism
273.4	6	Disorders involving metabolism of minerals
273.8	7	Congenital disorders of metabolism
275.0	11	Agammaglobulinaemia
275.1	20	Hypogammaglobulinaemia
282.2	1	G-6-PD deficiency anaemia
282.9	1	Hereditary haemolytic anaemia
285.0	1	Hypochromic anaemia with iron loading
286.0	40	Haemophilia A
286.1	11	Haemophilia B

TABLE 3 *(continued)*

ICDA code	*Number of persons affected*	*ICDA title*
286.9	1	Coagulation defect
312.9	1	Moderate idiopathic mental retardation
330.3	52	Progressive muscular dystrophy
330.4	1	Myotonia atrophica
377.3	24	Colour blindness
377.9	1	Unspecified disease of retina and optic nerve
742.0	1	Congenital hydrocephalus
752.7	4	Pseudohermaphroditism
756.7	2	Generalized anomalies of skeleton
752.2	3	Anomalies of skin
757.9	1	Unspecified anomaly of skin, hair or nails
759.8	2	Syndromes affecting multiple systems
Total	198	

Source: Based on the British Columbia Survey (576).
Note: See notes to table 1.
[a]Special registry code.

TABLE 4. DISEASES DUE TO SINGLE GENES OF UNCERTAIN DOMINANCE BY ICDA CODE

ICDA code	*Number of persons affected*	*ICDA title*
252.1	1	Hypoparathyroidism
282.4	1	Mediterranean anaemia
282.5	2	Haemoglobinopathies
286.9	3	Coagulation defects
744.6	5	Retinitis pigmentosa
Total	12	

Source: Based on the British Columbia Survey (576).
Note: See notes to table 1.

TABLE 5. AUTOSOMAL CHROMOSOME ANOMALIES BY ICDA CODE

ICDA code	*Number of persons affected*	*ICDA title*
759.3	972	Down's syndrome
759.4	44	Syndromes due to autosomal abnormality except trisomy 21
Total	1 016	

Source: Based on the British Columbia Survey (576).
Note: See notes to table 1.

TABLE 6. SEX CHROMOSOME ANOMALIES BY ICDA CODE

ICDA code	*Number of persons affected*	*ICDA title*
752.0	1	Syndrome due to sex chromosome anomaly with indeterminate sex
752.2	1	Syndrome due to sex chromosome anomaly with hypospadias
756.4	1	Syndrome due to sex chromosome anomaly with anomalies of ribs and sternum
759.5	44	Syndromes due to sex chromosome anomalies
Total	47	

Source: Based on the British Columbia Survey (576).
Note: See notes to table 1.

TABLE 7. CONGENITAL MALFORMATIONS BY ICDA CODE

ICDA code	*Number of persons affected*	*ICDA title*
740.0	123	Anencephalus
741.0	259	Spina bifida with hydrocephalus
741.9	317	Spina bifida without mention of hydrocephalus
742.0	372	Congenital hydrocephalus
743.0	20	Encephalocele
743.1	83	Microcephalus
743.2	85	Anomalies of brain
743.3	2	Anomalies of spinal cord
743.8	6	Anomalies of nervous system
743.9	27	Unspecified anomalies of brain, spinal cord and nervous system
744.0	9	Anopthalmos
744.1	32	Micropthalmos
744.2	18	Buphthalmos
744.3	198	Congenital cataract
744.4	20	Coloboma
744.7	106	Congenital blepharoptosis
744.8	196	Anomalies of eye
744.9	14	Unspecified anomalies of eye
745.0	65	Anomalies of ear causing impairment of hearing
745.1	179	Accessory auricle
745.2	55	Anomalies of ear
745.3	46	Unspecified anomalies of ear
745.4	93	Branchial cleft, cyst or fistula; preauricular sinus
745.5	2	Webbing of neck
745.8	8	Anomalies of face and neck
745.9	3	Unspecified anomalies of face and neck
746.0	22	Common truncus
746.1	72	Transposition of great vessels
746.2	163	Tetralogy of Fallot
746.3	1 014	Ventricular septal defect
746.4	499	Atrial septal defect
746.5	10	Ostium atrioventriculare commune
746.6	219	Anomalies of heart valves
746.7	41	Fibroelastosis cordis
746.8	101	Anomalies of heart
746.9	477	Unspecified anomalies of heart
747.0	347	Patent ductus arteriousus
747.1	91	Coarctation of aorta
747.2	22	Anomalies of aorta
747.3	102	Stenosis or atresia of pulmonary artery
747.4	8	Anomalies of great veins
747.5	13	Absence or hypoplasia of umbilical artery
747.6	12	Anomalies of peripheral vascular system
747.8	8	Anomalies of circulatory system
748.0	23	Choanal atresia
748.1	15	Anomalies of nose
748.2	4	Web of larynx
748.3	38	Anomalies of larynx, trachea and bronchus
748.4	8	Congenital cystic lung
748.5	4	Agenesis of lung
748.6	21	Anomalies of lung
749.0	460	Cleft palate
749.1	291	Cleft lip
749.2	571	Cleft palate with cleft lip
750.0	55	Anomalies of tongue
750.1	746	Pyloric stenosis
750.2	42	Tracheo-oesophageal fistula
750.3	27	Oesophageal atresia and stenosis
750.8	32	Anomalies of upper alimentary tract
750.9	11	Unspecified anomalies of upper alimentary tract
751.0	44	Meckel's diverticulum
751.1	24	Anomalies of intestinal fixation
751.2	73	Hirschsprung's disease
751.3	123	Atresia and stenosis of rectum and anal canal
751.4	107	Anomalies of intestine
751.5	16	Atresia of biliary ducts
751.6	18	Anomalies of gallbladder, bile ducts, and liver
751.7	4	Anomalies of pancreas
751.8	5	Anomalies of digestive system
751.9	2	Unspecified anomaly of digestive system
752.0	11	Indeterminate sex
752.1	612	Undescended testicle
752.2	692	Hypospadias

TABLE 7 *(continued)*

ICDA code	*Number of persons affected*	*ICDA title*
752.3	13	Epispadias
752.5	1	Anomaly of ovary, fallopian tube or uterus
752.6	32	Anomalies of vagina and external female genitalia
752.7	12	Pseudohermaphroditism
752.8	50	Anomalies of genital organs
752.9	5	Unspecified anomalies of genital organs
753.0	66	Renal agenesis
753.1	35	Cystic kidney disease
753.2	123	Obstructive defects of urinary tract
753.3	79	Anomalies of kidney
753.4	46	Anomalies of ureter
753.5	13	Extrophy of urinary bladder
753.6	257	Atresia and stenosis of urethra and bladder neck
753.8	21	Anomalies of bladder and urethra
753.9	10	Unspecified anomalies of urinary system
754.0	2 205	Talipes cavus
755.0	279	Polydactyly
755.1	252	Syndactyly
755.2	182	Reduction deformity of upper limb
755.3	62	Reduction deformity of lower limb
755.5	86	Anomaly of upper limb (including shoulder girdle)
755.6	1 076	Congenital dislocation of hip
755.7	238	Anomaly of lower limb (including pelvic girdle)
755.8	38	Generalized flexion contracture of limb joints
755.9	2	Unspecified anomaly of unspecified limb
756.0	147	Anomalies of skull and face bones
756.1	11	Anomalies of lumbosacral joint
756.2	63	Anomalies of spine
756.3	2	Cervical rib
756.4	125	Anomalies of ribs and sternum
756.5	8	Chondrodystrophy
756.6	3	Osteogenesis imperfecta
756.7	16	Generalized anomalies of skeleton
756.8	151	Anomalies of muscle, tendon and fascia
756.9	57	Anomalies of musculoskeletal system
757.0	4	Hereditary oedema of legs
757.1	123	Pigmented nevus
757.2	40	Anomalies of skin
757.3	4	Anomalies of hair
757.9	8	Anomaly of skin, hair, or nails
758.0	4	Anomalies of spleen
758.1	3	Anomaly of adrenal gland
758.2	43	Anomalies of thyroid gland
758.8	18	Congenital anomalies
758.9	1	Unspecified congenital anomaly
759.0	9	Situs inversus
759.2	14	Forms of monster
759.8	39	Specified syndromes
759.9	14	Unspecified multiple congenital anomalies
Total	15 728	

Source: Based on the British Columbia Survey (576).
Note: See notes to table 1.

TABLE 8. OTHER MULTIFACTORIAL DISORDERS BY ICDA CODE

ICDA code	*Number of persons affected*	*ICDA title*
242.0	2	Toxic diffuse goitre
250.0	401	Diabetes mellitus with mention of acidosis or coma
269.0	105	Sprue and steatorrhea
281.0	1	Pernicious anaemia
295.2	2	Schizophrenia, catatonic type
295.8	51	Schizophrenia
295.9	6	Unspecified type of schizophrenia
310.9	542	Borderline idiopathic mental retardation
311.9	327	Mild idiopathic mental retardation
312.9	311	Moderate idiopathic mental retardation
313.9	126	Severe idiopathic mental retardation
314.9	129	Profound idiopathic mental retardation
315.9	321	Unspecified idiopathic mental retardation
345.0	202	Generalized non-convulsive epilepsy
345.1	292	Generalized convulsive epilepsy
345.2	1	Status epilepticus
345.3	19	Partial temporal lobe or psychomotor type epilepsy
345.4	3	Partial motor type epilepsy
345.5	29	Unspecified partial type epilepsy
345.9	842	Unspecified type of epilepsy
370.0	40	Myopia
370.1	2	Hyperopia
370.3	2	Astigmatism
370.9	9	Unspecified refractive errors
373.0	3 517	Strabismus, convergent
373.9	6	Unspecified strabismus
493.0	203	Asthma
722.1	260	Juvenile osteochondrosis of hip
Total	7 751	

Source: Based on the British Columbia Survey (576).
Note: See notes to table 1.

TABLE 9. ESTIMATES OF THE FREQUENCY OF GENETIC DISORDERS IN A BIRTH COHORT

Cases per 100 live-born

Disease category	*Stevenson (566)*	*UNSCEAR (586, 587)*	*British Columbia Survey (576)*		*UNSCEAR present estimate*
			Minimal	*Adjusted*	
Dominant	3.32[a]	0.95	0.06	0.08	1.0[e]
Recessive	0.21	0.21	0.09	0.11	0.1
X-linked	0.04	0.04	0.03	0.04	[f]
Chromosomal	[b]	0.42[c]	0.16	0.20[d]	0.4
Congenital malformations	1.41	2.50	3.58	4.28	9.0
Other multifactorial	1.48	1.50	1.58	4.73	
Unknown	[b]	[b]	(0.60)[g]	(2.70)[g]	
Total[d]	6.46	5.62	5.50	9.44	10.5[h]

[a] Including both trivial and serious anomalies.

[b] No information.

[c] Including Down's syndrome (0.15), other autosomal trisomies (0.05), Klinefelter's syndrome (0.17), Turner's syndrome (0.03) and Cridu-chat syndrome (0.02) but excludes XXX females (0.12) and individuals with translocations (0.50).

[d] All but about 3 per cent are due to Down's syndrome.

[e] Including X-linked disorders.

[f] Included in the dominant category.

[g] Frequency of unknown diseases is not included in the total.

[h] For the evaluation of radiation hazards the figures used are slightly different; see table 50 and paragraphs 12 and 19.

TABLE 10. ESTIMATES OF MUTATION RATES FOR HUMAN GENES

Trait	*Population examined*	*Mutation rate*	*Number of mutants per 10^6 gametes*
	A. AUTOSOMAL MUTATIONS		
Achondroplasia	Denmark	$1\ 10^{-5}$	10
	Northern Ireland, UK	$1.3\ 10^{-5}$	13
	Münster, Germany, Fed. Rep. of	$6\text{-}9\ 10^{-6}$	6-9
Aniridia	Denmark	$2.9\text{-}5\ 10^{-6}$	2.9-5
	Michigan, USA	$2.6\ 10^{-6}$	2.6
Dystrophia myotonica	Northern Ireland, UK	$8\ 10^{-6}$	8
	Switzerland	$1.1\ 10^{-5}$	11
Retinoblastoma	England, UK; Michigan, USA Switzerland; Germany, Fed. Rep. of	$6\text{-}7\ 10^{-6}$	6-7
	Hungary	$6\ 10^{-6}$	6
	Netherlands	$1.23\ 10^{-5}$	12.3
	Japan	$8\ 10^{-6}$	8
	France	$5\ 10^{-6}$	5
Acrocephalosyndactyly (Apert's syndrome)	England, UK	$3\ 10^{-6}$	3
	Münster, Germany, Fed. Rep. of	$4\ 10^{-6}$	4
Osteogenesis imperfecta	Sweden	$0.7\text{-}1.3\ 10^{-5}$	7-13
	Münster, Germany, Fed. Rep. of	$1.0\ 10^{-5}$	10
Tuberous sclerosis (epiloia)	Oxford, England, UK	$1.05\ 10^{-5}$	10.5
	China	$6\ 10^{-6}$	6
Neurofibromatosis	Michigan, USA	$1\ 10^{-4}$	100
	Moscow, USSR	$4.4\text{-}4.9\ 10^{-5}$	44-49
Polyposis intestini	Michigan, USA	$1.3\ 10^{-5}$	13
Marfan's syndrome	Northern Ireland, UK	$4.2\text{-}5.8\ 10^{-6}$	4.2-5.8
Polycystic disease of the kidneys	Denmark	$6.5\text{-}12\ 10^{-5}$	65-120
Diaphyseal aclasis (multiple exostoses)	Münster, Germany, Fed. Rep. of	$6.3\text{-}9.1\ 10^{-6}$	6.3-9.1
von Hippel-Lindau syndrome	Germany, Fed. Rep. of	$1.8\ 10^{-7}$	0.18
	B. SEX-LINKED RECESSIVE MUTATIONS		
Haemophilia	Denmark	$3.2\ 10^{-5}$	32
	Switzerland	$2.2\ 10^{-5}$	22
	Münster, Germany, Fed. Rep. of	$2.3\ 10^{-5}$	23
Haemophilia A	Hamburg, Germany, Fed. Rep. of	$5.7\ 10^{-5}$	57
	Finland	$3.2\ 10^{-5}$	32
Haemophilia B	Hamburg, Germany, Fed. Rep. of	$3\ 10^{-6}$	3
	Finland	$2\ 10^{-6}$	2
Duchenne-type muscular dystrophy	Utah, USA	$9.5\ 10^{-5}$	95
	Northumberland and Durham, UK	$4.3\ 10^{-5}$	43
	Südbaden, Germany, Fed. Rep. of	$4.8\ 10^{-5}$	48
	Northern Ireland, UK	$6.0\ 10^{-5}$	60
	Leeds, England, UK	$4.7\ 10^{-5}$	47
	Wisconsin, USA	$9.2\ 10^{-5}$	92
	Bern, Switzerland	$7.3\ 10^{-5}$	73
	Fukuoko, Japan	$6.5\ 10^{-5}$	65
	North-east England, UK	$10.5\ 10^{-5}$	105
	Warsaw, Poland	$4.6\ 10^{-5}$	46
Incontinenta pigmenti (Bloch-Sulzberger)	Münster, Germany, Fed. Rep. of	$0.6\text{-}2.0\ 10^{-5}$	6-20
Oculofaciodigital syndrome (OFD)	Münster, Germany, Fed. Rep. of	$5\ 10^{-6}$	5

Source: Reference 599.

TABLE 11. INCIDENCE OF CHROMOSOMAL ABNORMALITIES IN NEW-BORN INFANTS

Survey centre	Number of infants			Sex-chromosome anomalies						Autosomal abnormalities														Total	Frequency (%)
				Males			Females			Numerical (trisomics)				Structural (euploid)				Structural (aneuploid)							
														Robertsonian		Reciprocal T and insertional	Inversions	Robertsonian	Reciprocal T	Inversions	Deletions	Supernumerary			
	Male	Female	Total	47, XYY	47, XXY	Others[a]	45, X	47, XXX	Others[a]	+D	+E	+G	Others[a]	D/D	D/G										
Hamilton, Canada	493	437	930[e]	2	1	–	–	–	–	–	–	–	–	–	–	1	1	–	–	–	–	–	–	5	0.54
London, Canada	1 066	1 015	2 081	4	1	–	–	–	–	–	–	2	–	1	–	–	–	1	–	–	1	–	–	10	0.48
Winnipeg, Canada	7 176	6 763	13 939	4	6	2	–	5	2	1	3	14	–	12	1	11	1	–	1	–	–	–	2	65	0.47
Arhus, Denmark	5 751	5 387	11 148	3	6	9	1	7	3	1	1	16	–	15	2	15	1	–	6[b]	–	1	6[c]	–	93	0.83
Edinburgh, UK	7 849	3 831	11 680	10	9	5	–	5	2	–	2	17	1	6	4	10	2	1	–	1	–	1	2	78	0.67
Boston, USA	9 048	–	9 048	3	6	8	–	–	–	–	–	7	–	5	2	5	2	–	–		2	4	–	44	0.49
New Haven, USA	2 176	2 177	4 353	3	4	–	1	3	–	1	1	3	–	2	1	3	–	–	–	–	–	–	–	22	0.51
Moscow, USSR	1 303	1 197	2 500[d]	–	1	6	–	–	–	–	–	4	2	–	1	3	1	–	–	–	1	–	–	19	0.76
Total	34 872	20 807	55 679	29	34	30	2	20	7	3	7	63	3	41	11	48	7	2	7	1	5	11	4	336	0.60
				122 (0.22%)						76 (0.14%)				107 (0.19%)				30 (0.05%)							

Sources: References 38, 212, 250, 289, 363.

[a] Most of these are mosaics.

[b] Unbalanced Y-autosome translocations.

[c] Supernumerary small metacentric chromosomes including two mosaics.

[d] These 2500 infants are a random sample of 10 237 infants born during the study period (1969-1972) and included 15 twin-pairs, 29 new-born infants with various congenital malformations, 5 stillborn and 13 delivered prematurely (38).

[e] Including 1 twin-pair and 1 triplet.

TABLE 12. CHROMOSOMAL ANOMALIES IN SPONTANEOUS ABORTIONS[a]

Karyotype	Canada Carr	United Kingdom Creasy et al.	France Boué	Germany, Fed. Rep. of Degen-hardt	United Kingdom Dhadial	United States Arakaki	United States Szulman	United States Thiede	USSR Kuliev	Japan Kaji et al.	Denmark Therkels-son
Monosomy X	12	68	140	8	31	18	5	5	1	12	39
Autosomal	–	–	1 (G)	–	–	1 (A)	–	–	–	1	–
Trisomy A	1	11	12	2	–	–	–	2	1	2	1
B	1	2	6	–	–	–	–	–	–	1	2
C	2	17	86	2	6	1	1	–	3	7	11
D	6	21	109	3	11	1	–	2	2	11	16
E	9	60	172	7	12	14	2	7	2	20	27
F	1	3	7	–	–	2	–	–	1	–	–
G	6	29	87	6	10	–	3	4	3	9	6
Double trisomy	1	–	16	2	2	–	–	–	–	1	2
Triploidy XXX	6	18	57	1	5	3	–	1	1	3	9
XXY	2	18	92	–	8	3	4	–	1	5	5
XYY	1	1	7	–	–	1	–	–	–	–	–
Not karyotyped	–	–	27	–	–	–	–	–	2	–	–
Mosaics 46/49	–	–	2	1	–	–	–	–	–	2	–
Hypertriploids	–	2[b]	–	–	–	–	–	–	–	–	–
Tetraploidy XXXX	–	7	33	–	3	–	–	2	–	2	6
XXYY	–	5	20	–	1	1	–	1	–	1	4
Not karyotyped	2	–	–	–	–	–	–	–	1	–	–
Other anomalies	–	25[c]	43	3	5	17	–	–	2	5[d]	10
Total	50	287	919	35	94	63	15	24	20	82	138

Sources: References 45, 403.

[a] Results from 11 series in 9 different countries.

[b] One had an extra C-group chromosome (70, XXY, +C), while the other was tetrasomic for an E-group chromosome (70, XXY, +E).

[c] Including 10 structural anomalies, the remainder being mixoploids or other anomalies.

[d] Including 3 structural anomalies and 2 mosaics.

TABLE 13. COMPARISON OF THE FREQUENCIES OF INCIDENCE OF DIFFERENT KINDS OF CHROMOSOMAL ANOMALIES IN SPONTANEOUS ABORTIONS

Kind of anomaly	Boué and Boué (45) Number	Boué and Boué (45) Frequency (%)	Other authors Number	Other authors Frequency (%)
Monosomy-X	140	15.2	199	24.6
Monosomy (autosomal)	1	0.1	2	0.2
Trisomy	479	52.1	393	48.6
Double trisomy	16	1.7	8	1.0
Triploidy	185	20.1	101	12.5
Tetraploidy	55	6.0	36	4.5
Others	43	4.7	69	8.5
Total	919	100	808	100

Source: Compiled from the data in table 12.

TABLE 14. RELATIVE FREQUENCY OF DIFFERENT TYPES OF AUTOSOMAL TRISOMIES IN SPONTANEOUS ABORTIONS

Extra autosome involved	Group of 392 trisomies[a]		Group of 479 trisomies[b]	
	Number	Frequency (%)	Number	Frequency (%)
A	20	5.1	12	2.5
B	6	1.5	6	1.3
C	50	12.8	86	17.9
D	73	18.6	109	22.8
E	160	40.8	172	35.9
F	7	1.8	7	1.5
G	76	19.4	87	18.2
Total	392	100	479	100

[a] The series of table 12, that of Boué excepted.
[b] References 45, 253.

TABLE 15. MATERNAL AGE IN RELATION TO DIFFERENT TYPES OF CHROMOSOMAL ANOMALIES

Karyotype	Number of cases observed	Mean maternal age (years)
Monosomy X	134	27.57 ± 0.88
Trisomy	448	31.25 ± 0.60
Triploidy	167	27.38 ± 0.79
Tetraploidy	53	26.79 ± 1.40
Translocation	26	26.96 ± 2.32
Normal	509	27.48 ± 0.45
Autosomal trisomy		
47,A+	13	29.62 ± 2.18
47,B+	7	33.43 ± 7.13
47,C+	72	30.93 ± 1.67
47,D+	92	32.49 ± 1.33
47,E+	157	29.58 ± 0.88
47,F+	8	30.13 ± 5.32
47,G+	78	33.17 ± 1.40
48	14	35.00 ± 6.09

Source: Reference 45.

TABLE 16. X-RAY-INDUCED DOMINANT LETHALS IN MALE MICE AT DIFFERENT POST-IRRADIATION INTERVALS

Mating ratio, 1 male to 3 females per week; 30 irradiated and 10 control males

Irradiation level 200 R

Group	Week of mating	Number of females paired	Number of females pregnant	Proportion of total (%)	Corpora lutea	Implants	Live embryos	Average number of live embryos per pregnant female	Pre-implantation loss (%)	Post-implantation loss (%)	Induced dominant lethality (%)	
											A[a]	B[b]
Control		31	28	90	259	239	221	7.9	7.7	7.5		
Irradiated	1	15	15	100	134	111	89	5.9	17.2	19.8	25	13
	2	16	15	94	118	103	78	5.2	12.7	24.3	34	18
	3	14	12	86	110	83	55	4.6	24.5	33.7	42	28
	4	14	12	86	102	71	57	4.8	30.4	19.7	39	13
	5	15	14	93	121	92	69	4.9	24.0	25.0	38	19
	6	13	8	62	70	47	36	4.5	32.9	23.4	43	17
	7	14	1	7	8	2	2	2.0	75.0	–	–	–
	8	13	11	85	126	93	84	7.6	26.2	9.7	4	2
	9	5	5	100	54	39	34	6.8	27.8	12.8	14	6

Source: Reference 133.
[a] Index A for dominant lethality is based on the number of live embryos per pregnant female.
[b] Index B for dominant lethality is based on the number of live embryos per total implantation.

TABLE 17. FREQUENCY OF DOMINANT LETHALITY IN LITTERS CONCEIVED IN THE FIRST AND THIRD WEEKS AFTER X IRRADIATION OF FEMALE MICE

Dose (rad)	Number of females	Corpora lutea	Total implants	Live embryos	Corpora lutea per female	Implants per female	Pre-implantation[a] loss (%)	Live embryos / Total implants	Induced post-implantation[b] loss (%)
0	22	222	201	194	10.1	9.14	9.5	0.965	–
First week									
100	18	199	162	151	11.1	9.00	18.6	0.932	3.4
200	16	154	125	110	9.6	7.81	18.8	0.880	8.8
300	15	164	138	121	10.9	9.20	15.9	0.877	9.1
400	14	165	141	116	11.8	10.07	14.5	0.823	14.7
Third week									
100	15	151	121	116	10.1	8.07	19.9	0.959	0.7
200	19	201	154	122	10.6	8.11	23.4	0.792	17.9
300	18	181	94	67	10.1	5.22	48.1	0.713	26.1
400	18	187	107	67	10.4	5.94	42.8	0.626	35.1

Source: Reference 513.

[a]Calculated as–Number of implants/Number of corpora lutea) × 100

[b]Calculated as $\left(1 - \frac{\text{Number of embryos/Number of implants in the irradiation series}}{\text{Number of embryos/Number of implants in the controls}}\right) \times 100$

TABLE 18. DOMINANT LETHALITY AFTER FISSION-NEUTRON IRRADIATION OF FEMALES

First-week mating

Dose (rad)	Pregnant females	Corpora lutea per female	Implants per female	Live embryos per female	Live embryos / Corpora lutea	Live embryos / Total implants	Induced lethality: Post-implantation	Induced lethality: Total
0	16	10.0	9.6	8.6	0.856	0.890	–	–
50	15	12.7	11.4	10.2	0.805	0.895	−0.6	6.0
100	18	11.3	9.7	8.4	0.749	0.869	2.4	12.5
150	16	9.6	8.7	6.0	0.627	0.691	22.4	26.8
200	16	9.9	7.8	5.0	0.503	0.645	27.5	41.2

Source: Reference 513.

TABLE 19. FERTILITY AND DOMINANT LETHALITY IN FEMALE GUINEA-PIGS AND GOLDEN HAMSTERS TREATED WITH X RAYS

Dose (rad)	Total number of females	Number not pregnant	Corpora lutea	Implants	Live embryos	Moles	Dead	Abnormal	Corpora lutea per female	Implants per female	Live embryos per female
					GUINEA-PIG						
					Mating at first oestrus						
0	20	0	72	62	60	2	0	0	3.6	3.1	3.0
100	25	0	101	85	82	3	0	0	4.0	3.4	3.3
200	21	0	93	69	61	7	1	0	4.4	3.3	2.9
400	26	5	94	60	49	9	2	0	4.8	2.9	2.3
					Second oestrus						
0	20	0	74	68	66	1	0	1	3.7	3.4	3.3
100	21	1	69	65	65	0	0	0	3.5	3.3	3.3
200	20	0	78	69	65	1	3	0	3.9	3.5	3.3
400	20	0	73	55	52	3	0	0	3.7	2.8	2.6
					Three months						
0	23	2	79	70	65	4	1	0	3.8	3.3	3.1
100	21	0	74	66	65	1	0	0	3.5	3.1	3.1
200	24	1	92	79	72	6	1	1	4.0	3.4	3.1
400	21	0	77	68	58	9	1	0	3.7	3.2	2.8
					GOLDEN HAMSTER						
					Mating at first oestrus						
0	11	1	178	165	138	19	3	5	12.7	11.8	9.8
100	23	2	270	245	196	38	6	5	12.9	11.7	9.3
200	21	2	245	192	147	36	3	6	12.9	10.1	7.7
400	23	4	278	180	112	65	1	2	14.6	9.5	5.9

Dose (rad)	Total number of females	Number not pregnant	Corpora lutea	Implants	Live embryos	Moles	Dead	Abnormal	Corpora lutea per female	Implants per female	Live embryos per female
				GOLDEN HAMSTER *(continued)*							
				Second oestrus							
0	13	2	143	133	104	21	6	2	13.0	12.0	9.5
100	20	2	226	204	161	32	5	6	12.6	11.3	8.9
200	20	2	231	190	135	40	12	3	12.8	10.6	7.5
400	20	3	280	211	142	47	11	11	16.5	12.4	8.4
				One month							
0	20	1	230	207	171	34	1	1	12.1	9.5	8.5
100	25	5	252	223	175	40	5	3	12.6	11.2	8.8
200	22	2	254	214	178	27	4	5	12.7	10.7	8.9
400	31	12	275	219	175	33	2	9	14.5	11.5	9.2
				Three months							
0	12	2	126	111	91	14	3	3	12.6	11.0	9.1
400	13	10	34	28	20	5	2	1	11.3	8.5	6.7

Source: Reference 121.

TABLE 20. FREQUENCY OF DOMINANT LETHALS IN FEMALE GUINEA-PIGS AND GOLDEN HAMSTERS TREATED WITH X RAYS

Dose (rad)	Implants / Corpora lutea	Live embryos / Implants	Live embryos / Corpora lutea	Fraction of dominant lethals (%): Pre-implantation	Fraction of dominant lethals (%): Post-implantation	Fraction of dominant lethals (%): Total
			GUINEA-PIG			
			Mating at first oestrus			
0	0.861 ± 0.041	0.986 ± 0.022	0.833 ± 0.044			
100	0.842 ± 0.036	0.965 ± 0.020	0.812 ± 0.039	2.2	0.4	2.6 ± 6.9
200	0.742 ± 0.045	0.884 ± 0.039	0.656 ± 0.049	13.2	8.6	21.3 ± 7.2
400	0.638 ± 0.050	0.817 ± 0.050	0.521 ± 0.052	25.8	15.6	37.5 ± 7.1
			Second oestrus			
0	0.919 ± 0.032	0.971 ± 0.021	0.892 ± 0.036			
100	0.942 ± 0.028	1.00 ± 0.030	0.942 ± 0.028			
200	0.885 ± 0.036	0.942 ± 0.028	0.833 ± 0.042	3.7	2.9	6.6 ± 6.0
400	0.753 ± 0.050	0.946 ± 0.031	0.712 ± 0.053	18.0	2.6	20.1 ± 6.7
			Three months			
0	0.886 ± 0.036	0.929 ± 0.031	0.823 ± 0.043			
100	0.892 ± 0.036	0.985 ± 0.015	0.878 ± 0.038			
200	0.859 ± 0.036	0.911 ± 0.032	0.783 ± 0.043	1.8	3.1	4.9 ± 7.2
400	0.883 ± 0.037	0.853 ± 0.043	0.753 ± 0.049	0.3	8.1	8.5 ± 7.6
			GOLDEN HAMSTER			
			Mating at first oestrus			
0	0.927 ± 0.020	0.836 ± 0.029	0.775 ± 0.031			
100	0.907 ± 0.018	0.800 ± 0.026	0.726 ± 0.027	2.1	4.4	6.4 ± 5.1
200	0.784 ± 0.048	0.766 ± 0.031	0.600 ± 0.031	15.5	8.5	22.6 ± 5.1
400	0.648 ± 0.033	0.622 ± 0.036	0.403 ± 0.029	30.1	25.6	48.1 ± 4.3
			Second oestrus			
0	0.930 ± 0.021	0.782 ± 0.036	0.727 ± 0.037			
100	0.903 ± 0.020	0.789 ± 0.028	0.712 ± 0.030	2.9		2.1 ± 6.5
200	0.823 ± 0.047	0.711 ± 0.055	0.584 ± 0.059	11.6	9.1	19.6 ± 9.1
400	0.754 ± 0.033	0.673 ± 0.047	0.507 ± 0.039	18.2	14.9	30.3 ± 6.5
			One month			
0	0.900 ± 0.031	0.855 ± 0.025	0.770 ± 0.051			
100	0.885 ± 0.020	0.785 ± 0.041	0.694 ± 0.038	1.7	8.2	9.8 ± 7.8
200	0.843 ± 0.039	0.832 ± 0.026	0.701 ± 0.042	6.4	2.7	8.9 ± 8.1
400	0.796 ± 0.041	0.799 ± 0.027	0.636 ± 0.043	11.6	6.5	17.3 ± 7.8
			Three months			
0	0.881 ± 0.029	0.820 ± 0.036	0.722 ± 0.040			
400	0.824 ± 0.065	0.714 ± 0.085	0.588 ± 0.022	6.5	13.0	18.6

Source: Reference 121.

TABLE 21. DOSE-EFFECT DATA FOR THE INDUCTION OF RECIPROCAL TRANSLOCATIONS IN MOUSE SPERMATOGONIA

Single exposures at a high exposure rate

Exposure (R)	*Number of animals*	*Number of cells scored*	*Time interval[a] (days)*	*Proportion of abnormal cells (%)*	*Proportion of translocations (%)*
0	6	600		0.0	0.0
50	6	600	27	0.7 ± 0.3	0.7 ± 0.3
100	6	600	28	1.5 ± 0.5	1.5 ± 0.5
150	6	600	32	2.5 ± 0.6	2.5 ± 0.6
200	6	600	35	4.0 ± 0.8	4.3 ± 0.8
300	6	600	48	7.8 ± 1.1	7.8 ± 1.1
400	8	800	54	12.1 ± 1.2	13.5 ± 1.3
500	8	800	62	14.8 ± 1.4	17.0 ± 1.5
600	8	800	68	16.0 ± 1.4	19.5 ± 1.6
700	8	800	91	11.6 ± 1.2	13.5 ± 1.3
800	9	900	121	8.7 ± 1.0	10.2 ± 1.1
1200	6	600	182	3.8 ± 0.8	14.5 ± 0.9

Source: Reference 419.

[a]Between irradiation and sampling.

TABLE 22. YIELD OF RECIPROCAL TRANSLOCATIONS IN SPERMATOCYTES FOLLOWING X IRRADIATION OF MOUSE SPERMATOGONIA

Repeated 400-R fractions separated by 8-week intervals

Total exposure (R)	*Number of cells scored*	*Yield of translocations (%)*
0	1 000	0
400	2 150	13.8 ± 0.8
800	1 450	19.7 ± 1.2
1 200	900	31.1 ± 1.9
1 600	600	47.8 ± 2.8
2 000	600	60.2 ± 3.2
2 400	600	64.5 ± 3.3
2 800	600	80.7 ± 3.7

Source: Reference 420.

TABLE 23. FREQUENCY OF CYTOLOGICALLY SCORED AND GENETICALLY RECOVERED RECIPROCAL TRANSLOCATIONS FOLLOWING X IRRADIATION OF MOUSE SPERMATOGONIA

Exposure (R)	*Frequency of translocations scored[a] (%)*	*Number of F_1 males tested*	*Minimum frequency of translocation heterozygotes[b] (%)*	*Ratio recovered/ scored*
0	0.0	2 633	0.0	–
150	2.5 (2.5)	993	0.6	0.25
300	7.8 (5.7)	1 018	0.88	0.12
600	17.2 (16.2)	1 075	1.90	0.11
1 200	4.5 (3.8)	1 038	0.50	0.13

Source: Reference 56.

[a]Values in parentheses are proportions of cells with a single translocation.

[b]Cytologically confirmed semisteriles.

TABLE 24. FREQUENCY OF CHROMATID ABERRATIONS IN MI OOCYTES AT VARIOUS TIMES AFTER AN ACUTE X-RAY EXPOSURE OF 200 R

Interval (days)	*Number of cells scored*	*Frequency of deletions (%)*	*Frequency of interchanges (%)*
1	100	1.0 ± 1.0	1.0 ± 1.0
3	100	4.0 ± 2.0	1.0 ± 1.0
5	125	4.8 ± 2.0	0.8 ± 0.8
7	100	6.0 ± 2.5	6.0 ± 2.5
14	125	10.4 ± 2.9	12.8 ± 3.2
21	100	6.0 ± 2.5	6.0 ± 2.5

Source: Reference 58.

TABLE 25. FREQUENCY OF CHROMATID ABERRATIONS IN MI OOCYTES 14 DAYS AFTER VARIOUS X-RAY EXPOSURES

Exposure (R)	*Number of cells scored*	*Frequency of deletions (%)*	*Frequency of interchanges (%)*
0	200		
50	150	1.3 ± 0.9	1.3 ± 0.9
100	150	4.0 ± 1.6	4.7 ± 1.8
200	125	10.4 ± 2.9	12.8 ± 3.2
300	150	16.0 ± 3.3	23.3 ± 3.9
400	100	37.0 ± 6.1	56.0 ± 7.5

Source: Reference 58.

TABLE 26. YIELD OF TRANSLOCATIONS IN SPERMATOCYTES FOLLOWING SPERMATOGONIAL IRRADIATION IN DIFFERENT MAMMALIAN SPECIES

(a) Data of Lyon and Cox (309).

	Rabbit				*Golden hamster*				*Guinea-pig*			
			Yield of translocations (%)				*Yield of translocations (%)*				*Yield of translocations (%)*	
Dose or exposure (rad or R)	*Animals*	*Cells*	*Definite and possible*	*Definite*	*Animals*	*Cells*	*Definite and possible*	*Definite*	*Animals*	*Cells*	*Definite and possible*	*Definite*
0	3	1 117	0.2	0.1	5	1 013	0.2	0.1	5	1 406	0.3	0.1
100	3	1 285	1.8	1.6	5	1 408	1.6	1.2	4	1 273	1.1	0.7
200	3	1 008	3.1	2.6	6	1 633	2.3	1.7	5	1 504	2.3	1.7
300	4	1 923	4.9	4.2	5	1 518	2.2	2.0	5	1 873	3.6	3.0
400	3	967	1.0	0.8	5	1 245	1.8	1.4	4	1 127	1.3	1.2
500	3	1 248	1.1	0.6	5	1 307	2.1	1.6	4	968	0.5	0.3
600	3	1 055	0.5	0.3	5	1 051	1.6	1.0	5	1 268	0.8	0.5

(b) Data of Brewen and Preston (54).

Dose or exposure (rad or R)	*Yield of translocations (%)*	
	Guinea-pig	*Chinese hamster*
0	0	0
50	1.4 ± 0.6	1.0 ± 0.6
100	2.7 ± 0.9	2.0 ± 0.8
200	6.1 ± 1.1	4.3 ± 1.2
300	8.0 ± 2.0	–

TABLE 27. TRANSLOCATION YIELDS AFTER VARIOUS X-RAY DOSES TO MONKEY SPERMATOGONIA

Monkey No.	Dose (rad)	Interval between irradiation and examination (months)	Number of cells analysed	Translocation yield	
				Definite and possible	Definite
		English monkeys (ref. 314)[a]			
1L	0 + S	8	124	0.8	0.8
R	300 + S	8	186	2.7	2.7
2L	S + 200	11	517	1.0	0.8
R	200 + S	9	82	4.9	4.9
3L	100	9	391	4.1	1.8
R	100	6.5	253	2.0	1.2
4L	100	9	248	0.4	0.4
R	100	6.5	146	1.4	1.4
		Dutch monkeys (ref. 314)			
1	300	8	291	0.0	0.0
2	300	8	1	0.0	0.0
3	200	8	36	0.0	0.0
4	200	8	495	1.6	1.2
5	100	8	777	0.3	0.3
Control	0		30	0.0	0.0
		Combined results			
	100		1 815	1.4	0.8
	200		1 130	1.5	1.2
	300		478	1.0	1.0
		Dutch monkeys (ref. 70)			
1-3	0		100 + 100 + 300		0.0
4	100	8	1 700		0.06
5	100	8	350		1.1
6	200	8	850		2.0
7	200	8	550		1.1
8	300	8	400		0.0
9	300	8	175		1.1
		Combined results			
	100		2 050		0.2
	200		1 400		1.6
	300		575		0.3

[a]English monkeys No. 1 and No. 2 were unilaterally irradiated; all others were bilaterally irradiated. L = left testis; R = right testis; S = shielded.

TABLE 28. YIELD OF RECIPROCAL TRANSLOCATIONS IN SPERMATOCYTES FOLLOWING SPERMATOGONIAL IRRADIATION IN MARMOSET AND MAN COMPARED WITH MOUSE DATA

Dose (rad)	Man			Marmoset			Mouse		
	Number of individuals	Cells	Yield (%)	Number of animals	Cells	Yield (%)	Number of animals	Cells	Yield (%)
0	2	200	0	2	600	0	6	600	0
25	–			2	600	2.8 ± 0.7	–		
50	–			2	600	3.3 ± 0.8	6	600	0.7 ± 0.3
78	2	371	4.0 ± 1.0	–			–		
100	–			2	600	7.8 ± 1.1	6	600	1.5 ± 0.5
200	2	300	7.0 ± 1.3	1	200	7.5 ± 1.9	6	600	4.3 ± 0.8
300	–			2	600	7.0 ± 1.1	6	600	7.8 ± 1.1
600	2	180	6.1 ± 1.8	–			8	800	19.5 ± 1.6

Source: References 57, 419.

TABLE 29. YIELD OF TRANSLOCATIONS IN SPERMATOCYTES FOLLOWING SPERMATOGONIAL IRRADIATION WITH SINGLE OR FRACTIONATED EXPOSURES IN THE GOLDEN HAMSTER AND GUINEA-PIG

			Golden hamster				*Guinea-pig*			
					Yield (%)				*Yield (%)*	
Total dose (rad)	*Radiation procedure*	*Interval between fractions*	*Number of animals*	*Number of cells scored*	*Definite and possible*	*Definite*	*Number of animals*	*Number of cells scored*	*Definite and possible*	*Definite*
0[a]			5	1 013	0.2	0.1	5	1 406	0.3	0.1
0[b]			5	1 118	0.2	0.1	4	778	0.1	0.0
0[c]			5	906	0.1	0.0	3	604	0.2	0.0
0[d]			–				4	765	0.3	0.0
200	single		6	1 633	2.3	1.7	5	1 504	2.3	1.7
400	single		5	1 245	1.8	1.4	4	1 127	1.3	1.2
400	2 X 200	24 h	6	1 607	4.5	3.9	4	881	4.8	4.1
400	2 X 200	8 weeks	5	1 350	3.5	3.1	4	1 039	3.2	2.5
400	8 X 50	1 week	7	1 800	2.7	1.9	–			
300	single		–				5	1 873	3.6	3.0
600	single		5	1 051	1.6	1.0	5	1 268	0.8	0.5
600	2 X 300	24 h	–				4	763	7.6	7.0
600	2 X 300	8 weeks	–				4	1 042	3.1	2.0
600	12 X 50	1 week	6	1 446	3.1	2.5	3	1 193	5.0	4.1

Source: Reference 308.

[a]Control for single-dose experiments.

[b]Control for 2 X 200 rad (24 h), 2 X 200 rad (8 week) experiments in golden hamster and for 2 X 200 rad (24 h) and 2 X 300 rad (24 h) experiments in guinea-pig.

[c]Control for 12 X 50 rad (1 week), 8 X 50 rad (1 week) experiments in golden hamster for 12 X 50 rad (1 week) experiments in guinea-pig.

[d]Control for 2 X 300 rad (8 week) and 2 X 200 rad (8 week) experiments in guinea-pig.

TABLE 30. EMBRYONIC MORTALITY IN PROGENY OF MALES WITH OR WITHOUT DETECTABLE TYPES OF CHROMOSOME ABERRATION

Category of male	*Number of pregnant females*	*Total implants*	*Live embryos*	*Dead implants*	*Embryonic mortality (%)*	*Implants per female*	*Live embryos per female*
With 1 RT[a]	120	806	369	437	54.2	6.72 ± 0.20	3.08 ± 0.15
With 2 RT	8	58	18	40	69.0	7.25	2.25
With insertion	2	14	7	7	50.0	7.00	3.50
Normal	849	6 743	6 161	582	8.63	7.94	7.26

Source: Reference 520.

[a]RT = Reciprocal translocation.

TABLE 31. EMBRYONIC MORTALITY IN PROGENY OF MALES WITH RECIPROCAL TRANSLOCATIONS (RT)

Male Number	*Number of RT*	*Total number of females*	*Number not pregnant*	*Corpora lutea*	*Implants*	*Live embryos*	*Dead embryos*	*Moles*	*Embryonic mortality (%)*	*Implants per female*	*Live embryos per female*
						Golden hamster					
1	2	5	0	71	45	11	1	33	75.6	9.0	2.2
2	1	9	0	125	99	39	3	57	60.6	11.0	4.3
3	1	8	0	104	76	36	3	37	52.6	9.5	4.5
4	1	9	0	107	78	31	4	43	60.3	8.7	3.4
6	1	8	0	108	93	47	8	38	49.5	11.6	5.9
8	1	10	0	112	106	69	4	33	34.9	10.6	6.9
12	1	3	0	34	33	14	0	19	57.6	11.0	4.7
13	1	9	0	105	85	40	2	43	52.9	9.4	4.4
Total (1RT)[a]		56	0	695	570	276	24	270			
								Average	52.6	10.3	4.87
Control[b]		43		542	478	393	12	53	13.6	11.1	9.14

TABLE 31 *(continued)*

Male Number	Number of RT	Total number of females	Number not pregnant	Corpora lutea	Implants	Live embryos	Dead embryos	Moles	Embryonic mortality (%)	Implants per female	Live embryos per female
					Guinea-pig						
2	1	10	5	22	14	7	0	7	50.0	2.8	1.4
4	1	10	1	42	31	25	0	6	19.4	3.4	2.8
6	1	8	1	34	30	15	0	15	50.0	4.3	2.1
9	1	12	1	52	37	30	1	6	18.9	3.4	2.7
11	1	6	3	13	8	5	0	3	37.5	2.7	1.7
15	1	4	0	21	13	9	1	3	30.8	3.3	2.3
17	1	7	4	9	8	1	0	7	87.5	2.7	0.3
Total (1RT)[a]		57	15	193	141	92	2	47			
								Average	42.0	3.2	1.9
Control[b]		40		146	130	126	0	4	3.1	3.3	3.2

Source: Reference 123.

[a]1RT = one reciprocal translocation.

[b]Control data taken from Cox and Lyon (121).

TABLE 32. FREQUENCY OF INDUCED X-CHROMOSOME ANOMALIES FROM IRRADIATION OF FEMALE GERM-CELL STAGES IN MICE

Cell stage sampled	Interval, irradiation to mating (days)	Exposure R	Exposure rate (R/min)	Number of females	Frequency of OX^P Total (%)	Frequency of OX^P Induced[a] (10^{-5} R^{-1})	Reference
Preleptotene through diplotene	> 42	221	*ca.* 80	1 221	0.08-0.33[b]	0.13-1.24[b]	452, 456
Control		0		391	0		
Dictyate	1-42[c]	400	66-78	15 006	0.61-0.77	1.38-1.78	468, 489, 490
Dictyate	1-42	50	66-78	12 256	0.02-0.08	0[d]	
Dictyate	> 42[c]	50	66-78	10 172	0.09	0[d]	
Dictyate	1-42	400	0.6	10 900	0.36-0.40	0.76-0.88	
Control		0		11 528	0.06		
Dictyate	0-7[e]	400	0.006	1 906	0.26	0.52	468, 484, 485
Dictyate	8-42[f]	400	0.006	1 779	0-0.06	0[d]	
Dictyate	> 42[g]	400	0.006	6 644	0.08	0[d]	
Control		0		12 163	0.04-0.05		
Dictyate	1-49	400	65-70	5 170	0.77-0.87	1.80-2.04	76, 468
Dictyate	1-49	8 X 50[h]	65-70	6 099	0.46-0.51	1.02-1.14	
Control		0		5 154	0.04		

Source: Reference 450.

[a]Calculated as treated minus overall spontaneous control frequency. Data for the contemporary control are shown grouped with the treated sets.

[b]The lower number (or the single number, where only one is given) represents only genetically and/or cytologically verified cases; the higher number represents cases observed in original phenotypic scoring. All are derived from XX mothers only.

[c]Considerable differences in frequency are observed within this interval. Readers wishing to make more precise quantitative comparisons between these results and those from lower dose rates are referred to the full data.

[d]Frequency of treated group not significantly higher than contemporary control.

[e]Matings made during this interval utilized oocytes that received almost the entire 400-R dose during the last six weeks of their development.

[f]Most matings made during this interval utilized oocytes that received only a small part of the dose during the last six weeks of their development.

[g]Matings made during this interval utilized oocytes irradiated prior to their last six weeks of development.

[h]With 75-minute intervals between the fractions.

TABLE 33. SPECIFIC-LOCUS MUTATION FREQUENCIES RESULTING FROM X IRRADIATION OF MALE MICE AT VARIOUS AGES

X rays, 300 R

Age at irradiation (days)	*Number of offspring screened*	*Number of mutations*	*Frequency per locus (10^{-5} R^{-1})*	*95% confidence limits*	
				Lower	*Upper*
New-born	55 456	16[a]	13.7	7.1[b]	22.6[b]
2	8 127	2	11.7	2.1	39.2
4	8 784	3	16.3	4.4	43.9
6	7 559	4	25.2	8.6	60.5
8	8 463	7	39.4	18.5	77.5
10	8 580	3	16.6	4.5	45.0
14	8 397	9	51.0	25.3	95.1
21	8 920	5[c]	26.7	7.3[b]	72.1[b]
28	10 009	6	28.5	12.4	61.0
35	9 056	4	21.0	7.2	50.5
Adult[d]	65 548	40	29.1	21.0	39.0

Source: References 526, 527.

[a] Including three clusters of two mutations each.

[b] Including correction for clusters using Russell's approach (480).

[c] Including two clusters of two mutations each.

[d] Data of W. L. Russell (474).

TABLE 34. ARBITRARY GROUPING OF SPECIFIC-LOCUS MUTATION RATE DATA FOR YOUNG MALE MICE TO ILLUSTRATE THE LIKELY TIME FOR TRANSITION IN MUTATIONAL RESPONSE

Age at the time of irradiation (days)	*Mutation frequency per locus (10^{-5} R^{-1})*	*95% confidence limits*	
		Lower	*Upper*
New-born	13.7	7.1[b]	22.6[b]
2-6	17.5	8.7	32.6
8-35	30.6	20.4[b]	42.3[b]
Adult[a]	29.1	21.0	39.0

Source: Reference 527.

[a] Data of W. L. Russell (474).

[b] Including correction for clusters using Russell's approach (480).

TABLE 35. A COMPARISON OF THE FREQUENCIES OF SPECIFIC-LOCUS MUTATION AFTER IRRADIATION OF MOUSE SPERMATOGONIA GIVEN IN ONE DOSE OR IN TWO EQUAL FRACTIONS SEPARATED BY VARIOUS TIME INTERVALS

X rays, 1000 R

Interval between fractions	*Total offspring*	*Number of mutations*	*Mutation frequency per locus (10^{-5})*	*95% confidence limits*	
				Lower	*Upper*
None (single exposure[a]	44 649	29	8.5	6.21	13.33
2 h[a]	148 791	12	11.52	5.95	20.12
24 h[a]	11 164	39	49.91	35.45	68.22
4 days[b]	7 168	11	21.92	10.94	39.22
7 days[b]	8 271	11	19.00	10.94	39.22
> 15 weeks[a, c]	4 904	10	29.13	13.98	53.57

[a] Data of W. L. Russell (472).

[b] Data of Cattanach and Moseley (92).

[c] 600 R + 400 R.

TABLE 36. YIELD OF SPECIFIC-LOCUS MUTATIONS OBTAINED AFTER IRRADIATION OF MOUSE FEMALES WITH ACUTE AND FRACTIONATED DOSES OF X RAYS

Group	Dose	Total progeny	Number of mutants	Mutations per locus (10^{-7} rad^{-1})	95% confidence limits		Total progeny	Number of mutants	Mutations per locus (10^{-7} rad^{-1})	95% confidence limits	
			Up to 20 days[a]		Lower	Upper		Up to 7 weeks[a]		Lower	Upper
A + B[b]	I X 200	21 578	7	2.32	0.93	4.78	34 813	9	1.85	0.85	3.51
C + D[c]	20 X 10	20 398	1	0.35	0.0088	1.95	39 887	1	0.18	0.0045	1.00

Source: Reference 312.

Note: The mutation rates given above are not corrected for controls.

[a]Duration from end of radiation treatment to conception.

[b]In group A, mating was soon after irradiation; in group B, it was one week later.

[c]In group C, 4 fractions each of 10 rad were administered at 2-h intervals in one day; radiation was given over a 5-day period (4 X 10 rad X 5); mating: 3 days after the last dose. In group D, 20 fractions each of 10 rad were administered over 5 days in a week (separated by 24-h intervals) for 4 weeks; mating: soon after completion of the last treatment.

TABLE 37. DISTRIBUTION OF OFFSPRING AND MUTATIONS AT SEVEN SPECIFIC LOCI IN CONCEPTIONS OCCURRING DURING SUCCESSIVE WEEKS AFTER IRRADIATION OF FEMALE MICE WITH VARIOUS EXPOSURES AND EXPOSURE RATES

Week	X rays, 200 R at 90 R/min		X rays, 50 R at 90 R/min		Gamma rays, 400 R at 0.8 R/min	
	Off-spring	Muta-tions	Off-spring	Muta-tions	Off-spring	Muta-tions
1	28 547	13	84 614	6	49 039	14
2	3 604	2	8 016	0	7 928	3
3	454	1	2 904	0	737	1
4	1 138	0	9 587	1	844	4
5	8 395	12	45 179	3	7 342	6
6	3 327	5	16 304	3	4 990	2
7	328	0	13 868	0	170	0
8	17	0	9 092	0	2	0
9	5	0	11 096	0	4	0
10	1	0	7 433	0	–	
11 on	–		50 570	0	–	

Source: Reference 483a.

TABLE 38. NUMBER OF MUTATIONS AT SEVEN SPECIFIC LOCI IN VARIOUS LOW-LEVEL RADIATION AND FRACTIONATION EXPERIMENTS ON FEMALE MICE

Exposure or dose given (R or rad)	Exposure rate or dose rate (R/min or rad/min)	Weighted mean effective exposure or dose[a] (R or rad)	Number of offspring	Number of mutations	Mutation frequency per locus (10^{-6})	Reference
0	51.		204 639	3 or 8	2.1 or 5.6	483a
215	51.6[b]	172	14 671	1	9.7	312
258	0.009	207	7 692	1	18.6	471
215	51.6[c]	212	21 204	0	0.0	312
400	0.009	283	13 742	2	20.8	471[d]
400	0.009	284	14 402	1	9.9	471
615	0.05	615	10 177	1	14.0	84a

[a]Dose delivered to oocytes in the 6 weeks prior to evaluation.

[b]Dose delivered over 4 weeks in 20 fractions of 10.7 rad.

[c]Dose delivered over 5 days in 20 fractions of 10.7 rad.

[d]Animals irradiated were old, previously bred females.

TABLE 39. INDUCTION OF DOMINANT LETHALS BY ^{239}Pu IN THE GERM CELLS OF MALE MICE

Experimental series	*Group*	*Week after mating*	*Total number of implants* N	*Dead implants (early deaths)* n_{ED}	*Frequency*[a] *(%)*	*Dead implants (late deaths)* n_{LD}	*Frequency*[b] *(%)*	*Total dead implants* n_T	*Frequency*[c] *(%)*
E4	Control	1-13	2 502	221	8.8	45	2.0	266	10.6
	0.05 μCi	1-13	2 962	298	10.1	71	2.7	369	12.5
E5	Control	1-18	3 971	331	8.3	40	1.1	371	9.3
	0.05 μCi	1-18	3 663	368	10.0	113	3.4	481	13.1
E3	Control	1-24	5 492	384	7.0	55	1.1	439	8.0
	0.1 μCi	1-24	5 182	564	10.9	161	3.5	725	14.0
E4	Control	1-13	2 502	221	8.8	45	2.0	266	10.6
	0.25 μCi	1-13	2 436	248	10.2	42	1.9	290	11.9
E5	Control	1-18	3 971	331	8.3	40	1.1	371	9.3
	0.25 μCi	1-18	3 773	424	11.2	112	3.3	536	14.2
E3	Control	1-24	5 492	384	7.0	55	1.1	439	8.0
	0.5 μCi	1-23	2 467	287	11.6	44	2.0	331	13.4

Source: Reference 304.

[a] $100\, n_{ED}/N$.

[b] $100\, n_{LD}/(N-n_{ED})$.

[c] $100\, n_T/N$.

TABLE 40. CHROMOSOME ABERRATIONS IN METAPHASE-I SPERMATOCYTES OF MICE AT DIFFERENT TIMES AFTER INJECTION OF ^{239}Pu OR AFTER CHRONIC GAMMA-RAY EXPOSURES

Series	*Weeks of exposure*	*Estimated testis dose*[a] *(rad)*	*Testis mass (mg)*		*Number of spermatocytes scored*[b]	*Number*[d] *with*		*Reciprocal translocations*			*Reference*
			Right	*Left*		*Fragments*	*Quadrivalents*[c]	*Rings*	*Chains*	*Totals*[d]	
I: ^{239}Pu	0	0 0	125 ± 2		300	4 (1.3)	1 (0.3)	0	0	0	33
	6	14 (10)[e]	91 ± 6		400	8 (2.0)	4 (1.0)	3	1	4 (1.0)	
	12	30 (25)[e]	88 ± 2		400	9 (2.2)	16 (4.0)	15[f]	4	19 (4.8)	
	18	44	73 ± 8		400	12 (3.0)	9 (2.3)	2	3	5 (1.3)	
II: ^{239}Pu	0	0	119.2 ± 3.7	–	600	2 (0.3)	2 (0.3)	0	2	2 (0.3)	516
	21	13 ± 1	111.4 ± 6.4	103.4 ± 6.4	700	11 (2.6)[j]	5 (0.7)	4	1	5 (0.7)	
	28	18 ± 2	102.7 ± 5.3	96.3 ± 8.0	800	12 (1.5)	8 (1.0)	6	2	8 (1.0)	
	34	18 ± 1	109.0 ± 5.8	111.0 ± 3.5	800	12 (1.9)[k]	4 (0.5)[g]	1	3[g]	4 (0.5)	
	Mean[h]	17 ± 1; 15.5[e]	107.7 ± 3.1	103.0 ± 3.4	–	(1.9)[j]	–	–	–	– (0.74)	
^{60}Co	0	0	118.9 ± 6.1	–	300	2 (1.0)[j]	–	–	–	0	
	28	1128; 1055[e]	42.2 ± 1.3	–	1 000	39 (4.1)[j]	16 (1.6)[h]	10[i]	6	17 (1.7)	
	Mean controls (^{239}Pu and ^{60}Co of series II)	–	–	–	–	–	–	–	–	0.22	

[a] Estimated from left testis.

[b] Scored in the right testis.

[c] Resulting from reciprocal translocations arising in spermatogonia (see next columns) or chromatid interchanges.

[d] Percentage in parentheses.

[e] Estimated spermatogonial dose, not taking into account the inhomogenous distribution of ^{239}Pu in the testis in the plutonium series.

[f] Three cells each had 2 rings of 4.

[g] Including a chain of 3 + univalent and 2 chains of 4.

[h] Including 1 ring of 6.

[i] Including 1 ring of 6, 9 rings of 4 and 6 chains of 4.

[j] Fragments per cell.

[k] One cell recorded as having both single and double fragments.

TABLE 41. RECOVERY OF FERTILITY OF X-IRRADIATED MALE MICE FOLLOWING SINGLE OR FRACTIONATED (24-H INTERVAL) EXPOSURES

Age (days)	*Number of replicates*	*Total number of females tested*	*Overall median day of return to fertility*
	(a) Various ages at 300 R single		
5	1	10	42
10	1	10	51
Adult	1	10	51
	(b) Various ages at 500 R single		
5	1	10	44
10	1	11	53
Adult	1	10	56
	(c) Various ages at 1000 R single		
3	1	10	79
5	1	10	84
10	1	10	74
Adult	2	20	102[a]
	(d) Adults at various exposures		
Exposure (R)			
300	2	20	52
400	2	20	53
100 + 300	1	7	53
300 + 100	1	10	51
500	5	47	56
600	5	50	67
100 + 500	2	20	62
500 + 100	3	29	62
300 + 300	1	10	57
700	2	20	67
800	4	40	71
100 + 700	2	20	81
700 + 100	2	20	73
300 + 500	1	10	82
500 + 300	2	20	81
900	2	20	88
1000	2	20	102
700 + 300	1	10	111
100 + 900	1	10	135
900 + 100	1	10	108
500 + 500	2	20	102

Sources: References 90, 94.

[a]Same data as for the adult at 1000 R in part (d)

TABLE 42. COMPARISON OF RADIATION-INDUCED MUTATION RATES WITH FREQUENCY OF LABELLED SPERMATOGONIAL STEM CELLS IN THE MOUSE 207 AND 414 HOURS AFTER X IRRADIATION

Exposure (R)	*Mutations per locus[a] (10^{-5})*	*Frequency of labelled cells (%)*				*Cell survival compared with control (%)*
		Labelling 6 × 12.5 μCi of ^{3}H-TdR 24 h before x irradiation		*Labelling 3 × 12.5 μCi of ^{3}H-TdR 24 h before x irradiation*		
		Time after irradiation		*Time after irradiation*		
		207 h	*414 h*	*207 h*	*414 h*	
0	0.75	7.8	0.7	29.2	22.8	
100		15.6	1.6	29.0	33.8[b]	
300	8.72			24.3	33.3[b]	26.8
500		16.3	1.7	27.5	39.9[b]	11.2
600	13.29			26.3	36.5[b]	9.3
1000	9.28	2.4	0.2	10.2[c]	15.3[b]	3.2
500 + 500[d]	49.91	39.1	3.1	47.2[b]	35.5[b]	2.3

Sources: References 367a, 657.

[a]From W. L. Russell (471).

[b]Significantly above control.

[c]Significantly below control.

[d]Fractions given 24 h apart.

TABLE 43. COMPARISON OF THE YIELDS OF DICENTRICS (IN LYMPHOCYTES) AND RECIPROCAL TRANSLOCATIONS (IN SPERMATOCYTES, AFTER SPERMATOGONIAL X IRRADIATION) IN MAN, MARMOSET, RABBIT AND THE RHESUS MONKEY

Dose (rad)	Dicentric yield (%)	Translocation yield (%)		Dicentric yield / Translocation yield
		Definite and possible	Definite	
		Man[a]		
0	–	–	0	–
78	8.0	–	4.0 ± 1.0	2
200	35.2	–	7.0 ± 1.3	5
600	250.0	–	6.1 ± 1.8	42
		Marmoset[a]		
0	–	–	0	–
25	3.0	–	2.8 ± 0.7	1
50	6.7	–	3.3 ± 0.8	2
100	16.3	–	7.8 ± 1.1	2
200	44.6	–	7.5 ± 1.9	6
300	84.9	–	7.0 ± 1.1	12
		Rabbit		
100	8.0[b] 6.3[c]	1.84 ± 0.38[d]	1.56 ± 0.34[d]	4-5
153	13.0	2.5 (estimated)	1.8 (estimated)	5-7
200	20.5	3.08 ± 0.54	2.59 ± 0.50	~7-8
203	23.0			
300	33.6	4.94 ± 0.85	4.20 ± 0.77	~7-12
305	50.0			
		Rhesus monkey[e]		
0	– (600)[f]	–	0- (500)[f]	–
100	4.9 (600)	–	0.2 (1 950)	25
200	13.9 (600)	–	1.6 (1 400)	8
300	26.6 (600)	–	0.3 (515)	89

[a] Data given in the paper of Brewen and Preston (57).
[b] Estimated from the data of Scott and Bigger (502); x irradiation at 100 rad/min.
[c] Data of Bajerska and Liniecki ((20) and personal communication); x irradiation at 18 rad/min.
[d] Data of Lyon and Cox (309), x irradiation at 88 rad/min.
[e] Data of van Buul (70).
[f] Number of cells in parentheses.

TABLE 44. COMPARISON OF INTRA-LOCUS FORWARD MUTATION RATES PER HAPLOID GENOME IN DIFFERENT ORGANISMS[a]

Low-LET radiation

Test system	Haploid DNA content (pg)	Loci and cell stages where mutations were studied	Mutation rate per locus (rad^{-1})	References: DNA content	References: Mutation rate
Hordeum vulgare (barley)	6.7	44 eceriferum loci	$3.0\ 10^{-9}$	440, 441	395, 442
	(10.0, 11.5)[b]	59 eceriferum loci	$2.2\ 10^{-9}$		443
		26 erectoides loci	$1.4\ 10^{-8}$		395
		86 chloroplast loci	$1.3\text{-}1.7\ 10^{-8}$		444, 445
		130 chloroplast loci	$0.85\text{-}1.2\ 10^{-8}$		443, 444
		1000 chloroplast loci (estimated)	$1.1\text{-}1.5\ 10^{-9}$		443
		1 locus (DDT resistant)	$1.7\ 10^{-8}$		444, 446
Zea mays (maize)	5.5	1 locus (bronze)	$<2.3\ 10^{-8}$	440, 441	447
Mus musculus (mouse)	3.0	Spermatogonia			
	(2.26)[b]	7 loci	$2.2\ 10^{-7}$[c]	448	195, 419
		7 loci minimum	$8.1\ 10^{-8}$[d]		see text
		6 loci	$7.8\ 10^{-8}$		449
		Maturing oocytes			
		7 loci, 50 R	$1.78\ 10^{-7}$[e]		195, 419
		200 R	$3.95\ 10^{-7}$		195, 419
		200 R	$1.78\ 10^{-7}$		211
		400 R	$5.50\ 10^{-7}$		195, 419
		Immature oocystes			
		7 loci, 50 R	≈0		195, 419
Arabidopsis thaliana (cruciferous plant)	0.27	4 thiamine loci	$1.1\text{-}1.5\ 10$	440	450

TABLE 44 *(continued)*

Test system	*Haploid DNA content (pg)*	*Loci and cell stages where mutations were studied*	*Mutation rate per locus (rad^{-1})*	*References*	
				DNA content	*Mutation rate*
Drosophila melanogaster (fruit fly)	0.14	Spermatogonia			
	0.18	8 chromosome III loci	$1.28\ 10^{-8}$	433, 448 451	405
	(0.17, 0.22)[b]	10 oogonia			
		10 X-chromosome loci	$0.5\text{-}1.54\ 10^{-8}$		452
		Post-meiotic sperm			
		8 chromosome III loci	$4.7\ 10^{-8}$		405
			$3.0\ 10^{-8}$		453, 454
		4 X-chromosome loci	$2.9\ 10^{-8}$		455
		5 loci	$1.4\ 10^{-8}$		456
		5 loci	$1.2\ 10^{-8}$		
Neurospora crassa (mold)	0.038	2 adenine-3 loci	$3.0\ 10^{-9}$	457	458
	(0.042)[b]	*(ad-3A, 3B)*	$5\text{-}6\ 10^{-9}$		459
		1 aza-3 locus	$2.0\ 10^{-8}$		410
		All 3 loci considered	$8.7\ 10^{-9}$		410, 458
		All 3 loci considered	$1.0\ 10^{-8}$		410, 459
Saccharomyces cerevisiae (yeast)	0.008	6 early adenine loci	$6.0\ 10^{-9}$	425, 460	416
	0.014, 0.015	1 can-1 locus	$1.6\ 10^{-9}$		358
	(0.024)[b]	1 can-1 locus	$1.0\ 10^{-10}$ (maximum)		411
Schizosaccaromyces pombe (yeast)	0.012, 0.015(1C)	5 early adenine loci	$0.8\text{-}1.1\ 10^{-9}$		414
	0.023, 0.029(2C)	5 early adenine loci	$0.4\text{-}0.8\ 10^{-9}$ [f]	461, 462	415

Source: Reference 562.

[a]The intra-locus rates given here must be viewed in conjunction with the differences between systems in their resolving power to detect intragenic change.

[b]DNA values given by Abrahamson *et al.* (4).

[c]This rate is not intragenic.

[d]For the mouse, except for the rate $8.1\ 10^{-8}$, the rates given may not all represent intra-locus rates.

[e]The rates obtained in the radiation experiments were corrected using the spontaneous rate of $1.4\ 10^{-6}$ per locus (589).

[f]The two ranges of mutation rate estimates were obtained by taking the rates given by the respective authors and dividing by 2 to allow for the fact that cells with 2C DNA amounts were treated.

TABLE 45. INTRA-LOCUS MUTATION RATE ESTIMATES FOR THE INDUCTION OF SPECIFIC LOCUS MUTATIONS IN POST-MEIOTIC MALE GERM CELLS OF *DROSOPHILA MELANOGASTER*, CYTOLOGICAL POSITION OF THE LOCI AND ESTIMATES FOR THE SIZE OF THE BANDS IN THE SALIVARY CHROMOSOME

Locus[a]	*Mutation rate per locus (R^{-1})*	*Salivary band position*[b]	*Estimated relative size of the bands from 1 = small to 5 = large*
g	$5.0\ 10^{-8}$	12B6-7±	1
f	(between that of	15F1-2	4
rb	*g* and *w*)	4C6-8	2
y		1B1	2[c]
w	$2.5\ 10^{-8}$	3C2 or 3C1.5	1[c]
ct[d]	(between that of	7B3 or 4	1
sn	*w* and *pn*)	7D1-2	4
v		10A1	5
cm		6E6	1
pn	$9.0\ 10^{-9}$	2D6-2E1	?
m	(between that of *pn* and *car*)	1OE1 or 2	3 or 4
car	$3.3\ 10^{-9}$ ($2.0\ 10^{-8}$)[d]	18D1-2	4
ras	$1.6\ 10^{-9}$ ($6.8\ 10^{-8}$)[d]	9E4-7	1
ac	$\approx 1.6\ 10^{-9}$	1B2	2[c]
sc		1B3-4	5

Sources: References 275, 593.

[a]The loci are ranked in descending order of mutation rate.

[b]Salivary band positions are from Lefevre (275), who in a personal communication makes the following amendment: *rb*, *cm* and *car* are not exactly where they are supposed to be.

[c]According to Lefevre (274), there appears to be more than a single complementation group associated with at least some of the bands in 1B. In addition, Lefevre (personal communication) points out that *y* and *ac* are the sole occupants of 1B1-2 and that cytogenetic analysis in collaboration with Garcia-Bellido suggests that *sc* is a duplicated gene which occupies 1B3-4. The possibility that *w* is associated with a very faint band between 3C1 and 3C2 has been discussed by Sorsa, Green and Beerman (546).

[d]In consideration of the arguments of Muller (351) that at *ct*, *car* and *ras* most of the mutations unaccompanied by chromosome aberrations are male lethal (and may therefore be considered as true gene mutations giving a lethal effect), the intra-locus rates given in parentheses include these mutations as well; for the *ct* locus the rate is $3.3\ 10^{-8}$.

TABLE 46. FACTORS WHICH POSSIBLY DISTURB THE EXACT DETERMINATION OF MUTATION FREQUENCIES IN CULTURED MAMMALIAN CELLS

Phenomena involved	*Factors possibly disturbing the exact determination of mutation frequencies*	*Factors as such relevant for selection of HG-PRT-deficient mutants in*		
		Human diploid skin (fibroblastic cells)	*V79 Chinese hamster (epithelioid cells)*	*L5178Y mouse lymphoma (cells in suspension)*
A. Recovery of mutants				
Growth	Occurrence of spontaneous mutants in course of experiment	+	+	+
	Differential growth rate of wild-type cells and fully expressed mutants	–	–	–
	Differential growth rate of wild-type cells and newly induced mutants	+	+	+
Cloning efficiency	Differential cloning efficiency of wild-type cells and fully expressed mutants	–	–	–
	Differential cloning efficiency of wild-type cells and newly induced mutants	+	+	+
	Absolute cloning efficiency of wild-type cells	+	–	+
Metabolic co-operation	Humoral metabolic co-operation	–	–	–
	Intraclone metabolic co-operation	+	+	+
	Interclone metabolic co-operation	+	±	–
B. Determination of expression time				
Rate of decrease of wild-type gene products	Dilution of normal gene products by cell division	+	+	+
	Rate of turnover of normal gene products	+	+	+
Treatment of cells	Dose-dependent reduction in growth rate	+	+	+
	Delay in mutation induction			

Source: Reference 538.

TABLE 47. RISK OF INDUCTION OF VARIOUS KINDS OF GENETIC DAMAGE IN MAN PER 1 RAD AT LOW DOSES OR AFTER CHRONIC EXPOSURES

Estimated in 1972

End-point	*Expected rate of induction per million*		*Expression in F_1 per million conceptions after spermatogonial irradiation*
	Spermatogonia	*Oocytes*	
1. Recessive point mutations	1 500[a] (36)[b]	Very low –	30-75 (1-2)
2. Dominant visibles	2	–	2
3. Skeletal mutations	4	–	[c]
4. Reciprocal translocations[d]	15[e]	Very low	2 congenitally malformed children, 19 unrecognized early embryonic losses and 9 recognized abortions[f]
5. X-chromosome losses	Very low	8	8 early embryonic losses and/or abortions[k]
6. Other chromosome anomalies	Very low	–	Very low
Total genetic damage	1 521[g] (57)[h]		
Total genetic damage[i]	300		6-15[j]

Source: Reference 589.

Note: Dashes indicate that inadequate or no information is available.

[a] Estimate based on mouse specific-locus data.

[b] Estimate based on the per genome rate for recessive lethals induced in mouse spermatogonia.

[c] Included under end-point 1 above (see paragraph 594 of Annex E of reference 589).

[d] Figures apply to low-dose x irradiation. Estimates for chronic gamma irradiation are 50 per cent lower.

[e] Balanced products.

[f] For low dose x irradiation; for chronic gamma irradiation, figures should be halved (see paragraph 621 of Annex E of reference 589).

[g] Obtained by adding 1 500 + 2 + 4 + 15 in the column.

[h] Obtained by adding 36 + 2 + 4 + 15 in the column.

[i] Relative to spontaneous incidence of genetic diseases among live-born, based on an estimated "doubling dose" of 100 rad.

[j] In terms of incidence of genetic disease among live-born.

[k] After oocyte irradiation.

TABLE 48. ESTIMATED EFFECT OF 5 RAD PER GENERATION ON A POPULATION OF ONE MILLION, INCLUDING CONDITIONS FOR WHICH THERE IS SOME EVIDENCE OF A GENETIC COMPONENT

Disease classification	*Current incidence*	*Effect of 5 rad per generation*	
		First generation	*Equilibrium*
Dominant diseases	10 000	50-500	250-2 500
Chromosomal and recessive diseases	10 000	Relatively slight	Very slow increase
Congenital anomalies	15 000		
Anomalies expressed later	10 000	5-500	50-5 000
Constitutional and degenerative diseases	15 000		
Total	60 000	60-1 000	300-7 500

Source: Reference 34.

TABLE 49. RISK OF INDUCTION OF VARIOUS KINDS OF GENETIC DAMAGE IN MAN PER 1 RAD AT LOW DOSE RATES OR LOW DOSES OF LOW-LET IRRADIATION

End-point	*Expected rate of induction per million gametes resulting from irradiation of*		*Expression in first generation per million births*
	Spermatogonia	*Oocytes*	
1. Autosomal mutations[a]	60	–	20[d]
2. Dominant visibles[b]	Very low	–	
3. Skeletal mutations[c]	4	–	
4. Balanced reciprocal translocations[e]	17-87	Low	Low[f]
5. Unbalanced products of end-point 4 above	34-174	–	2-10[g]
6. X-chromosome loss[h]	Very low	Low	Low
7. Other chromosome anomalies	–	–	–

Note: Dashes indicate that inadequate or no information is available.

[a]Presumed to include small deficiencies. Based on rate of induction of mutations in mice that are lethal in the homozygous condition, which is doubled to give the overall rate (para. 611).

[b]Based on those scored in the course of specific-locus experiments in mice.

[c]Detected in mice by dominant effects.

[d]Overall rate of dominant effects, based on skeletal mutations and presumably including dominant visibles and heterozygous effects of autosomal mutations.

[e]Derived from human and marmoset cytogenetic data under the assumption that the frequency of translocations in the F_1 progeny is one fourth of that observed in spermatocytes.

[f]Effects such as those given for end-point 5 in the next footnote will become manifest in generations following the first.

[g]Expressed as congenital malformations. In addition, there would be 11-55 recognized abortions and 22-109 early embryonic losses.

[h]Detected in mice by X-chromosomal markers.

TABLE 50. ESTIMATED EFFECT OF 1 RAD PER GENERATION OF LOW-DOSE, LOW DOSE-RATE, LOW-LET IRRADIATION ON A POPULATION OF ONE MILLION LIVE-BORN INDIVIDUALS

Assumed doubling dose, 100 rad

Disease classification[a]	*Current incidence*[b]	*Effect of 1 rad per generation*	
		First generation[c]	*Equilibrium*
Autosomal dominant and X-linked diseases	10 000[d]	20	100
Recessive diseases	1 100	Relatively slight	Very slow increase
Chromosomal diseases	4 000[e]	38[f]	40
Congenital anomalies Anomalies expressed later Constitutional and degenerative diseases	90 000[g]	5[h]	45[h]
Total	105 200	63	185
Percentage of current incidence		0.06	0.17
Recalculated BEIR assessments			
Autosomal dominant and X-linked diseases	10 000	20	100
Recessive and chromosomal diseases	10 000	Relatively slight	Very slow increase
Congenital anomalies Anomalies expressed later Constitutional and degenerative diseases	40 000	2-20[i]	20-200[i]
Total	60 000	25-40[j]	125-300[j]
Percentage of current incidence	100	0.04-0.07	0.21-0.50

[a] Follows that given in the BEIR Report (34).

[b] Based on the results of the British Columbia Survey with certain modifications; see table 9.

[c] The first generation incidence is assumed to be about one fifth of the equilibrium incidence for autosomal dominant and X-linked diseases; for those included under the heading "congenital anomalies etc." it is one tenth of the equilibrium incidence. For rationale see reference (34).

[d] See table 9.

[e] Based on the pooled values cited in Nielsen and Sillesen (363); includes mosaics but excludes balanced translocations.

[f] The first generation incidence is assumed to include all the numerical anomalies and three fifths of the unbalanced translocations (the remaining two fifths being derived from a balanced translocation in one parent).

[g] Includes an unknown proportion of numerical (other than Down's syndrome) and structural chromosomal anomalies.

[h] Based on the assumption of a 5 per cent mutational component.

[i] The range reflects the assumption of 5 and 50 per cent mutational components; see text for explanation.

[j] Rounded-off figures.

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ANNEX I

Experimental radiation carcinogenesis

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Introduction

1. Induction of neoplasia by ionizing radiation represents one of the first recognized radiobiological effects described in man soon after the discovery of x rays (715). Bergonié and Tribondeau (42) in 1906 in an attempt to rationalize the use of radiation for the treatment of tumours drew the attention of radiologists to this harmful consequence of over-exposure. The first documentation of sarcoma induction after repeated exposure to x rays of an animal's skin followed a few years later (424, 425), and the origin of what is presently known as experimental radiation carcinogenesis may probably be traced back to these classical reports.

2. In spite of some scattered papers which extended the initial observations to practically all common species of laboratory animals and to a variety of different tissues (for good historical reviews see 364, 675, 677), the years that followed until the middle 1940s did not, however, witness the configuration of experimental radiation carcinogenesis as a chapter separate from the field of general carcinogenesis, which was especially concerned at the time with the various aspects of chemically induced neoplasia. Important advances in radiation carcinogenesis were brought about by the experience in man with the reports of radiation-induced lung cancer among uranium miners (577) and of bone sarcoma in dial painters (428). Starting from the middle 1940s on, as a result of the A-bomb experience and within the framework of the renewed interest in biological and radiobiological research, a steady increase in concern and reports on the induction of tumours by radiation has taken place, amounting at present to an estimated few thousand specific bibliographic references. From time to time, the newest acquisitions have been reviewed and the relevant references may be found in Colwell and Russ (125), Furth and Lorenz (208), Lacassagne (362, 363), Furth and Upton (209), Brues (68), Lacassagne *et al.* (364), United Nations (668, 669), Harris (258), Casarett (91), Upton (672, 673, 675, 679), Curtis (140), Van Cleave (697), Casarett (92), Mole (459) and Moskalev and Streltsova (477).

3. Yet, after almost 80 years of arduous research in experimental animals and observations in man, it must be recognized that the complexity of the problem has so far defeated any effort for a reasonable understanding of its numerous implications. The growing concern from the wide-spread use of radiation in industry and medicine (see 562 as a general reference); the progress made in very recent years in all specialized fields of carcinogenesis, with special regard to the role of viruses and their interplay with radiation and to the role of the immune reaction in the development of neoplasia (see 38 for an updated treatise on all aspects of carcinogenesis); the availability of new experimental data in the specific field of neoplasia induction by radiation to be dealt with in the course of the present report: the desirability to keep under close scrutiny the newest development in the experimental animal systems for their implications in human radiation protection; the need to identify areas of special importance where effort might be preferentially addressed in the future (see 564 and 670 as general references); all these, have prompted the Committee to reconsider the information on the induction of neoplasia in experimental animals, after the latest review on the same subject appeared most recently (670).

4. As in the preceding case (670), the present review is not meant to provide an exhaustive and comprehensive treatment of the subject—a very difficult undertaking in view of the vast amount of information available—but a selection of illustrative papers. An effort has been made to identify those reports where the relevance of the hypotheses to the subject, the accurate planning of the experiments, the numerosity of the observation, and the application of careful statistical treatments to the data, render the conclusions amenable to a general interpretation and evaluation. Along these lines, the main scope of the review is therefore that of setting the newest acquisitions in the light of the general problem of cancer induction and of its recent developments, and to identify generalities and regularities emerging from the animal experience that may be of help for the interpretation of the human data.

5. The 1972 report of the Committee (670) has already discussed extensively the scope and the limitations of animal experimentation in radiation carcinogenesis and its role with respect to the interpretation of the epidemiological data. It should again be stressed that animal data are of great value in illuminating the effects in man but may not be used for numerical estimates. They are therefore as such an inadequate substitute for the existing paucity of data in the human species. There are at present insurmountable difficulties in extrapolating between different conditions of exposure, between high and low radiation doses and dose rates in the same species, and even more in the attempts to make generalizations about species having widely different physiological and pathological characteristics. But, partly for pragmatic reasons, owing to the pressing need to project the available data in man to conditions other than those where they were derived, and partly on scientific grounds, in view of the qualitative similarity of cancer induction in man and in other mammalian species, the experimentation on animals has acquired great significance for the understanding of the carcinogenic risk in man. According to the conclusions of the 1972 report (670) which are still valid at present, the contribution of experimental work to the general problem of risk evaluation in man may come about from three main lines of approach.

6. The first and most basic of these lines relates to the clarification of the mechanisms of carcinogenic action. It is obvious that this line still retains its overwhelming value since, in spite of the continuous advancements in our understanding of these mechanisms, we are still far from their detailed comprehension. It must, on the other hand, be realized that research in radiation carcinogenesis is a difficult and slow undertaking, where results cannot be expected within a short time.

7. The second line of approach, discussed by Mole (457), attempts to establish qualitative and possibly quantitative generalizations with respect to a number of

physical parameters (dose, dose rate, radiation quality) and biological parameters (age, sex, weight, body or organ size, metabolic rate, rate of DNA synthesis) which are known or suspected to affect radiation carcinogenesis. This course of action in fact yields useful data, although by no means adequate at present for the quantification of parameters generally applicable to all species with the necessary degree of certainty.

8. Finally, the search for experimental models of carcinogenesis which might respond to radiation in a manner qualitatively similar as in man, has been identified as the third possible objective of well founded experiments. It is thought that knowledge of the relationship of effect with dose and dose rate in such animal models (especially in the conditions relevant to radiation protection) could perhaps allow refinements in our risk estimates for humans, possibly by a consistent factor (564). The development of other models which facilitate the study of relations between tumour induction and such phenomena as radiation-induced cell killing and cell transformation, division and differentiation, could also be useful for that purpose.

I. METHODOLOGICAL ASPECTS OF RADIATION CARCINOGENESIS

A. EXPERIMENTAL APPROACHES

9. The work on experimental radiation carcinogenesis offers unique features that might be considered in a common context, partly to emphasize the difficulties in designing, performing and analyzing radiation carcinogenesis work, partly to draw attention to the many pitfalls that should be taken into account when reviewing results, and partly to warn the reader of the need for caution when generalizing the relevant conclusions.

10. Experiments on radiation carcinogenesis have been performed, especially in the past, on large populations of animals. There were well founded reasons for this experimental strategy, since quantiative assessments of the risk of late effects were needed and the use of large groups of animals was rightly considered as a reasonable, direct solution to the problems of obtaining overall estimates of the risks. The so-called "Greenhouse Experiment" carried out by a task force of scientists and published in its final form in 1960 (688) is probably the best known example of this type of approach involving major scientific efforts and complex organizational problems. The importance of this early experience is outstanding since through it the major long-term effects of irradiation could be documented and basic information about the significance of radiation quality, dose and time factors in mammalian carcinogenesis became available.

11. However, it became gradually apparent that a comprehensive approach involving actuarial, epidemiological and pathological observations of all possible lesions expressed by irradiated animal populations was unsuitable for a detailed investigation of mechanisms. The study of structural and functional modifications at the cellular and subcellular levels during the action of the carcinogenic agent can hardly be carried out on very large groups of animals.

12. For this reason and also because extrapolation of mechanisms between different animal species might perhaps be easier than the extrapolation of rates of induction of diseases which are typical of each species, a different experimental approach has been advocated. The new strategy is perhaps less ambitious since its main scope is to provide answers to very specific questions by designing and testing simplified models of radiation carcinogenesis *in vitro* and *in vivo* (127, 564). The conversion to this new experimental approach will probably be very gradual and in any case will not exclude entirely the traditional large-scale experimentation. Indeed, just as experimental work on model systems was also carried out in the past years, large-scale work may still be necessary in special cases in the future. However, the trend is towards a new equilibrium between both approaches, and only time and experience will allow a definite judgement on their merits.

B. CHOICE OF EXPERIMENTAL ANIMALS

13. From consideration of the available literature it appears that in some cases not enough attention has been paid to the choice of the experimental animals used in radiation carcinogenesis work; this can probably be attributed to unavailability of the relevant specific knowledge at the time when the experiments were planned. The choice of the animal species and/or the strain is however of paramount importance and should primarily be a function of the specific effect to be investigated. In this context, susceptibility of the experimental animal to the particular form of neoplasia under study is often the main consideration. Examples might be offered by the tumours of the kidney to which the rat is particularly susceptible (36, 422) or by the specificity of host-virus relationships in radiation-induced leukaemogenesis in mice (237).

14. In other cases, however, the choice of the animal is primarily dictated by the need to facilitate the extrapolation of the effects by extending the observations to different animal species (730, 638) or by the desire to simulate more closely the exposure of humans by using medium- and large-size mammals such as the dog (545, 622, 435), the pig (281, 278) and the monkey (440, 259). Within each species, however, the characteristics of particular inbred strains with respect to the spontaneous (630, 16, 413) or induced (566) rate of occurrence of special tumour types should also be considered as well as the effect of sex (paras. 68-73) and age at irradiation (paras. 289-300). As a very general proposition and for reasons to be examined later, a good model of carcinogenesis is one where the spontaneous incidence of the neoplastic lesion under investigation is very low in the intact animal and increases considerably after treatment; examples of such systems may be the radiation-induced mammary neoplasia in the young Sprague-Dawley rat (138) or the thymic lymphoma of the C57BL mouse (326). In special instances, however, the reverse condition (high spontaneous incidence of some tumour in normal animals, which is depressed by radiation treatments) may also be of value (135).

C. EXPERIMENT PLANNING

15. When dealing with marginal effects, often on the borderline of significance, it is imperative that the variability introduced by the presence of intercurrent diseases in the animal colony should not mask the effects of the radiation treatment. This calls for high hygienic standards in animal maintenance. It has also been shown (paras. 80-82) that the conditions of the animal intestinal microflora as affected by the living environment may introduce changes in the neoplastic response. Although such effects are probably not relevant to all tumour types, these observations stress the need for a permanent control of the animal facilities in order to allow a precise evaluation of the health conditions of the colony at all times during the execution of the experiments. There is certainly no need here to discuss in detail all procedures connected with animal handling (caging, identification, routine inspection, data collection etc.), but it should be stressed that, in view of the long duration of the experiments, even minor faults in the handling technique might result in the loss of precious data. In large-scale work, information storage, retrieval and processing have been handled by computers (234, 106).

16. Induction of cancer by radiation is a comparatively rare phenomenon, and to be established with the necessary degree of confidence by a comparison between treated and untreated animals this comparison requires therefore the use of fairly large groups of animals, the size of which must be related to the expected incidence of the tumour type and to the accuracy with which the induced change with respect to background incidence is to be assessed. Very large animal populations are particularly required at low radiation doses and dose rates where the incidence of tumours above the spontaneous level is very small and the resolution of the experiments critically depends on the number of animals tested. A good example of the criteria to be followed in the estimation of the sample size in an experiment on tumour induction designed for a particularly well known strain of animals has been provided by Upton *et al.* (681). The situation presented in that report may however be regarded as an extreme one in the sense that seldom are the starting conditions of an experiment so thoroughly defined and also because information is not often sought at such very low dose levels.

17. Calculations of this type may also be performed by other mathematical models (571), but they require, in general, preliminary knowledge of the tumour system to be investigated and, in particular, some background information on the form of the dose-effect relationship and on the latency period of the expected lesions. With regard to sample size, a distinction can probably be made in practice between those experimental series where the primary object is the estimation of tumour induction rates as a function of an independent variable like the dose, and other series concerned with the study of mechanisms, where internal comparisons between groups given different treatments usually allow working with smaller groups (335). The above considerations, however, emphasize the importance of careful planning and the convenience of utilizing animal model systems where basic information on tumour incidence and induction is already available so that previous experience on the model may help in designing further work.

D. DATA COLLECTION

18. The literature reviewed, particularly the earlier reports, show that there has been a tendency by the pathologists to underestimate the need for good planning and for quantitative observations on the irradiated animals and, conversely, that there has been inadequate attention given to the pathology of the induced lesions by radiation biologists mostly concerned with the statistical and epidemiological end-points. This tendency is disappearing in recent papers since it is now clear to all engaged in long-term experimentation that both types of end-point, the morphological and the actuarial, are equally important for a comprehensive evaluation of an experiment. It has also been realized that experiments on late effects, due to their size and cost, are often unique and the best possible use must therefore be made of all the information available. There is no need therefore in the present context to emphasize further the importance of regular animal follow-up and of a thorough macroscopic and histological examination of the animals, particularly at death. Specialized reports are available on this subject to which reference may conveniently be made (133, 106).

19. As far as pathology is concerned, it is important to point out that the object of post-mortem examination is not only to establish the immediate causes of death, but particularly to provide a complete description of the animal's condition at death, for the identification of the various syndromes and lesions brought about by the radiation treatment. In special instances more detailed pathological studies are required, and when the information is obtained at the time of death, it is inadequate for a full description of the time of onset, the rate of development and the final incidence of the various neoplastic lesions. To this end, serial sacrifice experiments are needed (9, 169). In other instances biochemical, microbiological or functional changes must be investigated by destructive tests. Animals for such parallel studies should however be kept separate from the experimental groups on which actuarial observations are made, since withdrawal of animals for sacrifice might seriously affect the estimates of mortality rates in the main experiment (681, 270).

20. Although it is accepted that radiation can induce a great variety of tumours having a wide spectrum of malignancy, the classification of these tumours into "benign" or "malignant" causes endless controversy among pathologists. In fact, the morphological aspects of the tumour cells, their tendency to invade the normal surrounding tissues, their ability to metastasize and to grow into host animals after transplantation, the capacity of the tumour to kill the animal, the immediate cause of death etc., may be assumed to be singly or jointly the criteria to assess malignancy. The present report avoids such a controversial field by referring as much as possible to the nomenclature of tumour types used in the papers reviewed.

21. Recording and classification of the pathological observations may follow extensive (124) or more frequently, compact computerized schemes (520, 106) conveniently adapted to the special needs of the experiments. Special attention should be drawn to the desirability of uniformity in the classification of the various diseases, bearing in mind that late pathological syndromes in animals are often unique to the various species. Efforts for standardization in this field are currently being made on an international scale and to this end cross-reference programmes between specialized laboratories are also desirable (667). Similar criteria of uniformity should also be applied to the conditions of radiation exposure, for which reference is made to general publications (294, 295). Programmes of radiation dosimetry standardization among laboratories specifically active in the field of late effects are also being made and should be continued in order to improve the reproducibility of the physical parameters (550).

E. STATISTICAL ANALYSIS

22. According to Berenblum (38), there are at least four ways of expressing quantitatively tumour induction among treated animals. These are widely used in chemical carcinogenesis work, but are as such inadequate to provide a comprehensive description of the final tumour incidence and incidence rate in radiation work. They are: *(a)* the percentage of animals bearing one or more tumours; *(b)* the average number of tumours per tumour-bearing animal or per treated animal; *(c)* the average and distributional latency times in the appearance of tumours after the application of the carcinogenic stimulus; and finally *(d)* the doses of carcinogen to obtain minimal effective and maximal carcinogenic response in the tumour system under study. The last type of data is precisely what is usually sought in radiation work, that is, the establishment of complete dose-effect relationships; however, the precise assessment of such relationships based on final tumour incidence rate is to a variable extent influenced by the mortality from other diseases in the course of the experiment.

23. In spite of the fact that the effect of competing risks on the induction estimates has been recognized for some time, and that attention has been drawn repeatedly to the possible consequences of not properly allowing for such risks in radiation carcinogenesis work (455, 175), many reports are still found lacking precise actuarial analyses. Appropriate advanced statistical treatments (144, 318) and guidelines to the analysis of tumour and death rates in the presence of competing causes of death are however available (569, 270, 533). Special procedures for the case of continuous exposure to the carcinogenic agent have also been devised (534).

24. A reasonable analysis of the epidemiological and pathological data in radiation carcinogenesis work rests in practice on the following steps. First of all, the construction of the cumulative mortality curve for each experimental group under study, with appropriate estimates of the fifty-per-cent end-points (mean and median) and of their variability. This preliminary step may be carried out by elementary statistical and graphical analysis. Consideration of the general trend of these curves is however inadequate for the identification of possible irregularities in the rate of extinction of the animal population, except in cases where such phenomena are particularly important. Only a second step consisting in a careful study of the instantaneous and cumulative rate of mortality intensity as a function of time, with appropriate corrections for the actual number of animals at risk in any particular time interval (343), will allow the identification of peaks or plateaus in the death rate of the population, which may possibly be traced back to special pathological lesions or syndromes operating in the animals at that particular time. Computation of such death-rate curves at varying time intervals will help to evaluate the importance of these changes, which, especially in small groups of animals, may sometimes be regarded as the spurious result of the system's variability rather than the effect of consistent pathological phenomena. Finally, attention should be focused on any particular disease (or group of diseases) diagnosed, in order to estimate its age-specific rate of occurrence and its final incidence, with appropriate corrections for competing risks (571, 270).

25. It is appropriate to mention at this point that comparisons between different treatment groups in order to derive numerical estimates of tumour induction (such as, for example, in relative biological effectiveness (RBE) or dose-rate-effect studies) should only be performed after elementary criteria of homogeneity between the groups under comparison are satisfied, namely that the mean and median longevity and the rate of mortality of the two animal populations are actually comparable. Unfortunately, reference is seldom made in the reviewed papers to the use of such cautions in the statistical analysis of the data. Calculation of age-specific incidence curves may be considered the only appropriate and complete method of actuarial analysis, since it allows the precise evaluation of both acceleration and true induction phenomena in radiation carcinogenesis (paras. 92, 93). Although the numerical estimates of tumour induction obtained from this type of analysis may not be strikingly different from the results of less refined methods in the case of early-appearing tumours such as the thymic lymphoma, age-specific calculations are absolutely required for all pathological conditions occurring gradually and late in life, such as the malignant solid tumours or the systemic lymphoreticular neoplasms. It is desirable that a more extensive use of these actuarial techniques be made in the future, since they will clarify the conditions under which numerical estimates of tumour induction are actually made.

26. Many aspects of radiation-induced carcinogenesis are closely related to life-span shortening, another important effect of irradiation readily apparent in treated animal groups as a reduction of the mean age at death. There have been discrepancies in the interpretation of this phenomenon and its relevance to tumour induction. On the one hand, the results of experiments where large groups of animals were irradiated with high instantaneous whole-body doses (688, 383) has been interpreted to favour the hypothesis of a non-specific premature ageing of the irradiated animals, since all diseases associated with senescence seemed to appear earlier, with no evidence that life-span shortening could be correlated with any particular cause of death. On the

other hand, as has already been mentioned (para. 19), the use of data derived from post-mortem examinations may be misleading and inadequate to give end-points free from the distortion of the intercurrent mortality (9, 10, 270).

27. Owing to inadequacies of the statistical treatment of the data, the conclusions of these early experiments were thus challenged and the non-specific life-span shortening attributed to a technical artefact (716). Actually, other experimental series where appropriate death-rate analyses have been performed (718) and where the effects of dose fractionation (449), chronic exposure (451, 227) and age at irradiation (451, 749) have been tested, have shown rather conclusively that the concept of a non-specific ageing effect of radiation is no longer tenable. At present, the consensus seems to be that life-span shortening is to be attributed almost entirely to the induction of neoplasia, especially at low doses and dose rates. A non-specific component may however become apparent in the high-dose range (227).

II. MECHANISMS OF RADIATION CARCINOGENESIS

A. GENERAL HYPOTHESIS

28. Since it is the purpose of the present report to discuss the problem of radiation carcinogenesis in the more general context of carcinogenesis as a biological phenomenon, it seems appropriate to review briefly some of the current "theories" of carcinogenesis. It is becoming increasingly clear in view of much experimental evidence that this phenomenon is extremely complex, and therefore one should not expect that early naive concepts postulating, for example, that a tumour might result from the energy imparted to a cell by an ion-pair or solely from a somatic mutation might apply: dosimetric calculations or biological considerations (420) may easily disprove such assumptions.

29. The very low likelihood of an event of neoplastic transformation[1] in relation to the number of possible target cells (429, 459) and the essentially random character of the processes of energy deposition in irradiated tissues have often justified in the past analysis of tumour induction in probabilistic terms. On these bases, mathematical models have been applied to the study of human spontaneous tumours (17, 76) and also to radiation carcinogenesis in man and experimental animals following external irradiation (452, 30, 430) or exposure to internally administered radioisotopes (452, 453, 430). Inferences have also been drawn concerning the shape of the dose-risk curve of relevance to radiation protection (77, 743). In all cases, models of the multi-event type have been supported by the data on neoplastic incidence as a function of time and dose, in the sense that such data are consistent with the general hypothesis that the appearance of a tumour is the final outcome of a succession and/or interplay of rare discrete events. This interpretation would also be in accordance with our notions of the biology of cancer, although it would be unrealistic at present to attribute any precise biological significance to such postulated events.

30. Recently a new interpretation of radiobiological phenomena has been published. This approach is known as the theory of dual radiation action (348). The theory is based on microdosimetric concepts and takes account, not only of the mean absorbed energy of radiation, but also of possible fluctuations of the energy deposited in volumes of micron dimensions. According to the theory of dual radiation action, the primary biological effect takes place only if two events occur in a sensitive volume. The probability of each such event is proportional to the specific energy absorbed in the microvolume. For densely ionizing radiation, a particle traversing the sensitive volume has sufficiently high probability to cause both events. On the other hand, for ionizing radiation with low linear energy transfer (LET), two charged particles are often necessary to provide the pair of events leading to the primary biological lesion. On the basis of these considerations the quantitative theory of dual radiation action has been developed. This theory has been applied to the interpretation of the RBE dependence on dose for a number of biological effects (339), including carcinogenesis (338). Specially interesting for the present report is the consideration of the induction of mammary neoplasia in the rat (575, 613) and of human leukaemia in Japanese A-bomb survivors (576). Remarkable agreement has been shown between the experimental observations and the theory that predicts at the cellular level linear dose-effect relationships for neutrons and curvilinear relationships for low-LET radiations. This approach has obvious implications in practice for the design of new experiments and for the prediction of certain trends of the phenomenon of cancer induction as a function of radiation quality, dose, dose rate, fractionation etc. However, from the point of view of the biological theories of carcinogenesis, the good correlations found, though very suggestive, cannot be taken as absolute proof of the validity of the starting hypotheses. Unfortunately they also do not identify the mechanisms involved.

31. Within the framework of a biomathematical reconnaissance of the most basic problems of carcinogenesis and radiation risks, Mayneord and Clarke (430) have proposed a formulation which relates the dose to the risk of a rare event such as a neoplastic transformation in a population of cells. In spite of the recognized limitations, this formulation has been used to examine a number of practical problems, including the form of the dose-effect relationship, the effect of dose inhomogeneity, the LET, and the estimate of the absolute carcinogenic risk per unit dose. The main value of this contribution lies in the attempt to identify and define the quantities which may be more significant for the analysis of these problems, and as such it is of great interest to the theoretical, experimental and practical aspects of radiation carcinogenesis.

32. In very general conceptual terms, by analogy with the classical experiments on chemically induced skin neoplasia—following, for example, the application of

[1] In the context of the present document the terms "neoplastic transformation" and "cell transformation" are used in a descriptive sense to include all changes that confer upon a normal cell (some of) the properties of a viable neoplastic cell.

benzopyrene and croton oil in optimal doses—the induction of any tumour may be envisaged as the outcome of two independent actions referred to as "initiation" and "promotion" (37). The former is viewed as a fast irreversible process acting on a normal cell and conferring upon it tumorous characteristics. Initiation would precede in time the slowly acting process of promotion but would never result, in the latter's absence, in a growing tumour, since the induced cell might remain indefinitely in a "dormant" state without further division. These different actions may experimentally be resolved in time and quality, since the final yield of tumours is generally a function of the initiator's dose, but their rate of appearance is mainly dependent upon the time and dosage of the promoter.

33. Ionizing radiation, in view of its extreme unspecificity of action on living tissues, cannot be considered as either a "pure" initiator or promoter but shares the properties of both classes, and for this reason it represents a very special carcinogenic agent. In spite of this duality, which might in itself give rise to ambiguous answers, radiation has been tested in a number of experiments in association with chemical carcinogenic substances known to act, under the specific experimental conditions, through initiating or promoting mechanisms. An exhaustive list of references up to 1966 may be found in a review by Kondrateva (356).

B. COMBINED ACTIONS

34. Much of the work on the combined action of chemical carcinogens and radiation was carried out on the skin, the tissue where the two-stage mechanism of carcinogenesis was originally identified (37) and can be more easily tested. Electrons or uv light in association with other carcinogens usually results in a higher yield of tumours than any of the agents administered alone. This applies to methylcholanthrene (113), 7,12-dimethylbenz [*a*]anthracene (171, 639) and 4-nitroquinoline 1-oxide (276). Reversing the order of administration does not change the result in case of beta rays (276) but may lead to an inhibitory effect with uv radiation (640). In the mouse, the tumour induction rate did not change by increasing the interval between the exposure to beta radiation and the subsequent painting with 4-nitroquinoline 1-oxide, showing the persistence of the latent carcinogenic action of radiation (275). The action of croton oil, which is a typical promoter of chemically induced skin tumours, seems uncertain when combined with radiation, since either enhancement of effects with uv (172) and electrons (624) or negative results (233, 71) have been obtained. However, it may be said in very general terms that initiation and promotion have been verified in the case of skin radiation carcinogenesis. The results of combining two independent carcinogenic treatments on the skin might also be interpreted on the base of other concepts of the fundamental processes of carcinogenesis. Some of the previously mentioned experiments (171, 172, 276) would in fact be regarded by others (486) as clear examples of syncarcinogenic summation of chemical and physical agents.

35. The situation appears to be definitely more confused with respect to the induction of tumours in other tissues or to systemic leukaemogenesis. In the case of the lung, urethane (a specific inducer of lung adenomas in mice) has been used in association with x rays with various dose and time schedules and after single or fractionated radiation treatments. A reduction in the percentage incidence and tumour multiplicity per animal has been obtained in one experimental series (200), and this result has been attributed to an inhibitory action by the high radiation dose on the urethane-induced tumours. Recalculation of these data by another group of workers (388) led to an entirely different interpretation. Additive effects were reported by the same authors in another set of experiments. The resulting effect was explained as the end-point of two competing mechanisms, cell killing and cell transformation, whereby, depending on the dose of the two agents, any effect becomes possible. As a further complication, an immunological component might also interfere with these phenomena (116). Mice irradiated *in utero* with a small dose of x rays (36 rad) have shown a significantly increased incidence of lung tumours induced by urethane given after birth (511).

36. Concerning leukaemogenesis, an increased effect with the combined treatment of urethane and radiation seems to be the general finding (337, 41, 154, 376, 40, 707, 216), especially in young mice (40, 707), perhaps due to differences in catabolism rate of the drug with age rather than to changes in the intrinsic susceptibility of target cells (100). However, at least in one case, thymic lymphoma and myeloid leukaemia were found insensitive to the combined action of the two agents (686). Croton oil acts also as an effective promoter of systemic leukaemia (297). Differential actions on the myeloid leukaemia or on the thymic lymphoma have been reported in the mouse by the combination of myleran (695) or novoembichin (12) with radiation.

37. Intragastric administration of 3-methylcholanthrene followed by x-ray (604) or fission-neutron (619) irradiation gave rise to additive effects for induction of mammary adenocarcinoma; however, in another system, brain tumours, where the same chemical was applied locally, beta-ray irradiation resulted in an inhibition proportional to radiation dose (423). As far as other tumours were concerned, no changes were found with respect to x rays alone or in association with 3,4-benzopyrene (348). Dibutylnitrosamine (DBNA) or 4-ethylsulphonyl-naphtalene-1-sulphonamide (ENS) combined with x rays showed no effect on tumours of the urinary bladder but a reduction of mammary tumour incidence (199). A synergistic action on the production of liver and gastric carcinoma by fission neutrons in combination with N,N'-2,7-fluorenylenebisacetamide (2,7-FAA) was reported, but no additivity or potentiation for intestinal tumours (713) was found. Localized x irradiation in association with the same drug administered in the diet accelerated the induction of hepatomas (485), and similar effects were reported with the association of x rays and o-aminoazotoluene (342) and of ^{144}Ce and dimethylaminoazobenzene (DBA) (416). Experiments on additive carcinogenic effects of 9,10-dimethyl-1,2-benzanthracene or 1,2,5,6-dibenzanthracene in association with chronic internal irradiation from ^{90}Sr were also reported (759, 758). Finally, survival and tumour induction were tested in three strains of rats following x-irradiation in

association with urethane. In spite of some interesting differences observed between strains, the overall effect of the joint treatment was not greater than the sum of the separate effects at the dosage level studies (482).

38. In view of the complex pathogenesis of the tumour systems tested, where the conceptual distinction between induction and promotion cannot easily be proven, the conflicting evidences available are consistent with the assumption that associated treatments decrease, rather than increase the induction of neoplasia, in cases where the toxicity of the two combined agents outweighs their additive carcinogenic properties (675). A possible quantitative approach to these problems could possibly come from studies at the cellular level (519 and 518). In embryo hamster cells, for example, the transformation by benzo[*a*]pyrene administered prior to irradiation has shown, both per cell and per total colony, maximum enhancement when the drug treatment was given 48 hours post-irradiation and when the radiation doses range from 250 to 500 rad. At higher radiation doses and at longer intervals between treatments the transformation efficiency actually decreased (149). No definite conclusion with respect to any special tumour model system may therefore be drawn before the dose, dosage schedule, order of administration and modality of the combined treatment with physical and chemical agents are properly and thoroughly explored, which is seldom the case in the works reviewed.

C. "THEORIES" OF RADIATION CARCINOGENESIS

39. The concepts of induction and promotion provide some insight into the possible mode of action of carcinogenic agents, but they don't exhaust the problem of tumour etiology and pathogenesis for which definite biological mechanisms must be traced. To this effect, a good number of theories have been proposed in the past, but most of them were gradually abandoned since none could account for the large array of properties of the tumorous cell. A critical review of most of these theories in a historical perspective has recently been provided by Berenblum (38).

40. At present, only a few of the original theories are still viable and will be discussed in the present report especially for their relevance to the action of radiation. The genetic foundation is common to all of them since it appears at present as the most logical way to account for the irreversibility and the continuity of the neoplastic transformation in the course of cell division. This common molecular genetic basis makes it conceivable that the distinction that is still drawn between the somatic mutation and the viral hypotheses of tumour induction might soon become unnecessary.

41. The somatic mutation theory of cancer induction stems from the notion that tumours are often carrying abnormal mitotic configurations which were originally interpreted as the phenotypic expression of the genetic alteration responsible for cell transformation. Also, the fact that unique chromosomal configurations (201, 290, 722, 213, 444) or biochemical markers (382) are often found in all the cells of primary tumours, as if they would be derived from a single mutated clone, lent support to this theory. However, the fact that aberrant unviable mitoses are often secondary changes or the end-result of excessive tumour growth rather than its cause (353, 354), the gradual realization that mutagenesis at the chromosomal level and carcinogenesis by a number of agents are not necessarily closely linked phenomena, at least in mammals (198), and the notion that carcinogenesis is better explained as a multi-step process involving the interplay of many factors and mechanisms (120, 141, 143), made the theory less appealing, at least at the chromosomal level. At the DNA level, however, the hypothesis of somatic mutation may still be entertained (although with some difficulties in explaining the multi-stage nature of malignant transformation) and could well explain the spontaneous occurrence of cancer as well as its induction by chemical, physical or viral agents. There are as yet no data at the molecular level to validate such a theory in the case of radiation-induced neoplasia, although modern techniques of cell and DNA hybridization and of somatic mutation analysis might render this possible in the future.

42. The refined knowledge of the mechanisms of damage and repair in uv-irradiated eukaryotic cells (see for general references (513)) has developed in recent years in a new line of research. It becomes apparent that, at least in the case of actinic radiation, lesions to cellular DNA and defective repair of this molecule might result in neoplastic transformation of the damaged cells. There are several arguments pointing in this direction and they have recently been discussed at the VIIth International Congress of Photobiology (296). The first argument is the demonstration that exposure of cells to uv results in neoplastic transformation, that the action of a photoreactivating treatment decreases the incidence of transformants and that the initial lesion in DNA is probably the formation of pyrimidine dimers (600). The second is the fact that treatment of the uv-irradiated cells with inhibitors of the repair of photolesions reduces the incidence of tumours produced by uv radiation (756) presumably by decreasing the likelihood of mutations resulting from the misrepair of photolesions in DNA. The third is the detection of defective DNA repair in some human diseases (xeroderma pigmentosum (55) and ataxia teleangiectasia (526)) showing predisposition to malignancy. It should be pointed out, however, that the correlations observed do not represent direct proof that derangements in the repair of DNA lesions might be the primary genetic cause responsible for malignant transformation of the defective cells. Also, although it may be regarded as an attractive general proposition, the model of the misrepair of uv-induced DNA lesions could not as such be acceptable in the case of ionizing radiation, owing to the profound differences in the nature of molecular lesions produced by the two types of radiation.

43. A comprehensive treatment of the numerous viral hypotheses of tumour induction would be unwarranted in the present context and the reader is referred to specialized reviews (237, 38). In experimental radiation work the neoplastic diseases of importance for which sufficient documentation of a viral etiology is available are leukaemia, mammary cancer and osteogenic sarcoma,

and they are discussed in the present report. Since in all of them RNA oncoviruses are implicated, the molecular mechanisms of induction should at present be viewed in the context of one of the hypotheses which postulate the virus to be vertically inherited by the animals and integrated into the cellular genome as a DNA intermediate synthesized on the viral RNA under the action of a specific RNA-directed DNA-polymerase known as reverse transcriptase.

44. The "oncogene" hypothesis (282,139) is founded on the notion of the vertical transmission of type-C RNA virus particles in most animal species. These particles are postulated to act as the potential etiological agents of all forms of cancer, carrying with them the genetic information, transmitted by an oncogene integrated in the genome DNA. Derepression of this information by chemical or physical agents or through spontaneous mutational events would lead to the activation of the oncogenic action. At variance with the oncogene theory, the "protovirus" hypothesis (654, 655) postulates that during normal development RNA is transcribed from a section of DNA of a somatic cell and then transmitted to another cell which may in turn synthesize upon this information, *via* the reverse transcriptase, new DNA sequences to be incorporated into predetermined regions of its genome. This mechanism would be one normally acting in differentiation: cancer would result from the wrong evolution of the protoviruses caused by somatic mutations or by their misplacement in the genome of the cell.

D. ETIOPATHOGENESIS OF RADIATION-INDUCED TUMOURS

45. The most common forms of leukaemia in the mouse are the thymic, the myelocytic and the reticular types. The viral origin has been ascertained only for the first two of them (236, 310), while attempts to isolate a viral agent from reticular neoplasms (253) have not yet been confirmed. Some strains of mouse develop the disease spontaneously, such as the AKR strain in the case of the thymic (237) or the SJL/J for the reticular form (481). After irradiation, leukaemia is found to increase in strains that do not normally show it, and this is most typically the case of the C57BL mouse, which, under suitable conditions of dose fractionation, may develop up to 90 per cent thymic lymphoma (330). Differences have been reported between strains and even among congenic lines of the same strain (317) in the susceptibility to leukaemia induction by radiation. In the course of almost thirty years of work (summarized in 326 and 328), Kaplan and his associates have systematically explored the various conditions affecting the radiation induction of this disease, which is a good example of the complexities of tumour pathogenesis. Reviews on radiation-induced leukaemias and its viral and host factors may also be found in references 325, 126, 167, 407, 674, 678 and 680.

46. Although the thymus was first identified as the target organ for the lymphoid leukaemia type (321), local irradiation of the thymic area (322) or of the upper half of the body (329) was ineffective for induction. Partial-body irradiation may sometimes accelerate the appearance of malignant lymphoma without increase of its incidence (596). Protection against leukaemia incidence was also afforded by shielding of the spleen (367) or the marrow (329) or the lymph node (289) or by transplantation of intact isogenic marrow cells (331) or spleen cells (99). Isologous thymus grafts to irradiated thymectomized mice were shown to undergo malignant transformation (332), and cells of these tumours were found to be of donor and not of host type (333). All this definitely pointed to an indirect induction mechanism which was later to be identified as an RNA oncovirus (377). Advances in the techniques of virus titration (254) made it possible to study extensively, in addition to the morphology of the type-C viral particles, the biochemistry of the purified virus (327), its antigenicity (528, 178), host range (326) and localization (148). It is known that this virus, referred to as Rad LV, is vertically transmitted through the embryo in C57BL mice (327) and that the action of physical and chemical agents is required for its activation and release in young, normally resistant animals (325, 368). Radiation-induced lymphoid leukaemia in chickens through a possible activation of a latent virus (365) and in guinea pigs (697) has also been reported.

47. The initial step in the pathogenesis of radiation-induced thymic leukaemogenesis in the mouse is the release of the viral particles from the injured marrow (247, 238, 304) where they are normally harboured in an oncogenically inert state. In the course of post-irradiation thymic hyperplasia (625, 328, 302, 336, 303), the virus is then taken up by the thymic target cells, identified as the immature lymphoblasts of the outer cortex (376, 53, 90). Since these cells are incapable of giving rise to tumours in the absence of the epithelial-reticular thymic stroma, it is thought that their contact with such a cellular microenvironment is essential for their complete progression to full neoplastic state (327).

48. An important factor in the pathogenesis of thymic lymphoma is the bone marrow, which either by favouring the regeneration of the irradiated thymic cells (331) or by effective scavenging viral particles from the blood stream in the course of the post-irradiation viremia (327), may render their interaction with target cells less probable. Another humoral factor, mediated through the haemopoietic tissue and capable of inhibiting the occurrence of radiation-induced leukaemia, has also been described (379, 380) and identified as a 19S alpha-2-globulin (39). Depression of the host immune response by the whole-body radiation treatment is also an important factor in the pathogenesis of the disease (248, 255). Finally, a range of host factors may influence induction: in addition to the already mentioned genetic constitution, age (320, 251), sex (319) and other endocrine factors (possibly through their action on the thymus) (323, 334, 483, 484) have been shown to interact in various ways with the virus and the radiation exposure in the development of lymphoid leukaemia (747, 746).

49. Information on the viral etiology and pathogenesis in the induction of myeloid leukaemia by radiation in the mouse is far less complete. In the RF strain incidences of up to 25 per cent have been reported after

single doses of radiation, starting from an incidence of less than 1 per cent in untreated animals (67). Age, sex and hormonal effects on the viral transmission of the disease have also been shown (686), as well as changes in the induction rate introduced by environmental factors such as the microbial flora in the mouse colony (720, 719) or by a subsequent re-irradiation (408). These observations clearly point to complex interactions between viral, host, environmental and physical factors which remain to be fully elucidated.

50. A viral agent (241, 35) in association with hormones and other factors (54) is also involved in the induction of mouse mammary tumours by radiation in the strain 020 of mice which do not normally develop such tumours spontaneously (664). The virus has been shown to be widely present in many mouse strains; in some strains however it is released at a young age, with good correlation between the time of release and the onset of spontaneous mammary tumours. On the other hand, in strains releasing the virus late in life, irradiation early in life causes the production of viral antigens (34) and of mammary tumours with infective virus particles (664).

51. It is not known yet whether the viral etiology would also apply to another important model system in radiation carcinogenesis, namely mammary carcinogenesis in the Sprague-Dawley rat. In these animals irradiation leads to induction of tumours which is a function of dose and may go up to 80 per cent (50, 611), starting from a background incidence of less than 2 per cent (138). Sex and hormonal influences are also operating in the mammary carcinogenesis of the rat (63, 138, 615, 609), as well as a number of other modifying factors (608), but primary damage to the mammary gland is necessary for the occurrence of neoplasia (52). Recent biophysical evidence (575) indicate the possible need for interaction between radiation-damaged cells for the production of a viable tumour in this system. Studies have been undertaken to elucidate the effect of genetic strain in radiation-induced mammary carcinogenesis of the rat. Results of an experiment involving Sprague-Dawley, Long-Evans, Buffalo, Fischer-344 and Wistar-Lewis rats strongly suggest the presence of a genetic component (710). Another study (63) on Sprague-Dawley, WAG/Rij and Brown-Norway animals is still in progress.

52. Osteogenic carcoma, a rare form of tumour in the mouse, inducible by bone-seeking radionuclides such as ^{90}Sr (198, 185, 196) has been serially passed by cell-free extracts to isogenic new-born mice of the CF1 strain. In the CBA mouse, on the contrary, ^{90}Sr-induced bone tumours contained very few virus particles, cell-free extracts being ineffective in transferring the neoplasms. A virus termed FBJ (374) is involved in the etiology of bone tumours of the CF1 mouse; its morphology (45) and its interaction with radiation have been described in the mouse (187, 192). It belongs to the class of murine sarcoma viruses (MSV) which may also induce bone tumours in rats and hamsters (632). There is actually evidence that the FBJ virus might require the association of a helper in a complex with murine leukaemia virus (MLV) for its replication (314). Two other viruses inducing bone tumours, termed RBF and FBR, have recently been identified in the mouse (193, 197). Transplantation (199) and immunological evidence (536, 555) seem to imply the extension of the viral etiology also to human tumours.

E. CELL TRANSFORMATION *IN VITRO*

53. There have been attempts for a number of years to study radiation carcinogenesis in cellular systems *in vitro*. There seems to be hardly any doubt that radiation enhances the transformation of animal cells by chemical carcinogens (149, 519, 518) and by a number of infecting DNA viral agents such as polyoma (643), SV_{40} (542) and adenovirus type 31 (114). The existence of a linear relationship between the logarithm of the excess transformation and the dose, with a doubling dose of 200 rad of 250-kVp x rays in the range of 75 to 1200 rad has been reported in one case (542). These data are consistent with the hypothesis that non-lethal damage induced by radiation in cellular DNA might facilitate, in the course of repair, the integration of the viral genome into the genetic material of the host cell. Rescue of lethally damaged cells by the integration of the viral genome has also been considered as a possible mechanism.

54. Induction of a latent leukosis virus in chicken cells (739) and possibly of a murine leukaemia-sarcoma complex in Balb/3T3 cells (541) has also been described. It might be reasonable to assume (although it has not yet been demonstrated) that the activation of an oncogenic virus could be responsible for the induction of neoplasia in fragments of rat mammary tissue irradiated *in vitro* (618, 606). In many reported experiments the criteria used to assess cell transformation were purely morphological, based on the multilayer and irregular arrangement of cells in the transformed colonies, but in other cases malignant tumour growth was actually tested by retransplantation of the transformed cells into the donors (606) or into suitably conditioned, genetically compatible hosts (541).

55. Experimental results have been published on the capacity for transformation of radiation *per se* in the presumed absence of viral agents. According to one group of workers, x-ray-induced transformation is possible and has actually been shown (59): it would result in a change of regulatory mechanisms of the transformed cell lines, such that transformed cells may be contact-inhibited only by a different and not also by the same cell type. In another report, a single x-ray dose of 300 rad resulted in a high proportion of transformed clones in primary and secondary cultures but not in later passages of hamster embryo cultured cells (60). In primary hamster cell cultures, these results were extended down to doses of the order of 1 rad of x rays. A dose-effect curve for transformation of these cells was established, which on a log-log plot increases up to a plateau of approximately 1 per cent transformed clones at doses between 150 and 300 rad. Further increases of dose resulted in a marked decrease of the percentage of transformation. In some cases, in addition to morphological criteria, neoplastic transformation was also tested by the ability of cells to form clones in semi-soft agar or by their agglutinability by concanavalin A and wheat-germ agglutinin (57).

56. On the contrary, exposure of spleen cell cultures (344, 345) under carefully controlled conditions to a range of weekly irradiation treatments up to a total accumulated dose in excess of 15,000 rad of 250-kVp x rays did not result in malignant changes, although the same cell line did turn malignant under the action of methylcholanthene. Urethane alone or in combination with radiation was found similarly ineffective. The conditions affecting the possible failure to show malignant transformation *in vitro* (viability, cell concentration, presence of damaged or unviable cells) were investigated recently (346, 347) on mouse cells. Under certain conditions and on some cell lines, transformation was actually obtained and tested *in vivo*. It was concluded that the presence of large amounts of dead cells and cellular debris, whether induced by radiation or mechanically, in close contact with viable cells is a condition favouring the induction of transformation. This would argue against a direct carcinogeneic effect of radiation *in vitro*. This same conclusion was reached on a different transplantation system of skin carcinogenesis *in vivo* developed in the same laboratory (25).

57. Recently x-ray-induced transformation has also been reported on a C3H mouse embryo cell line (658, 659). In this case the effect was assessed both morphologically and by transplantation of the transformed cells: it did not appear to be mediated by non-specific cell killing. Differences were also noted with respect to the previously reported data (57, 56). In fact, the yield of transformation per surviving cell appeared to increase between 50 and 400 rad and then to level off at higher doses when given to exponentially-growing cells. However in the treatment of plateau-phase cells the transformation frequency was enhanced for doses up to 100 rad. These observations suggest the existence of yet unexplored relationships between the molecular events responsible for neoplastic transformation and those processes controlling cell survival and the kinetics of cell division.

58. Although a certain variability of the results should be expected (in view of the above-mentioned experimental variables, the difficulties of relating morphological changes at the cellular level with the actual malignancy demonstrable *in vivo*, the possible presence and activation of latent tumour viruses, and other biological considerations by which neoplastic transformation can hardly be viewed as an all-or-none phenomenon), the available evidence is too conflicting to allow any firm conclusions. It seems clear, however, that the use of these highly controlled techniques *in vitro* may, in the future, be a powerful tool to disentangle the problem of cancer induction at the cellular level in the absence of other interactions operating at the whole-body level.

F. THE IMMUNE SYSTEM

59. Among the factors which are involved in cancer induction, the immune reaction has gained much attention in recent times. However, since transformation can be obtained by chemical, viral and possibly physical agents in entirely *in vitro* conditions, it must be inferred that immune phenomena play only a secondary role in the development of neoplasia, perhaps associated with the development rather than with the induction of tumours. We shall therefore group this factor under the general heading of the promoting agents. The whole problem of immunity and tolerance in oncogenesis has been discussed at length by Severi (601) and the aspects connected with radiation particularly by Cole and Nowell (121). The Committee also reviewed in 1972 the relevant evidence, both the general concepts (670, Annex F, paras. 247-250) and their specific importance in radiation carcinogenesis (670, Annex G, paras. 13-15). Recent reviews may also be found in Kersey (341), Martin (427), and Weiss (738, 739).

60. Rather than attempting to outline the premisses on which the current hypotheses of immune reactions in oncogenesis are based (375), it seems more appropriate in the present context to review the most recent advances in the field, in the light of these general hypotheses. The discovery of tumour-specific antigens in chemically induced tumours and of tumour-associated antigens as products of the oncogenic viral infection, has led to the general concept that such antigens might be present in all tumours and might be relevant to the tumour evolution.

61. It has been proposed originally by Thomas (660) and later expanded by Burnet (78), that the immune response stimulated by such antigens might actually be effective in controlling and eliminating potentially malignant clones, and that only those clones which escape this mechanism of "immune surveillance" (carried out by the body through cellular (132) and humoral (392) factors) might finally show up as clinically-evident tumours. According to these theories, immune reactions could only be effective in inhibiting tumour growth, but there are data showing that, depending on the stage and intensity of the reaction, stimulation or inhibition of tumour growth may actually result (548, 547).

62. Radiostrontium-induced osteosarcomas were reported to possess tumour-specific transplantation antigens (504), and the degree of this antigenicity, in any case rather weak (464), could be related to tumour histotype (505). Changes in the antigenic constitution of the gastro-intestinal mucosa after a radiation dose which gave rise to tumours in later age were also reported (147). Animal strains carrying vertically inherited RNA tumour viruses react immunologically when injected with such viruses (249, 527). Evidence of the pathological expression of the reaction is found in the kidney of intact non-infected animals: in the course of time, antigen-antibody complexes which have specificity for the murine leukaemia viruses are deposited in the glomeruli and their presence results late in life in nephrosclerosis.

63. This is the case for the AKR mouse (516), for the $B6C3F_1$ mouse (29) and for the RF strain, where analysis of the leukaemia incidence in glomerulosclerotic mice has indicated that immune response may reduce the probability of leukaemia to about one half by comparison with non-glomerulosclerotic animals (752, 753). Viral antigens and infectious virus titres are low in young animals but increase consistently in old age (532,

251), and the reduced immune capacity of aged $B6C3F_1$ mice has been related causally to the subsequent development of lymphatic and non-lymphatic tumours (246). Evidence against this causal relationship has however been produced in NZB/W mice (1).

64. An important factor in radiation-induced leukaemia is the transient immunosuppression caused by radiation with respect to endogenous viruses. Data to support this concept have been reported in the case of the lymphatic leukaemia of the C57BL strain (248, 250) and for the reticular, lymphoid and myeloid leukaemias in the RF strain (753), in which the severity of nephrosclerosis is shown to be inversely related to leukaemia incidence (108). In accordance with this interpretation, stimulation of the immune response should logically result in a reduction of tumour incidence. In fact, treatment of C57BL animals with interferon (379) or with immune and non-immune foreign sera (179) or with methanol extraction residues of BCG (256) under appropriate schedules of administration, actually reduced the incidence of thymic lymphoma. A delayed development and a decreased incidence of ^{90}Sr-induced osteosarcoma was also reported after injection of CBA mice with BCG (506).

65. Effects in line with the above findings were also reported after immunosuppression which resulted in activation of murine leukaemia virus in animals grafted with foreign skin (266), and also in other cases it resulted in a higher incidence of tumours (121, 360, 359). Data have also been reported on the role of immunological factors in the induction of leukaemia in swine by ^{90}SR (279, 202). The role of immunological surveillance against neoplasia and the possible influence of immunodepression have been discussed (203, 24).

66. Radiation-induced immunosuppression is however not the sole immunological factor implicated in the pathogenesis of tumours since the virus itself may depress the immune response. Although there may be uncertainties as to the importance of this latter mechanism in view of the lack of correlation between the immunosuppressive effect and the actual development of tumours (528), it has however been shown rather conclusively that the viral infection *per se* may result in an impairment of the animal's capacity to mount an immunological response to various agents. This is true in the case of both the mammary tumour virus (235) and the murine leukaemia viruses (541, 102). Analyses of the cellular bases of these phenomena point to a great specificity of action. In fact, not only has the virus derived from C57BL mice no suppresive effect on SJL/J animals (602), but in the case of C57BL mice the immunosuppressive effect is expressed at the level of immunocompetent thymus-derived cells (529, 102), while in SJL/J mice the viral infection depressed both thymus- and marrow-derived immunocytes (602).

67. In essence, it might be concluded that there is no doubt as to the presence of an immunological component in carcinogenesis related both to viral or to other etiological factors. The evidence available points rather to an inhibition than to an enhancing action of the immune system on radiation-induced tumour development. The problem is one of ascertaining the actual importance of the immunity among the many factors of cancer induction. The data available however seem to point to a secondary role of the immune reaction in radiation-induced cancerogenesis.

G. HORMONAL ACTIONS

68. Consideration of the hormonal influence on radiation carcinogenesis seems appropriate, since it has been amply documented that the action of hormones may affect tumour induction. This action is not only evident in the cancerization of hormone-responsive organs but may also be present in tumours of other tissues where hormonal control is not readily apparent. Reports on this subject have dealt mainly with radiation-induced carcinogenesis of the ovary, the thyroid, the mammary tissue, the bone and the haemo-lymphopoietic system.

69. X-ray-induced neoplasia of the ovary in the mouse is inhibited by oestrogen treatment (211) and this effect seems to be in accordance with the finding that transformation of irradiated transplanted ovaries is decreased if ovarian function is intact (324). In the rat, local ovarian irradiation produced a high yield of tumours, unaltered by treatment with chorionic gonadotropins (603). Promotion of the sequence of events leading to permanent hyperplasia and/or carcinogenesis of the **thyroid gland** by the thyroid stimulating hormone has been reported in the dog (406) and in other species (389, 159).

70. In the Sprague-Dawley rat the incidence of spontaneous tumours of the **mammary gland** is extremely low in the intact male (615) and approaches 2 per cent in the intact female at 1 year (138). Orchidectomy raises this incidence to 6 per cent (615) and ovariectomy results in a decreased incidence (138). Irradiation with 400 rad of x rays induces breast tumours in 50 per cent of the male (615), and in 79 per cent of the female, rats (138). Ovariectomy produces a decreased yield of tumours in irradiated animals and the implant of normal ovaries restores the incidence to about 80 per cent (138). Thus, the presence of a functioning ovary is required in this system for expression of maximal neoplastic response, although cycling ovarian activity is only a secondary mechanism with respect to the radiation damage to the target organ (52, 606). The effect of thyroid hormones in mammary carcinogenesis is very minor, on the other hand the administration of stilbestrol depresses the neoplastic response to irradiation (614). This latter observation is however at variance with what was reported in the AxC rat strain, where stilbestrol acts synergistically with radiation in producing mammary tumours (598) and the continuous administration of progesterone shows a protective effect against this synergistic action (597). Alterations in the ovarian and pituitary hormonal regulation have also been invoked to explain the changes of mammary tumour incidence in irradiated parabiotic rats (66). The combined action of pituitary isograft and neutron irradiation in $B6CF_1$ mice produced a reduction of the latency period and an increased incidence of mammary tumours. Harderian gland tumours also

showed a shorter latency, a marked increase in incidence and a greater tendency to metastasize. The inductive *versus* promotive role of the pituitary isograft has not yet been ascertained (206).

71. The endocrine functions related to gestation and lactation lead to a significant delay and to a reduced incidence of ^{90}Sr-induced bone tumours in the CBA mouse (495). This effect is probably related to changes in ^{90}Sr retention induced by pregnancy and lactation (503, 568). Treatment with oestrogens, on the contrary, increases considerably bone tumour induction, perhaps through a stimulation of osteoblast repopulation (507). The important role played by the parathyroid hormone was shown in the case of the induction of bone tumours by ^{45}Ca (152, 153). When the action of ^{45}Ca and the hormone are combined, the incidence of osteosarcomas in rats is a factor of about 2 higher than with ^{45}Ca alone. On the other hand, the removal of the parathyroid glands decreases the osteosarcoma incidence by a factor of 3. It appears therefore that the reduction of the hormone level decreases carcinogenesis in bone.

72. Hormonal effects in radiation leukaemogenesis have been reported by many authors. Susceptibility to myeloid leukaemia is higher in male than in female RF mice (694, 686), while the response to lymphoma induction in the same strain is higher in females than in males (694), or about equal in both sexes in the A mouse (436) and in the C57BL (323). Splenectomy reduces susceptibility to myeloid leukaemia but does not alter the induction of lymphoma in the RF (694) and in the C57BL mice (323); thymectomy, on the contrary, does not influence the induction of myeloid leukaemia in the RF (694) but effectively prevents the occurrence of lymphoma in irradiated RF (694) and in C57BL mice (323). As for the action of the gonads, ovariectomy decreases lymphoma incidence and does not alter myeloid leukaemia in RF mice (694) nor does it affect thymic lymphoma in C57BL (323). Orchidectomy has no effect on both types of leukaemia in the RF (694) and on lymphatic leukaemia in C57BL (323). However, in another report, castration has been shown to increase lymphoma incidence and this effect is brought back to normal levels by oestrogen treatment. When administered to intact C57BL animals of both sexes, oestrogens markedly increase the incidence of lymphoma; this effect is not seen in the Balb/C strain (665). On the other hand, the induction of myeloid leukaemia in virus-infected RF mice is inhibited by estradiol treatment (686, 309). Hypophysectomy does not alter the induction of thymic lymphoma by radiation (483). Hypothyroidism inhibits the incidence of this neoplasia in females but not in males implanted with thymic grafts (484). Finally, pregnancy and lactation increase all types of leukaemia in ^{90}Sr-treated CBA mice (495).

73. It is impossible from this long list of scattered observations to draw any consistent conclusion. Clearly, various radiation-induced tumours are differently affected by the animal's hormonal balance in the course of the carcinogenic processes. The effects vary with the tumour system, with the animal strain and sex, and it is therefore likely that the mechanisms of action, at present completely unknown, may be very different in the various experimental conditions.

H. THE ROLE OF CELL PROLIFERATION

74. A discussion of the role of cell proliferation among the promoting factors in radiation carcinogenesis may reasonably be centred around two questions: whether there is any relationship between the rate of tissue renewal and the induction of cancer and whether the phenomenon of cancerization is linked with any specific biochemical or kinetic changes of the transformed tissues. At present, the precise formulation of these questions is very difficult, due to the following considerations.

75. Firstly, cell proliferation often results from the application of a variety of toxic stimuli to any tissue and many physical and chemical carcinogens are toxic to cells: it is difficult therefore to recognize any specificity to the phenomenon of cell division as such. Secondly, the identification of target cells for neoplastic transformation is not always possible and therefore evaluations of kinetic changes on the whole tissue may not be relevant to the target-cell compartment. Thirdly, the usual parameters for the quantification of cellular proliferation in any tissue compartment (mitotic index, labelling index, labelled-mitoses curves, rate of DNA or of specific protein synthesis, etc.) are entirely inadequate to describe the kinetics of the tissue as a whole, including the stem, proliferating, maturing and functional compartments and, in any case, only for a very few animal tissues has such a comprehensive analysis been performed. A series of papers with a detailed quantitative analysis of different cell populations in the course of mouse leukaemogenesis may be pointed out as a first original attempt in this direction (593, 595, 594). Finally, the tissue steady state, which is often the necessary condition for kinetic estimates *in vivo*, is completely disrupted by the application of toxic stimuli and, under such conditions, the description of fine kinetic changes becomes practically impossible.

76. In spite of the above limitations, which substantially confuse the problem, there have been a number of attempts to stimulate by various treatments the cellular proliferation of tissue in order to modify their susceptibility to cancer induction. In the rat, the stimulation of unspecific tissue reactions by stable caesium hydroxide in conjunction with exposure to the daughter products of radon and thoron has resulted in accelerated lung tumour induction (530, 97, 380). Treatments with hormones which are known to stimulate cell division in the mammary gland have increased the yield of breast tumours following x irradiation (207). Treatments of animals with growth hormone increased the incidence of radiation-induced osteosarcomas, and treatment with thyroxine produced a shorter induction period (96). The application of goitrogen substances such as methylthiouracil in association with external x-ray treatment or internal exposure to ^{131}I has produced a higher incidence of thyroid neoplasia (158, 389, 724, 728), and the same observation was made in hamsters (105). In mice, stimulation of osteoblast formation by oestrogens has increased appreciably the incidence of ^{90}Sr-induced bone tumours (507, 508), although bone fracture attempting to enhance tissue proliferation before the application of ^{224}Ra has not significantly modified

bone tumour formation (222). Proliferation of the mucosa of the stomach induced by immunological treatment of the animals has increased the incidence of gastric carcinoma by x irradiation (264).

77. The role of hyperplasia during the post-irradiation regeneration of the thymus is an important factor in the pathogenesis of leukaemia (326, 327, 593, 336, 176): in agreement with this finding, urethane, which also caused injury and regeneration in the thymus (252), has been shown to increase the incidence of thymic lymphoma in association with x rays (40). Stimulation of cell division in mouse liver can increase the yield of various types of radiation-induced tumours: thus, carbon tetrachloride intoxication before or after x rays and neutron irradiation produces a considerably higher incidence of hepatomas (119, 124), and the same applies to a purely proliferative stimulus like partial hepatectomy following gamma or neutron irradiation (740). Urethane in association with x rays produced an increased incidence of lung adenomas (44) and the incidence of neoplasms approached 100 per cent after uninephrectomy in irradiated kidneys (570, 120, 123). Isoproterenol, an agent promoting DNA synthesis in cells of the salivary glands, has been shown to enhance the induction of tumours of these organs when given in combination with x rays (649).

78. Specialized reviews of the cellular and kinetic changes induced by radiation have been published (51, 13). In very general terms, there is nothing in these changes that would point to any specific pattern of cellular and tissue reaction with respect to other carcinogens (561, 27, 553, 38). The assumption that a rapid rate of renewal is a favouring condition for the neoplastic transformation seems therefore unwarranted, without adequate qualifications pertaining to the specific model of carcinogenesis under discussion. Exceptions to this general assumption, sometimes justifiable on biological grounds (393), may be as common as the general rule, and the preceding discussion has made it abundantly clear that the complexities of radiation carcinogenesis hardly point to a simple scheme of mechanism of action.

79. Cellular proliferation is implicit in the notion of promoting action and is clearly necessary for the tumour progression, and the evidence reviewed is generally in accordance with these concepts. However, so far there is no unequivocal evidence that the induction of proliferation in the target cells is a key event in radiation carcinogenesis: on the contrary, there is recent evidence from work in chemical carcinogenesis showing that hyperplastic changes and promoting action are quite independent phenomena (552). In any case, a systematic comparative analysis of events associated with the induction of tumours in target cells would be required before any postulated promotional role of cell proliferation could be fully elucidated.

I. OTHER MODIFYING FACTORS

80. Environmental conditions have been reported to influence the induction of specific tumour types in irradiated animals, through their action on the microflora and possible intercurrent diseases. The response of animals to carcinogenic stimuli, including radiation, may thus be affected to a variable degree by changes in the number of target cells and in cell turnover rates or by immunological factors which may interfere with the expression of carcinogenic damage. These effects have recently been reviewed (717), especially with regard to possible differences in the immunological competence of gnotobiotic and germ-free animals (245). It has been shown rather conclusively that the humoral immunological competence of germ-free and conventional mice is qualitatively and quantitatively very similar (62, 421, 599). In the very old animals, however, a great variability of response is noted, leading generally to a depression of the immune competence both in BC3F1 and in SJL/J mice. The immune competence is minimal in animals affected by lymphoreticular tumours (421, 599), suggesting that in ageing mice such tumours may arise as a result of a decline in their immunological capacity. As with the primary response, the living conditions of the animals do not affect to a great extent the secondary formation of IgG antibody-synthesizing cells (420). Infectious diseases, totally absent in the germ-free state, have little influence on the life span of mice (103, 719). In intact animals the development of spontaneous non-haemopoietic tumours is practically unaffected by the germ-free condition; among haemopoietic tumours, reticulum cell sarcoma incidence is higher in conventional than in germ-free mice, but thymic lymphoma and myeloid leukaemia have similar incidences in both conditions (719).

81. After irradiation, the incidence of myeloid leukaemia is decreased in the absence of microbial flora (719) and this effect is attributed to the reduced myelopoietic cell proliferation in the germ-free animals (720, 717). Radiation-induced lymphatic leukaemia, on the contrary, is not altered under germ-free conditions in Swiss, C3H, C57B1, ICR and C57BL mice (539, 721, 719). There are no qualitative differences in the pathological lesions of gnotobiotic and conventional animals and virus particles are found in germ-free just as in conventional mice (539). The induction of other solid tumours in irradiated animals gives variable results (15, 717). No special features were seen in radiation-induced malignant and benign tumours of the germ-free rat (540).

82. In summary, the data available at present show that the etiology and the pathogenesis of radiation-induced cancer are essentially similar in conventionally reared and in gnotobiotic animals: the host's microbial flora may only play a secondary role in the development of some haemopoietic neoplasms, perhaps through modifications of the immune competence, as in the case of the reticulum cell sarcoma or through the abnormal proliferation of target cell lines, as for myelogenous leukaemia. It seems doubtful that non-systemic tumours may respond to these actions.

83. The need to investigate in more detail specific mechanisms of radiation carcinogenesis and special conditions of practical importance, has often in the past justified attempts to modify tumour induction in irradiated animals by physical, chemical or biological treatments. The relevant work is reviewed in this report,

but owing to the heterogeneity of the conditions and agents employed, no general conclusions are really to be expected.

84. Among the physical treatments, the influence of permanent (466) or of transitory (467) high-altitude exposure has been tested in irradiated RF mice. It was found that the overall incidence of tumours was lower in mice kept at sea level after irradiation for the duration of their life, although thymic lymphoma and granulocytic leukaemia were higher at all radiation doses in these mice. Animals residing at high altitude for only three months after irradiation showed also an enhanced induction of leukaemia owing perhaps to the abnormal stimulation of the bone-marrow stem cells before their full recovery from radiation damage. The combined effects of high or low temperature and radiation were also investigated in the rat (88, 89), but only longevity data without tumour pathology were reported. The carcinogenic action of mechanical damage and x rays on intramandibular tissue of the mouse was also reported (173, 174). Finally, severe metabolic stresses such as starvation, water deprivation or prolonged physical exercise had no additional influence on tumour induction by radiation in the rat (559, 556).

85. In regard to chemical treatments, a number of studies have appeared on radioprotective drugs, but their results appear rather conflicting. Mewissen and Brucer (441) reported a significantly higher incidence of tumours in cysteamine- and cystamine-protected mice, but treatment with another radioprotective chemical (AET) failed to produce any change in the induction of the most common neoplasms of the mouse after whole-body irradiation (129), in ovarian tumour induction by localized x irradiation (129) or in breast-tumour induction in partial-body irradiated rats (616). Protection was reported in the case of kidney irradiation (168). AET alone or mixtures of five different radioprotectors reduced the total incidence of cancers and leukaemias by a factor of about two in mice irradiated with 1350 rad with respect to non-protected animals; complex dose effect relationships might have been operating in this case, since at a dose of 700 rad, the difference between protected and non-protected animals disappeared (418). Protection by cysteamine upon fractionated irradiation was also reported in the case of leukaemia induction (488). Clearly, more experiments are required to clarify this issue.

86. Among the biological treatments tested, parabiosis has been used in order to permit longer survival in animals irradiated with an otherwise lethal dose of 1000 rad of x irradiation. Under these conditions, radiation-induced osteogenic sarcoma was found in about 5 per cent of the animals (732), kidney tumours in about 8 per cent and leukaemia of the irradiated parabiont was lowered, although not to the level of the spontaneous incidence (587). There are indications that parbiosis *per se* may alter the incidence of some forms of cancer in the treated rats. Autologous, homologous and isologous haemopoietic chimaeras were also studied for their susceptibility to tumour induction. The incidence of lymphosarcoma and reticulum cell sarcoma is decreased by spleen shielding (403, 271), lymph-node shielding (289) and bone-marrow shielding (329), 134). The injection of syngenetic bone-marrow cells—but not of homologous marrow (146)—was repeatedly shown to be very effective in protecting the mice from the induction of lymphoma (331, 129), myeloid leukaemia (11) and reticulum cell sarcoma (135). The incidence of other neoplasms was practically unaffected by bone-marrow transplantation (129, 135). Acute loss of blood (2 ml) before exposure (to 270 R) was reported to increase the incidence of tumours in male rats (557). Similarly, an acute anaemic stress has been reported to act as a trigger mechanism for the induction of myelogenous leukaemia in unirradiated (221) and irradiated RF mice (179), but iron-deficient chronic anaemia is ineffective to this end in irradiated Wistar rats (307).

III. PHYSICAL PARAMETERS IN RADIATION CARCINOGENESIS (EXTERNAL IRRADIATION)

A. GENERAL

87. The purpose of this chapter is to discuss the main physical variables influencing radiation carcinogenesis, in an attempt to identify from the vast amount of scattered information in various animal systems common trends in the effect of such variables, and with the aim of assessing their qualitative and, if possible, their quantitative role. Since obtaining precise relevant data in man is extremely difficult, animal experimentation in this field is absolutely necessary to interpret and support the human evidence: this is the reason why such studies, very interesting in their own right for their fundamental implications, are also very important for human radiation-risk assessments, and therefore relevant to radiation-protection development.

88. The relationships of tumour induction with dose, radiation quality, dose rate, fractionation and protection will be examined, with main emphasis on the biological effects themselves and little discussion on the procedures of estimating the values of the physical parameters. It should be realized that technical and dosimetric uncertainties do affect in practice the determination of the physical parameters; they are, however, less important than the uncertainties associated with the biological end-points, probably by an order of magnitude at the doses where the carcinogenic effect is usually studied. Physical parameters will therefore be considered as independent and well controlled variables in the present context, since the variability of the biological end-points outweighs the errors of the physical measurements.

B. DOSE-EFFECT RELATIONSHIPS IN RADIATION CARCINOGENESIS

89. As usual in radiation biology, any attempt to analyze quantitatively the carcinogenic action of radiation must of necessity be based on the observed relationships between the dose delivered to the biological system and the ensuing effect of tumour induction. It should immediately be pointed out,

however, that the establishment of precise dose-effect relationships in animal systems is by no means an easy undertaking and that the interpretation of the relevant data must take into proper account a number of methodological and technical deficiencies encountered in research at various levels. At the most basic level, the virtual absence of adequate *in vitro* techniques is at present the main obstacle to the understanding of the fundamental mechanisms of tumour induction. Essential cellular properties like the susceptibility of single cells to neoplastic transformation, the distribution of susceptibility among cell populations having different division and differentiation potentials, the influence of initiation and promotion actions, the interplay of other cellular effects of radiation such as the loss of reproductive integrity, must somehow be reflected at each dose level in the final number of tumours scored. However, there is no means at present to resolve these phenomena in highly organized tumour models *in vivo* and, consequently, it is to be expected that the analysis of the dose-effect relationships may not be of great help in the study of basic mechanisms.

90. In chapter II it has been shown that after the event of neoplastic transformation has already taken place in one or a few cells, several permissive, enhancing or inhibiting actions may still affect the capacity of these cells to give rise eventually to visible tumour nodules. Thus, the balance between cell production and loss in a transformed clone, the complex immunological relationships between the antigenic stimulation by the newly established neoplastic cells and the immunological surveillance system of the host, and the promoting or inhibiting actions of the endocrine system influence the final yield of tumour nodules and, consequently, the general shape of the dose-effect relationships. Information on these actions is however very inadequate at present to evaluate their relevance.

1. Theory and practice

91. Modern concepts of quantitative radiobiology, as well as practical considerations, must be taken into account when dose-effect relationships for tumour induction are discussed. The most firmly defined concepts of quantitative radiobiology are reflected in the classical hit-and-target "theories". According to these the occurrence of the biological effect under study requires 1, 2 or n "hits" in some "sensitive volume", or "target", of the biological system under consideration.

92. In figure I(a) theoretical dose-effect curves are shown for cases where 1, 2, 10 or 50 events in one target are required for the occurrence of the effect. The doses in figure I are expressed as multiples of $D_{50\%}$, which is the dose inducing effect in 50 per cent of the irradiated specimens. The one-event curve is exponential. However, if the required number of events is larger than 1, the character of the curve changes and it becomes clearly of the sigmoidal type.

93. When the effect under study is the loss of a cell's reproductive ability, the same type of information is represented in the form of the so-called "inactivation curves," plotting the probability of the effect W as a function of dose. If, instead of the probability of the effect, the probability of its absence is plotted ($S = 1 - W$), "survival curves" are obtained. Usually survival curves are shown on semilogarithmic plots. The sigmoidal characteristic of multi-event curves persists in semilogarithmic plots and the "shoulder" of such curves becomes more clearly expressed the larger the values of n.

94. The most interesting part of the dose-effect curve is that corresponding to low doses. In that region of dose, simple one-event exponential relationships are approximately linear and multi-event curves can be approximated by power functions or by power function combinations. These approximations are known as polynomial functions (fig. I(c)).

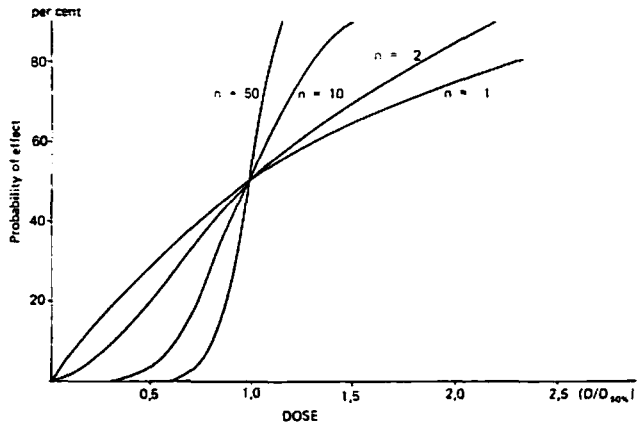
95. An intrinsic peculiarity of multi-event curves is that observable increases of the effect occur only after some definite dose, which can be called the "quasi-threshold dose". In fact, the probability of effect is a monotonically increasing function of dose but the increment up to the "quasi-threshold" is negligible.

96. For a dose-effect relationship with a real threshold, there is no observable effect for doses up to the threshold. In practice, however, the difference between threshold and quasi-threshold relationships cannot be defined. In the case of tumour induction the distinction is made impossible by the high frequency of spontaneous tumours. The variability of tumour incidence in the control group is for example shown on figure I(c) by the shaded band. In this case even a two-event curve would appear to have a threshold D_{qt1}.

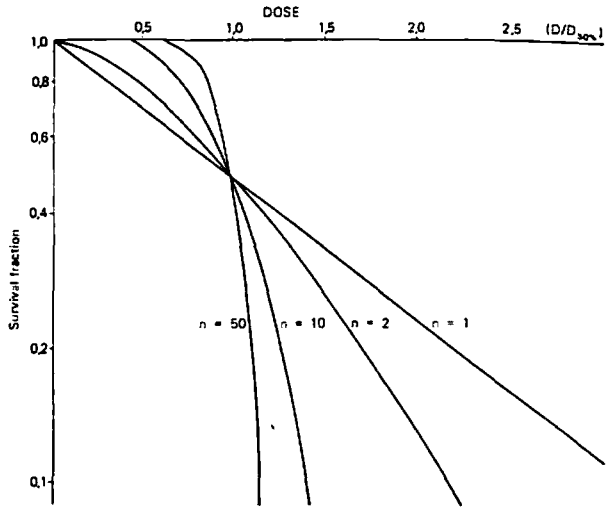
97. Different from the multi-event models discussed so far are the multi-target models which have been used to describe the survival of mammalian cells. These models postulate that several targets must be affected to kill the cell, each of the targets having to receive at least one hit (event) in the most simple case. A "survival" curve corresponding to such a model is shown in figure I(d). The curve is also sigmoidal, but in contrast to the curves shown in figure I(b), this curve becomes exponential for large values of dose. The slope a of the exponential part in a semilogarithmic plot can be characterized by the inactivation dose, D_0 ($D_0 = 1/a$). The intersection of the extrapolated exponential part of the curve with the unity survival line can be considered as a quasi-threshold dose, D_{qt}.

98. Sometimes the relationship between dose and effect is presented in a log-log plot (fig. I(e)). Apart from the fact that this presentation permits the inclusion of a wide range of values, it also emphasizes the variation of the effect at low doses. From the slopes of the straight lines in the log-log plot it is possible to assess the exponents of the power functions involved. In the simplest case a slope of 45° corresponds to an exponent = 1.

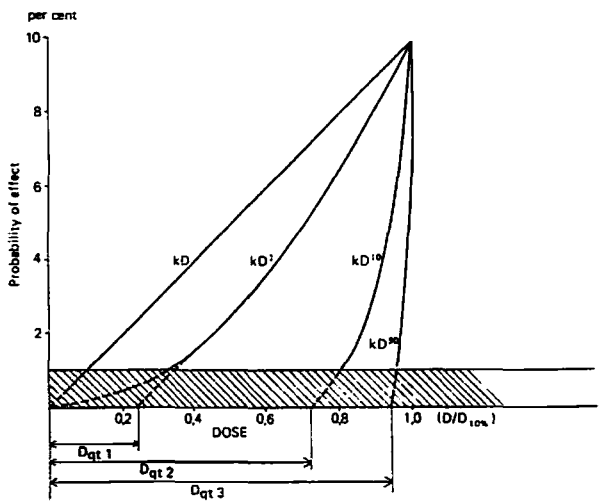
99. It is also of interest to consider a simple model postulating two types of competing processes: *(a)* the process leading to the effect (in this case to tumour); and *(b)* the process leading to cell death and therefore avoiding the manifestation of the effect. The combination of both processes, working in the opposite



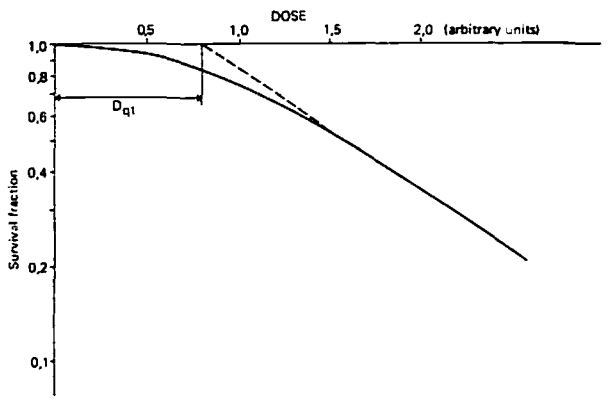
(a) Dose-effect curves relating probability of an effect to the dose expressed as a ratio of dose administered to that yielding 50-per-cent probability of occurrence (D_{50}); n is the number of events required to produce the effect



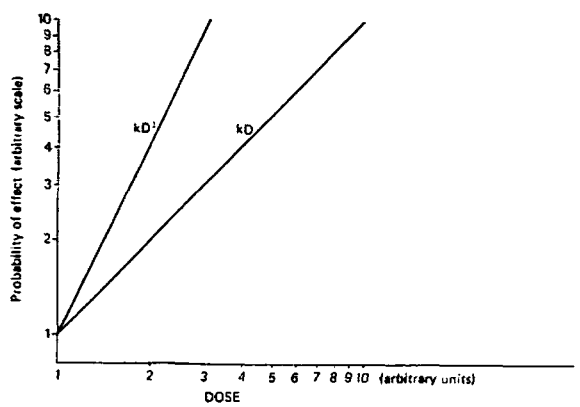
(b) Dose-effect curves relating fractional cell survival to the dose expressed as a ratio of dose administered to that yielding 50-per-cent survival; multi-event model; n is the number of events required by a cell to lose its reproductive capacity



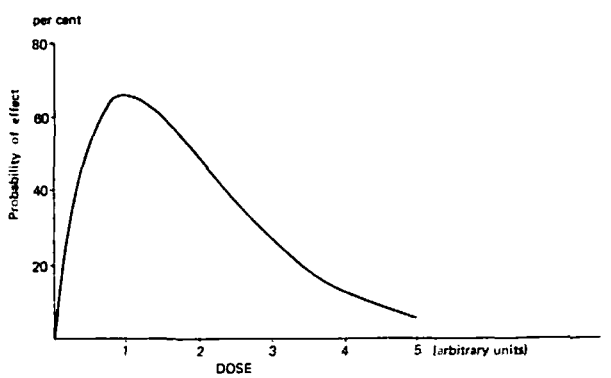
(c) One- and multi-event dose-effect curves approximated by polynomial functions of the power of dose = 1, 2, 10 and 50. "Quasi-threshold" doses for 2, 10 and 50 event curves are also shown (D_{qt1}, D_{qt2} and D_{qt3}, respectively). Dose (abscissa) expressed as a ratio of dose administered to the dose required for 10-per-cent probability of the effect to occur. Shaded area: spontaneous (control) incidence of the effect studied



(d) Typical dose-effect curve for the multi-target model. Fractional survival (ordinate) expressed in a logarithmic scale. D_{qt} = dose corresponding to the "quasi-threshold" reflecting presence of the so-called "shoulder"



(e) Polynomial dose-effect curves (see (c)) presented in a log-log plot for the effects occurring with probability proportional to the first and second power of dose (one- and two-event phenomena, respectively)



(f) Theoretical relationship between dose and probability of an effect (e.g. cancer) resulting from two competing processes: induction of malignant transformation in a cell and killing of the transformed cells.

Figure I. Theoretical dose-effect relationships for effects at the cellular level

directions, leads to a dose-effect relationship with a maximum of the type shown in figure I(f). As will be discussed in paragraph 143, a number of dose-effect relationships found for carcinogenesis are similar to the curve of figure I(f).

100. In experimental work, the most frequently used indicators of carcinogenesis are the mean number of tumours per animal at time t, $R(t)$, and the frequency of animals with at least one tumour, the "incidence" $I(t)$. If Poissonian statistics apply, the two quantities are related by the simple expression

$$I(t) = 1 - e^{-R(t)} \qquad (1)$$

When the two quantities are much smaller than one, it may be assumed that $R(t) \approx I(t)$, and both indicators of carcinogenesis become identical.

101. Several statistical approaches can be used for treating experimental results (571, 613). One approach (613) for the calculation of the mean number of tumours per animal at time t is

$$R(t) = \sum_{i=1}^{n} \frac{1}{N(t_i)} \qquad (2)$$

where t_i is the time of appearance of the tumour number n in the experimental group, and $N(t_i)$ is the number of animals still under observation at time t_i.

102. Either of the quantities $R(t)$ or $I(t)$ may be plotted as a function of dose. $I(t)$ can be obtained out of $R(t)$ by the use of equation (1). The validity of this equation requires that all scored tumours be real primary tumours. To avoid possible complications, it is possible to score only the first tumour of the animal. However, in practice it was shown that there are no statistically significant differences between the results obtained when all tumours are scored or when only first tumours are scored (620).

103. In this review the results will be expressed mainly in terms of the total tumour incidence over lifetime I in per cent. It must be mentioned that such an approach leads to some loss of experimental information, namely the temporal variations of $I(t)$. Another approach is possible (620) where the indicator is the time-integral of $R(t)$

$$P(t) = \int_0^t R(\tau)\, d\tau \qquad (3)$$

By such an approach it is possible to collate all the experimental data for the period of observation. Furthermore, the number of tumours are weighted according to their time of appearance. The quantity $P(t)$, called the "effect period", is expressed in "tumour-days" and represents the mean number of tumours per animal multiplied by the time the animal bears these tumours. The use of the "effect period" should, in principle, decrease the statistical uncertainty of the experimental results.

104. For any approach which may be selected it is also necessary to take account of the influence of the following factors: the competitive risk of other diseases or causes of death (see paragraph 13), the modifications introduced by spontaneous death of the animals or by the serial sacrifice techniques (see paragraph 19), and the possible effect of radiation-induced life-span shortening (see paragraphs 26 and 27). Additionally, the question of tumour acceleration *versus* tumour induction needs separate consideration.

105. A widespread observation which refers generally to all radiation-induced tumours is that their latency time, that is the time from irradiation to the occurrence of the actual neoplastic changes, usually follows some function of the dose and frequently is shorter in highly irradiated animals. Since radiation-induced neoplasms cannot be distinguished from spontaneous ones, the shorter latency could conceptually be interpreted in some cases as an acceleration of the occurrence of the neoplastic diseases rather than as a true induction of new tumours. These phenomena are readily analyzed using curves describing the age-specific cumulative rate of incidence of tumours (see paragraphs 24 and 25), and there are two extreme conditions that may be observed in comparing intact and irradiated animal groups under such circumstances.

106. In the first condition, typical of animal strains having a particularly low spontaneous yield of some tumour type, radiation may act by inducing this tumour within a confined time period, and a good example may be the thymic lymphoma of the C57BL mouse. The probability of observing such a tumour will be essentially zero in the normal animals at all times, but in irradiated animals this probability will gradually increase around the time which is characteristic for appearance of the thymic lymphoma (200-400 days) (330) and will eventually reach a plateau well before the irradiated animal population is extinguished. Clearly, if the appearance of tumours is very unlikely before the normal animals die, the tumours arising at the characteristic age in the irradiated animals may be attributed to a true induction phenomenon brought about by the radiation treatment.

107. The second extreme condition is observed, on the contrary, in animal strains having a high probability of neoplasia in the control population, as, for example, with the mammary neoplasia in the ageing Sprague-Dawley rat. In this case the cumulative incidence of tumours in normal animals will continuously increase with time and this rise will eventually be terminated by the extinction of the whole animal population. In the irradiated animals, however, the rise of the curve will begin at an earlier age and will proceed roughly parallel to or somewhat steeper than the control curve, until all animals die. Such a phenomenon might be interpreted as a radiation-induced anticipation or acceleration in the occurrence of tumours that might possibly have appeared in the normal animals, had they lived long enough.

108. The experimental situations to be dealt with in practice rarely conform to these extreme examples, since, depending on the dose of radiation, both effects of induction and of anticipation or acceleration can

often be observed, even in the same tumour system. For the purpose of comparing the overall effect of different doses or of different experimental treatments, the parameter of importance is the total number of tumours expressed by a population of animals from the time of irradiation to death. An alternate indicator would be the "effect period" referred to in previous paragraphs. In any case, the comparison between groups is often made difficult by the fact that their life spans may be different and also depend on the radiation dose.

109. A reduction of the latency time with irradiation appears to be a rather general phenomenon in most tumour systems studied in many animal species and for all types of radiation. To cite only a few of the many possible examples: In the mouse, skin tumours tend to appear earlier after higher doses of low-energy electrons (285); lung tumours are accelerated but not induced in RF mice (687) and CBA mice (726); the mean ages at death of both male and female LAF_1 animals with thymic lymphosarcoma, non-thymic lymphoma, granulocytic leukaemia, hepatoma, ovarian and mammary tumours decrease progressively with increasing gamma-ray doses (688); myeloid leukaemia occurs earlier at high doses of x or gamma rays in RF mice (685); osteosarcomas (284) and ossifying fibromas (222) induced by ^{224}Ra injection show a steeper rate of induction with increasing isotope dose; the cumulative incidence of bone malignancies at death in CF1 mice after ^{226}Ra treatment is similarly increased in proportion to dose (191); bone tumours (499, 701) and carcinomas of the mucous membranes of the head (496) are accelerated in the CBA strain following intraperitoneal injection of ^{90}Sr; oesophageal cancer after local ^{60}Co irradiation shows an acceleration at increasing doses (733).

110. In the rat, skin tumour appearance is hastened by irradiation with fast electrons and alpha radiation (80) as well as with x rays and fission neutrons (312); the induction of mammary cancer in female Sprague-Dawley rats within one year of ^{60}Co irradiation is progressively accelerated by the dose administered with a possible saturation effect of 500 rad (611); fast neutron and x-ray irradiation show a similar effect within 700 days from exposure (714); the latency time of ethionine-induced liver tumours is decreased by treatment with radiation (653). In the swine, acceleration phenomena in the induction of myelo- and lympho-proliferative diseases are observed after ^{90}Sr feeding (280).

111. In the dog, alpha radiation from ^{226}Ra and beta radiation from ^{90}Sr accelerate the induction of myeloproliferative disorders and of osteosarcomas in proportion to the dose level of the two nuclides (218), and a consistent decrease of the latency time is observed for the induction of malignant tumours of the bone by a variety of bone-seeking isotopes such as ^{239}Pu, ^{228}Th, ^{228}Ra, ^{226}Ra and ^{90}Sr (163). It is to be expected that the time of evolution of the neoplastic disease and also the time of its occurrence with respect to the age of the animals should influence the precision of estimates of the acceleration as a function of dose, and in this respect rapidly killing tumours of high malignancy occurring early in the life span of the animals will produce the most reliable estimates.

2. Experimental dose-effect relationships

112. It seems appropriate at this point to examine in detail the existing data on the dose-effect relationships for the induction of the most common radiation-induced malignancies in various animal species and strains, in order to see whether and to what extent common features and trends can be identified. For this purpose published final cumulative tumour incidence data will be used. These data have inherent limitations due to the fact that corrections for intercurrent competing diseases and death were applied only in some instances. Single exposures of short duration to various types of radiation will be examined in this context, leaving the effects of other radiological factors such as radiation quality, fractionation and dose rate for consideration under separate headings. Some of the most informative experimental series to be discussed have been plotted in figures II-IX. The bars superimposed on the data points in these figures represent the standard errors of the estimates when the necessary information was available.

113. *Myeloid leukaemia.* LAF_1 mice exposed to gamma-ray doses up to 697 rad showed a corrected final incidence of granulocytic leukaemia rising from less than 1 per cent in the control to a maximum of 1.5 per cent in males at 578 rad and of 1.7 per cent in females at 223 rad. At higher doses the incidence seemed to decrease, but the changes observed were on the whole too small to allow any definite statement as to the shape of the induction curve (688). Susceptibility to myeloid leukaemia is higher in the RF strain and fairly complete data are available on the dose-effect relationship (694, 671, 685, 686) (fig. II). When several hundred male mice were whole-body irradiated with x or gamma doses in a single brief exposure early in adulthood, the incidence of myeloid leukaemia was increased from a background level of about 5 per cent to about 40 per cent at 200-300 rad and then declined gradually at higher doses to a level of about 10 per cent at 500 rad (685). In female mice susceptibility was generally lower and attained a maximum of around 20 per cent in the two most complete series available, involving thousands of animals studied by macroscopic and microscopic pathology (685, 107). The peak incidence occurred at 300 rad in one case (685) and at 200 rad in the other (107) after exposure to x rays; exposure to high-energy protons yielded a maximum at around 300 rad (107). In both cases a tendency to decrease with higher doses was reported. Other data on RF male and female mice are in general agreement with the above findings (692).

114. After 5-MeV neutron irradiation in males a plateau incidence of about 40 per cent at 200 rad and a further decline were observed. A lower peak incidence was observed in females (692). After 14-MeV neutron irradiation in female mice a monotonic rise up to 28 per cent at 400 rad was described (145). In summary, after x, gamma, proton and neutron irradiation the overall relationship between incidence and dose appears to be complex. Over the dose range of 0-200 rad of sparsely ionizing radiation the tumour yield has been reported to vary with the square of the dose (671, 685), although the presence of a linear component cannot confidently be excluded (686). Upon neutron irradiation the linear component might be prevailing at the lower doses (613),

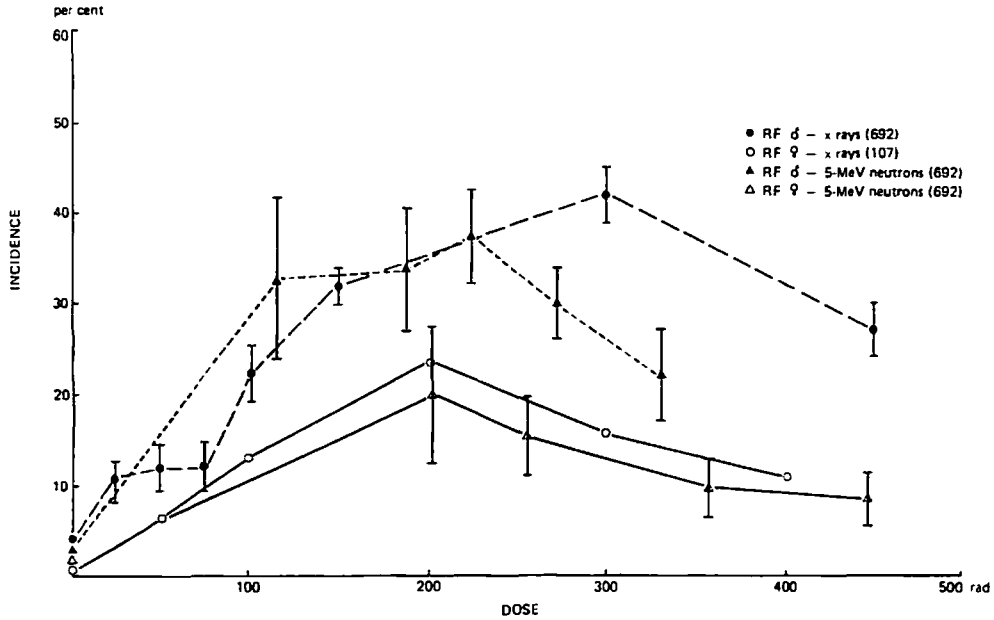


Figure II. Dose-effect relationships for the induction of myeloid leukaemia by x rays and neutrons in RF mice

but the plateau and the later decline are still observed. Some of the data (671) were analysed by Gray (233) and mechanisms were proposed to explain the rise, plateau and ensuing decline; the significance of these mechanisms will be discussed later (see paragraphs 151-154).

115. *Thymic lymphoma* (fig. III). In the RF mouse strain, the incidence of this disease shows a positive relationship with dose for both x rays and 60-MeV proton irradiation up to approximately 300 rad, which might be curvilinear both in male (694) and in female animals (107, 686). A plateau is observed at higher doses up to 400 rad of 300-kVp x rays or of 60-MeV protons (107) or 600 rad of sparsely ionizing radiation (683), but no actual decrease in incidence has been reported. In both sexes, x- or gamma-ray exposures produced a statistically significant increase of thymic lymphoma at dose levels of 200 rad or more. Less consistent effects were described in the case of 5-MeV neutron irradiation (692). After 14-MeV neutrons the incidence increased from 3 per cent in the controls to 19 per cent in the 200 rad group, with a slight decrease at 400 rad (145). The initial rise with dose might be described as approximately linear.

116. In the LAF_1 strain, susceptibility to thymic lymphoma is lower than in the RF in both male and female animals and, within the scatter of the experimental points, the corrected incidence of this tumour appeared to rise until approximately 700 rad with what might be regarded as a roughly curvilinear trend. Within the large variation of the estimates, an approximately linear rise up to a dose of about 140 rad was observed following fission neutron irradiation (688). The susceptibility to thymic lymphoma is however

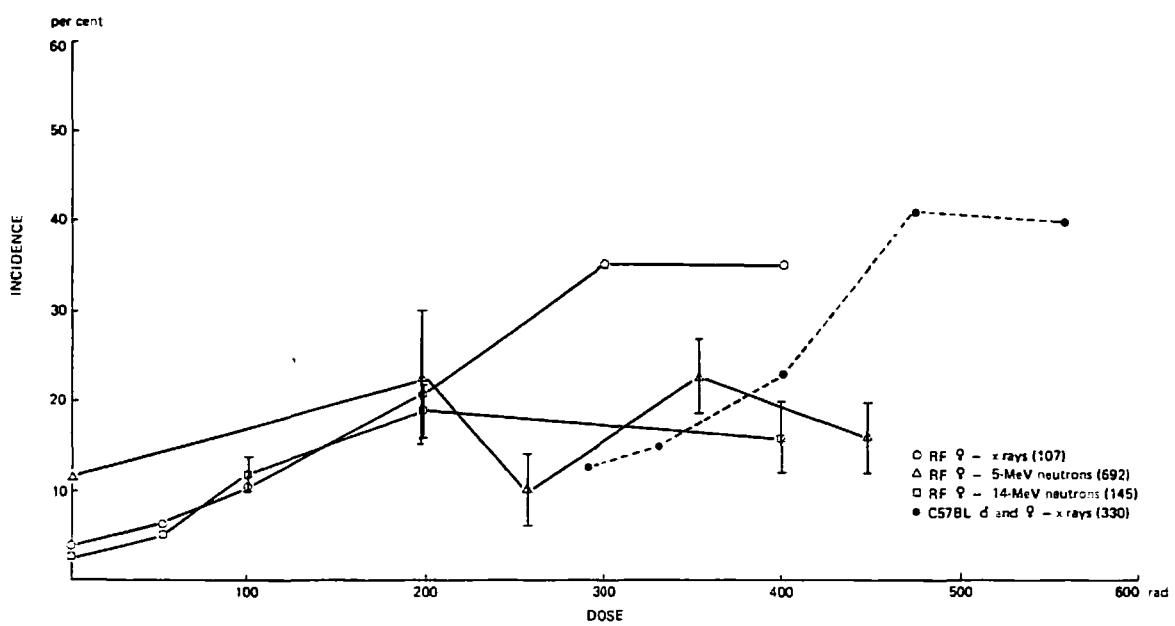


Figure III. Dose-effect relationships for induction of thymic lymphoma in RF and C57BL mice irradiated with x rays and neutrons

maximal in the C57BL mouse where the dose-effect relationship shows a curvilinear trend up to about 450 rad of x rays with an incidence of approximately 40 per cent. An ensuing plateau but no further decline is seen up to about 570 rad (330). It may therefore be concluded that the efficiency of the induction of the thymic lymphoma by sparsely ionizing radiation is greatest in the intermediate dose range between about 100 and 400 rad and lower at doses outside this range, but no clear-cut decline below the peak incidence has been reported. It seems possible that a linear rise at low doses could occur after neutron irradiation and it should be noted that neutron treatment often seems to give a biphasic response with a peak, a trough and a further rise at higher doses, which, if true, would indeed be a very difficult phenomenon to explain.

117. *Reticulum cell sarcoma and other reticular neoplasms* (fig. IV). The dose response relationship in RF female mice shows a continuously decreasing trend

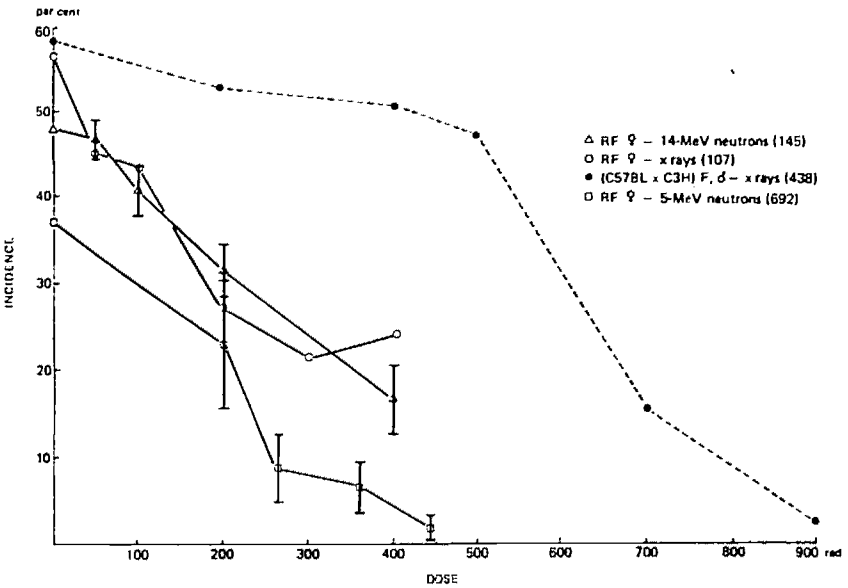


Figure IV. Dose-effect relationships for reticulum cell sarcoma and other reticular tumours in RF (female) and (C57BL X C3H)F_1 (male) mice irradiated with x rays and neutrons

from the control incidence levels of 30-50 per cent (according to various reports) to 15-25 per cent incidences between 300 and 400 rad of x rays (694, 681, 130, 466). The most complete experiment carried out with 330-kVp x rays and 60-MeV protons, suggests that the decrement might be more appreciable at low than at high doses since the incidence tends to level off at about 25 per cent between 300 and 400 rad of both radiations (107). Discrepancies in the pathological classification between non-thymic lymphomas and reticulum cell sarcomas among various workers may have contributed to the considerable variability observed between the reports cited. In the RF male the spread of results appears somewhat smaller and a linear function could possibly be fitted to all data in the interval 0-450 rad of sparsely ionizing radiation (694, 686, 681, 692, 130). The same decreasing trend with dose applies after 5-MeV neutron irradiation in both sexes (692) and after 14-MeV neutron irradiation in females (145), although the slope of the curve appears to be generally steeper with neutrons than with x rays in the same experimental series. Also in the LAF_1 strain, non-thymic lymphoma incidence varies inversely with gamma dose between 0 and 487 rad, with considerable differences between the two sexes (688). The changes induced by x rays in female (101 X C3H)F_1 mice—a strain with a particularly low control incidence of these reticular tumours— were negligible up to 750 rad (129).

118. In male mice of the hybrid strain (C57BL X C3H)F_1 having a spontaneous incidence of reticulum cell sarcoma approaching 60 per cent, radiation had a small effect on the final incidence up to doses of 400 rad of x rays, but higher doses (up to 900 rad in bone-marrow-shielded (134) or in transplanted animals (135)) produced a reduction of tumours to 3 per cent or less. It was pointed out that the final portion of the curve approached the slope of the survival curves of haemopoietic stem cells in this strain of mouse (629). Finally, although induction on non-thymic leukaemia was reported in CBA females irradiated to a dose of 500-rad fractionated x rays, it was also remarked that larger fractional doses tended to reduce the incidence of these neoplasms, an effect which would be in line with all the above data (446). It may therefore be concluded that, within a rather large strain and sex variability, both densely and sparsely ionizing radiation decrease the incidence of reticular tumours in an inverse relationship with dose. It should be pointed out that a decrease of tumour incidence with dose is a rather frequent finding in tumour model systems in which a high spontaneous incidence is encountered.

119. *Lung tumours.* In the case of lung tumours a distinction should be made between whole-body and localized irradiation. Although no complete dose-effect relationship was obtained, a lower incidence of pulmonary adenomas was reported with respect to controls (24 per cent) after treatment with 800 rad and isologous marrow infusion (8 per cent) or after whole-body doses of 290-580 rad of 8-MeV neutrons in LAF_1 mice (514). In the same strain a generally

decreasing dose-effect relationship was observed for lung tumours (essentially adenomas) up to 700 rad of gamma rays: the slope of the curve was steeper in males, which had almost five times as many spontaneous lesions as females (688). Scattered data on pulmonary tumour induction in male LAF_1 mice after single whole-body doses of 300 rad of x rays were also reported by Cole and Foley (116), while 15-MeV electron doses up to about 450 rad produced little change in the incidence of lung tumours in SAS/4 mice of both sexes (325). In the RF female mouse a decreasing trend up to about 400 rad was reported after x-ray and proton irradiation (107) or after neutron treatment at energies of 5 MeV (692) or 14 MeV (145). Some acceleration of lung tumour occurrence but no real induction was also found in RF females after 500-600 R of x rays (687). In male mice of this same strain, graded doses of x rays and 5-MeV neutrons produced an inverse relationship without any apparent difference in slope between the high- and low-LET radiation (692).

120. In an experimental series comprising 1149 male $(C57BL \times C3H)F_1$ animals, the final observed incidence of lung tumours increased from 9 per cent to 15 per cent following a curvilinear function up to 500 rad of x rays and decreased thereafter up to 900 rad down to control levels (137). After lung cancer induction had been reported in rats and hamsters irradiated on the chest with doses of 3 and 4 krad (239), a complete set of data was published more recently, obtained by localized x irradiation of RFM male mice (754) (fig. V). The incidence of pulmonary nodules and the mean number of nodules/mouse scored at 11 months post-exposure showed an increase directly related to exposure (probably following a curvilinear function) up to 1500 R and sharply declined at higher exposures, reaching control level at 2750 R. There can be no question about the significance of these latter data but they are difficult to reconcile with the previous ones obtained by whole-body irradiation in other strains or even in the same strain, since some small increase, rather than the actually observed decrease in incidence would be expected after sublethal doses. Differences in the experimental design or in biological factors could possibly justify the discrepancies (754).

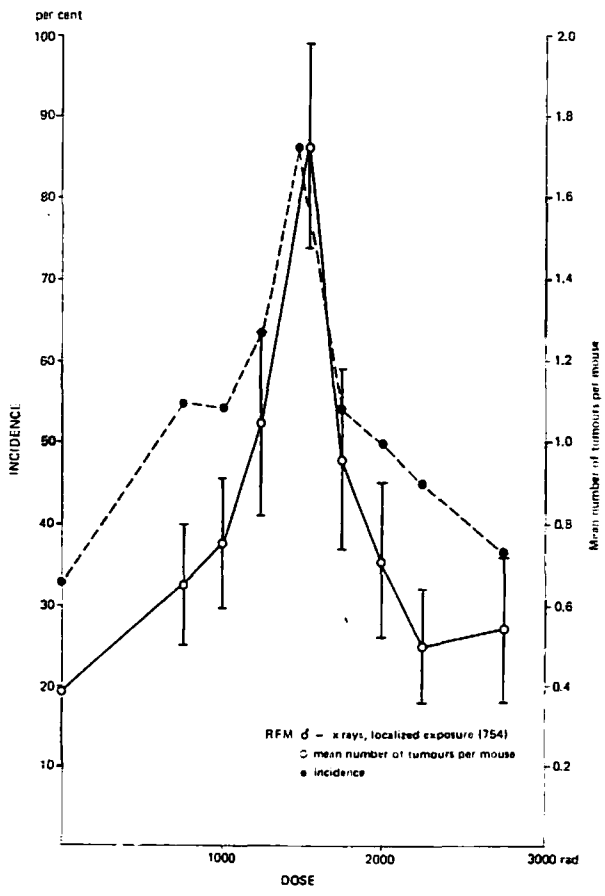


Figure V. Dose-effect relationships for induction of lung tumours in the RFM mouse

121. *Ovarian tumours.* A list of early references on radiation-induced tumours of the ovary is given by Garner (211). The data referred to are very scattered and insufficient for a reconstruction of a tentative dose-effect curve. The incidence of ovarian adenomas increased consistently, over the control level of 11 per cent in LAF_1 mice, after doses of 800 rad of x rays (36 per cent) or of 290-580 rad of 8-MeV neutrons (52 per cent) (514). More complete data were published on gamma-irradiated animals of the same strain (688), showing an increased incidence to about 40 per cent at around 350 rad and an ensuing fall up to 700 rad. The data in the low-dose range seem insufficient to draw conclusions as to the initial shape of the dose-effect relationship. Similar considerations apply to the dose incidence curve for tumours of the ovary in SAS/4 mice (385) and in ddY/F or C3H/Tw animals (355).

122. In the RF strain (fig. VI) acceleration and increased induction of ovarian tumours by single doses of 500-600 rad of x and gamma rays was first reported by Upton, Kastenbaum and Conklin (687). In a more extensive experiment performed with 14-MeV neutrons, the incidence of ovarian neoplasms markedly increased from 15 per cent in the control group to a maximum of 62 per cent at 100 rad, with a plateau at higher doses. The induction rate between 0 and 50 rad might be higher than between 50 and 100 rad (145). The latter observations are in contrast with the results of lower-energy neutrons (692), although in the same series, doses as low as 50 rad of gamma rays consistently increased the incidence of ovarian neoplasms. In this case the dose-incidence relationship followed a sigmoid curve, rising from the control level of 9 per cent somewhere between 25 and 50 rad and reaching a maximum of 45 per cent at 200 rad, declining at increasing doses. Oscillations over a generally decreasing trend were observed further up to 700 rad (692).

123. A similar large increase of ovarian tumour induction was shown in a recent report where 300-kVp x rays and 60-MeV protons were used in single whole-body exposures. The dose-effect curves produced by the two radiations were almost superimposable and showed an extremely high susceptibility without apparent threshold at doses of 50 rad, a further but smaller rise to 100 rad, and a gradual decrease from 100 to 400 rad, the highest dose used (107). Finally, seven different dose-effect relationships at different dose rates were reported for the induction of ovarian tumours by gamma-ray irradiation of the BALB/c mouse. At the highest dose rate of 112 rad/day, a curvilinear

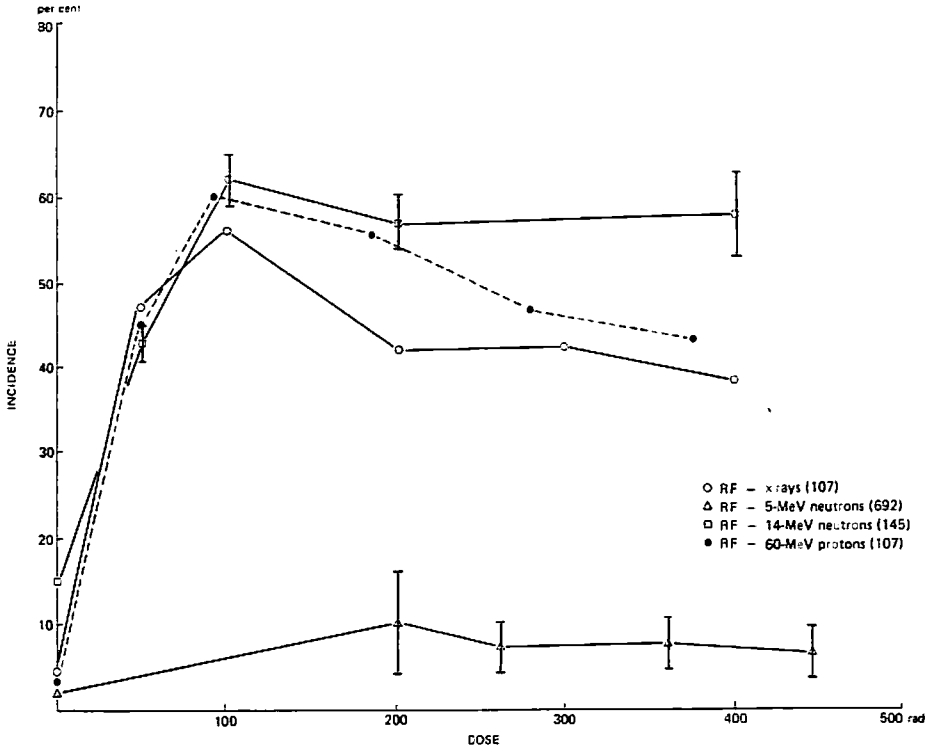


Figure VI. Dose-effect relationships for induction of ovarian tumours in the RF mouse

relationship was found between zero and about 200 rad, with an ensuing plateau up to 390 rad. The non-linearity of the dose-incidence curve was confirmed by the observation that at constant exposure time, the incidence varied as the square of the dose (750).

124. In conclusion, the great majority of the reports seem to confirm that the dose-effect relationship for the induction of ovarian tumours has a very steep rise for doses of radiation between 0 and 50 rad. The maximum yield of tumours is then obtained between 100 and 200 rad and a decrease follows at higher doses. Biological factors such as the strains and radiological variables such as LET and dose rate influence the induction of ovarian tumours.

125. *Mammary tumours.* The RF mouse has a low spontaneous incidence of mammary tumours and is not easily susceptible to the induction of this neoplasia: histological observations on more than 2500 female mice irradiated with x rays or fast protons failed to show any consistent trend with doses up to 400 rad (107). The hybrid $B6CF_1$ mouse also has a low susceptibility to mammary tumour induction by gamma rays or fission neutrons (206). In the LAF_1 mouse, on the other hand, the incidence of breast sarcoma declined monotonically from 15 to 0.5 per cent between 0 and 700 rad, while the observed incidence of carcinoma increased from 1 to 5.5 per cent at around 350 rad and then decreased up to the highest tested dose of 700 rad. The high correlation between mammary sarcoma and granulosa cell tumours of the ovary observed in these studies (688), as well as other data in rats (138) point to a strong influence of hormonal factors in the induction of mammary tumours (see paragraphs 68 to 73). Limited or lifetime whole-body exposures to gamma rays in doses of 30-2100 rad and exposure rates of 0.062-121 R/day were carried out on RAP mice, possibly harbouring a mammary tumour virus. In accordance with other data (see paragraph 70), a similarity of the dose range for ovarian and mammary tumourogenesis but no correlation between the two types of neoplasia was found in this strain. Complex systemic changes in the induction of breast tumours were confirmed (736).

126. The Sprague-Dawley rat is the animal where most studies on the dose-related induction of breast tumours have been carried out (fig. VII). Female animals irradiated with x or gamma rays at the age of about 40 days, were examined during about one year after irradiation for the presence of mammary nodules, which were then excised and histologically diagnosed (614, 611). A fairly good linear relationship with exposure of the observed percentage incidence of tumour-bearing animals or of the cumulative number of tumours per rat was found in the range of 16-250 R for both types of radiation. From this observation it was concluded (50) that a threshold did not exist, the data extrapolating satisfactorily to control incidence. The linear relationship holds (with different slopes) for both the adenofibromas and the adenocarcinomas (611). The response to fission neutrons was examined in the same tumour model system with a range of doses and in this case the animals were followed for the entire life span. The observed percentage incidence of rats carrying mammary neoplasia rose from 48 per cent to 78 per cent after only 5 rad of neutrons and then a plateau with values up to 87 per cent at 150 rad was observed; a further increase of the dose to 250 rad produced a small decline to 76 per cent. A close similarity of response to similar doses of x or gamma rays was also confirmed in these experiments (714). Other data on mammary carcinogenesis in various strains of rats irradiated with single doses of x rays or fast neutrons are to be found in

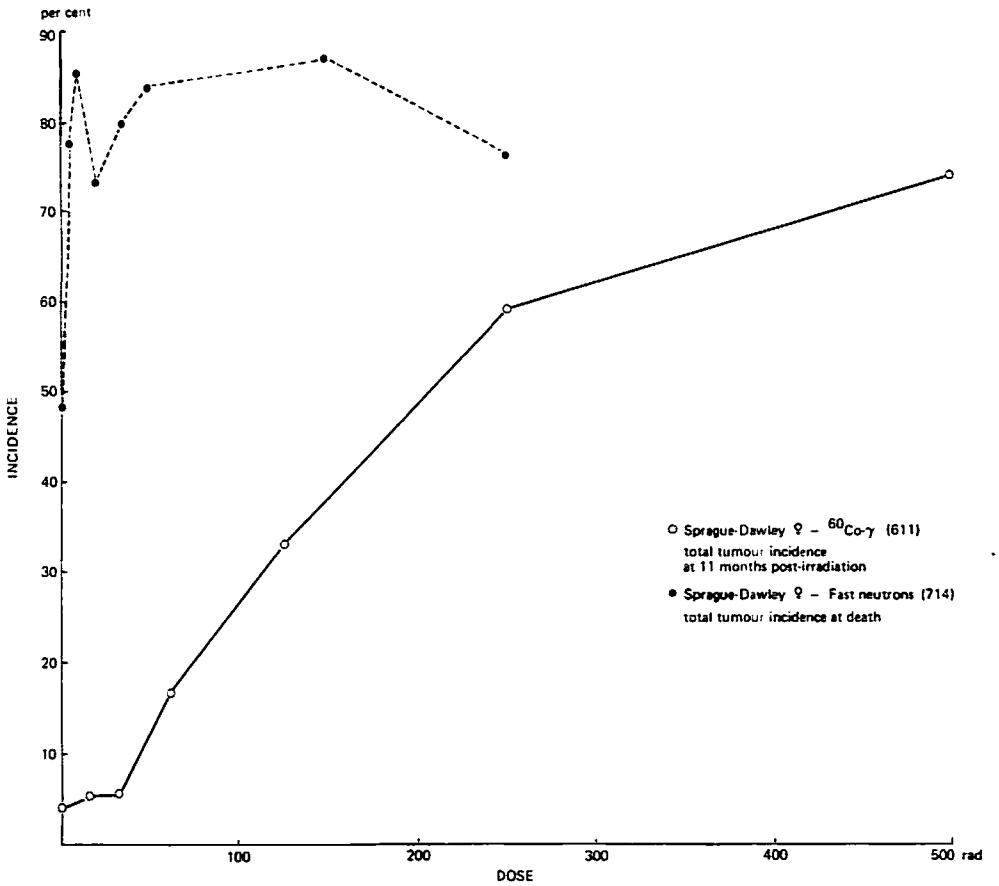


Figure VII. Dose-effect relationships for induction of mammary tumours in the Sprague-Dawley rat irradiated with cobalt-60 gamma rays or neutrons

a paper by Shellabarger (607) or will soon become available from experiments in progress (63, 605). In the dog a lower yield of mammary tumours (10 per cent) has been reported (621, 579) in animals irradiated with a mixed gamma-neutron field, with respect to a control incidence of 40 per cent.

127. The evidence reviewed allows the conclusion that the dose-effect relationship for mammary tumour induction in the rat after x or gamma irradiation appears to be linear down to very low doses. In the mouse the neoplastic response of the mammary gland is more variable, and depends on the strain and on tumour histotype.

128. *Kidney tumours.* Low incidence of kidney neoplasia after whole-body irradiation with x, gamma or proton radiation up to doses in the mid-lethal range have been frequently reported in various mouse strains (351, 36, 688, 107), but no reasonably complete dose-effect relationships have yet been produced. Similarly, in the rat (which is more susceptible to these tumours) most information was obtained after single or only a few doses of x rays (366, 569, 570, 36). A thorough series was however carried out by Maldague (422) with Wistar male rats irradiated locally with x-ray doses ranging from 570 to 14 250 rad (fig. VIII). Spontaneous kidney carcinogenesis in this strain is absent and doses up to 570 rad were ineffective in inducing tumours. A few tumours appeared at 855 rad and the dose incidence curve rose sharply thereafter up to a maximum at around 1700 rad, which may be considered in this strain as the optimal carcinogenic dose, producing tumours in 84 per cent of the animals. The dose-effect relationship declined at doses in excess of 1700 rad down to incidence levels of 5 per cent at the highest dose. Both benign and malignant lesions followed the same general pattern. The initial part of the dose-incidence curve for this type of neoplasia appears therefore to be of the sigmoid type, with a very definite threshold at about 500 rad.

129. *Skin tumours.* The frequency of skin neoplasms in LAF_1 or RF mice irradiated with x or gamma rays, protons and neutrons is only affected to a small extent by radiation up to the mid-lethal dose range (688, 692, 107). Higher doses of localized irradiation are necessary to induce this type of tumour. In CBA mice irradiated with low-energy beta particles, tumours were observed after doses of 750 to 12 000 rad (285). A plot of the number of tumours per irradiated area of skin gave dose-effect relationships of different shape according to the type of the tumours (benign or malignant) and to their origin (dermal or epidermal). Although for some tumours a linear non-threshold response would not be incompatible with the data within the experimental errors, curvilinear relationships seem to fit the data better. A plot of tumour yield per rad, allowing for dose distribution in the skin layers, shows a very rapid increase up to 1650 rad and a considerable fall-off at higher doses for both dermal and epidermal neoplasms (285). A dose-effect curve for the induction of skin tumours in Swiss mice was reported by Albert *et al.* (7) in the range of 500-4000 rad of fast electrons. The initial

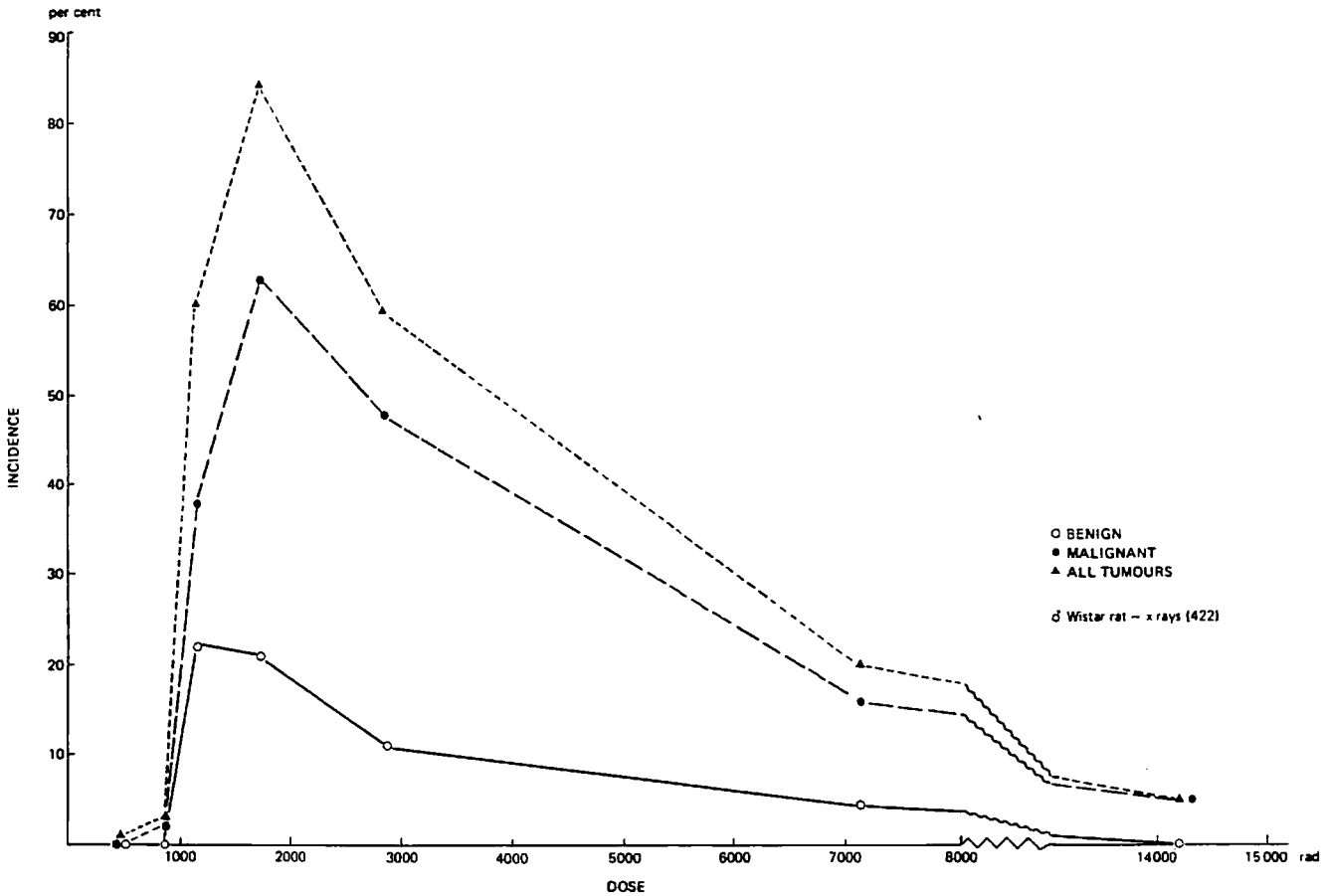


Figure VIII. Dose-effect relationships for induction of kidney tumours after x irradiation of the Wistar rat

shape of this curve appears to be highly curvilinear for both epithelial and connective tissue tumours. There is a peak at around 2500 rad for the induction curve of epidermoid carcinomas, while sarcoma induction constantly rises up to the highest dose. The problem of the relative susceptibility of mice and rats to skin tumour induction has also been discussed in this paper, and the relatively lower susceptibility of the mouse has been attributed to its failure to develop tumours of the cutaneous annexes, which are the predominant type of neoplasms in the irradiated rat skin. Dose-effect relationships for the induction of skin tumours in CD-1 mice by accelerated helium ions of various energies have also been reported (369).

130. In Sprague-Dawley rats whole-body irradiated with two doses of x rays or fast neutrons, a considerable incidence of skin tumours was reported (up to 60 per cent of animals with tumours, starting from a control incidence of about 18 per cent). The data were analyzed carefully on the basis of age-specific incidence rates, but they are insufficient to establish detailed relationships with the dose and type of radiation (94). Good dose-effect curves were obtained, on the other hand, in CD male rats irradiated with the cyclotron-accelerated helium nuclei in the dose range of 210-6950 rad and with high-energy electrons from 910 to 12 300 rad (80) (fig. IX). Tumour incidence per animal increased at the lowest doses of electrons as the fourth power of the dose, levelled off between 2 and 4 krad and gradually declined at doses up to 9 krad, which produced severe skin ulceration. The dose-effect curve for alpha particles showed the same general shape but was displaced towards the origin of the abscissa by a factor of about 3. The low number of tumours obtained at the lowest doses did not allow a definitive evaluation of the initial shape of the dose-effect curve for alpha particles.

131. It seems reasonable to conclude therefore that the initial slope of the dose-effect relationship for the induction of skin neoplasia by sparsely ionizing radiation in mice and rats is curvilinear and that a power function with smaller exponent may apply to densely ionizing particles. A progressively decreasing yield of tumours is observed in both cases at very high doses.

132. *Tumours of the liver and of the gastro-intestinal tract.* Partial data on the occurrence of hepatoma in LAF_1 mice have been published repeatedly (514, 515, 122, 117, 119). Complete dose series were reported by Furth, Upton and Kimball (210) and by Upton *et al.* (688). The latter paper shows that the control incidence of hepatoma in males (22 per cent) is gradually depressed to about 2 per cent after 700 rad of gamma rays from a nuclear detonation. In the female animals, on the contrary, the background incidence of 1.5 per cent is raised to about 8 per cent at 368 rad and again brought back to control levels at 697 rad. The occurrence of hepatomas in the SAS/4 strain is 10 per cent in males and 2 per cent in females and is hardly changed at all by 15-MeV electron doses up to 460 rad (385). In the RF mouse the spontaneous incidence of liver tumours is very low (less than 1 per cent in females and less than 2 per cent in males); radiation does not

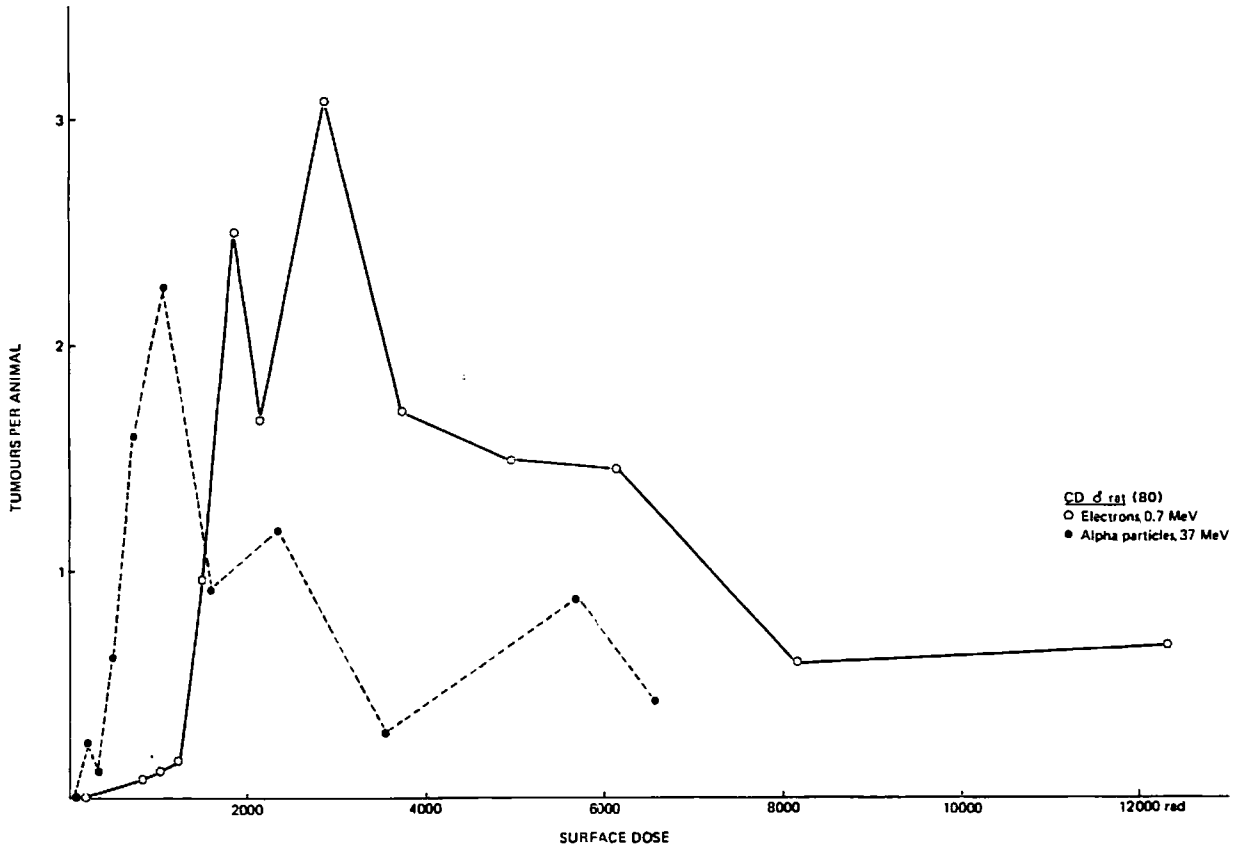


Figure IX. Dose-effect relationships for skin tumour induction in CD rats irradiated with electrons and alpha particles

appear to affect it to any appreciable extent (145, 692, 107). Radiation-induced hepatic tumours in the rat have also been described by Zatsarnaya and Bykorez (760).

133. High localized radiation doses to the various organs are usually required to elicit the formation of tumours of the gastro-intestinal tract (212, 263, 666), but the observation of some tumours at lower doses is not infrequent. The dose-effect data for the occurrence of hyperplastic and tumoural changes of the gastro-intestinal tract in whole-body irradiated mice were reviewed by Cosgrove *et al.* (131) and by Upton *et al.* (684). By combining the three series available of LAF_1 mice exposed to A-bomb radiation (688) and to x rays or neutrons of various energies (514) and CF_1 mice exposed to radiation from nuclear detonations (409), it was concluded that the incidence of gastro-intestinal tumours increased up to a maximum of 5 per cent as a curvilinear function of the dose for both sparsely and densely ionizing radiations, the latter being definitely more effective. Intestinal polyps in dogs and rats following exposure to mixed gamma-neutron beams or feedings of ^{210}Po or ^{144}Ce were also reported, mostly occurring in the large intestine with a tendency to malignant evolution and showing different latencies in the two animal species (367).

134. *Tumours of the bone.* Bone tumour production has been reported in the mouse after partial-body x irradiation of the hind limbs of 70-day-old CF1 females. Results at 442-575 days (194) and at 650 days post-irradiation (185) showed a linear correlation between dose and osteosarcoma incidence (expressed as tumours/mouse) in the exposure range of 250-1000 R. In the rat, irradiation of the knee joint with a radium-iridium source induced a total of 34 osteosarcomas appearing between 300 and 800 days in 116 mice with doses of 3000 rad. The incidence of neoplasia was higher in animals treated with growth hormone; thyroxine treatment reduced the induction period (96, 28). The histological changes and the induction of bone tumours were followed in the hind limbs of 257 rats exposed to x-ray doses of 500-3000 rad. In some cases the highest dose was subdivided into 3 or 6 equal fractions. The greatest number of tumours was found with 3000 rad; one tumour arose in the 500 rad group (32).

135. Male F_1 (Marshall X August) and August strain rats, 6-8 weeks old, were irradiated with 3000 rad of x rays on the right limb or with doses of 1000 rad each at 0, 2 and 4 weeks, or with 6 doses of 500 rad each at 0, 1, 4, 5, 6 and 7 weeks on both limbs, and then observed for 27 months. Twelve tumours were found in 34 rats of the first group within 6 and 12 months; the group receiving 3 doses (15 rats) had only 1 bone tumour; in the group receiving 6 doses, 7 bone tumours developed in 34 irradiated limbs. No significant difference between the 3000 rad group and the 500 X 6 rad group was seen at 27 months (177). A 4-per-cent incidence of osteosarcoma was reported in 125 Wistar rats whole-body irradiated with 600 rad (222) and about 5 per cent of osteogenic tumours were also found in parabiosed rats receiving an x-ray dose of 1000 rad (732). Finally, osteosarcomas developed in rabbits irradiated by gamma rays (500-1400 rad) or by fission neutrons (200-600 rad). The induction period was shorter with neutrons and an RBE value of about

three was proposed. The data however appear too scanty to allow any conclusion about the form of the dose-effect relationship (286). Additional scattered data on bone tumour induction under various conditions may also be found in Upton *et al.* (694, 688, 692), Darden *et al.* (145), Hori *et al.* (274) and Clapp *et al.* (107).

136. *Tumours of the thyroid.* This organ can be irradiated both by external radiation and by the administration of iodine radioisotopes. Data on dose-effect relationships are available in several animal species. In the mouse an extensive series of papers on thyroid damage by radiation reported by Walinder and colleagues have been summarized in reference 723. In the CBA strain, adult animals experience a dose-related increase of the frequency of thyroid tumours following x-ray exposures (500, 1000 and 1500 R) and ^{131}I administrations (1.5, 3.0 and 4.5 μCi). Within this dose range the induction curve is probably biphasic, with a shallow slope at very low doses and an increased slope at higher ones (724). For very high doses, the carcinogenic effect probably passes through a maximum (389, 159). It seems likely that thyroid carcinogenesis may be initiated by radiation and promoted by hormonally stimulated epithelial hyperplasia (725, 104) and that the initial shape of the dose-incidence curve may be the result of the interplay of these factors. The anatomical and functional processes related with ageing of the thyroid gland in CBA mice were described by Walinder *et al.* (727). Other data on mouse thyroid carcinogenesis can be found in Upton *et al.* (688, 692).

137. In the rat, thyroid tumours have been described by Doniach (155, 156, 157, 162) and by Lindsay's group (390, 391, 215, 546). These papers deal with the dose-effect relationships, fractionation effects and comparative studies of x ray and ^{131}I-irradiation effects. A comparison of the carcinogenic effects in rats of ^{131}I (3.2 to 125 μCi, five administrations) and ^{125}I (administered activities four times larger) has been reported by De Ruiter *et al.* (150). Animals were sacrificed two years after injection for scoring of the effects, but the ratio of the administered activities of the two isotopes was found to be too low. In fact, the maximum of lesions (hyperplasia, cysts and tumours) was obtained in the ^{131}I group with the lowest activity injected, while for the ^{125}I the peak induction was at 80 μCi. Some data on tumour induction in dogs irradiated with x rays or ^{131}I were reported by Michaelson *et al.* (443).

138. *Tumours of other organs.* The incidence of these is usually extremely low. As there are few relevant reports referring to varying irradiation conditions and animal strains, and as the doses tested are very few, it is impossible to derive dose-effect relationships for these neoplasms. Often all the control and all the irradiated animals are grouped irrespective of dose in order to reach statistically significant numbers, and under these conditions it is possible to observe in many cases an increased incidence in the irradiated animals. However, the actual significance of these changes is often doubtful. Since reference to these data, however heterogeneous, is sometimes useful, the following list of relevant papers which have been reviewed, subdivided according to the various organs, is provided.

139. Tumours of the pituitary gland have been reported by Upton *et al.* (694, 688, 692) and by Clapp *et al.* (107); of the uterus by Upton *et al.* (692) and Clapp *et al.* (107), of the salivary glands by Glucksmann and Cherry (214) and Takeichi (650); of the adrenal glands by Upton *et al.* (694, 688, 692); of the prostate by Hirose *et al.* (265); of the testis by Upton *et al.* (694, 688), and of the brain (412, 423). Tumours of the harderian gland have been reported by Upton *et al.* (694, 688, 692), by Darden *et al.* (145) and by Clapp *et al.* (107). Most recently Fry *et al.* (206) have reported a considerable increase of harderian gland tumours in $B6CF_1$ mice with doses in the range of 0 to 788 rad of ^{60}Co gamma rays and 0 to 240 rad of fission neutrons in single irradiations. The dose-effect relationships were of the type described in paragraph 143. Analysis of total solid tumour incidences at *all sites*, sometimes as a function of dose but more often after one or a few doses, may be found in the following publications: Upton *et al.* (694, 692) Nowell and Cole (514), Lindop and Rotblat (385), Cole and Nowell (119), Reincke *et al.* (560), Kohn and Guttman (350), Samuels *et al.* (584), Castanera *et al.* (94), Hulse (286) and Vesselinovich *et al.* (706).

3. Conclusions

140. It appears very difficult indeed to identify a common trend of the incidence as a function of dose for all the tumour systems examined experimentally and reviewed in the present report. However, if the discussion is confined to the most commonly observed neoplasms, three major patterns of response have been documented.

141. The first pattern refers to those tumours for which the spontaneous incidence is not significantly changed by the radiation treatment in the low to mid-lethal dose range. This is typically the case for myeloid leukaemia in LAF_1 mice (688), for pulmonary and liver tumours in SAS/4 (385), for mammary tumours in the $B6CF_1$ strain (206) and for mammary and liver tumours in RF female mice (107). The lack of neoplastic response in this dose range does not necessarily imply that these tumours cannot be radiation-induced, but may simply mean in some cases that the dose applied was too low for detectable induction. Actually, increasing the dose to the lung in RF mice well over the mid-lethal range (which gives an uncertain or even a negative response) results in the appearance of adenomas with a peak incidence at 1500 rad of x rays (754) (fig. V). The question remains open in such cases as to the real shape of the dose-effect curve (threshold or quasi-threshold type) but such questions are only of theoretical relevance since for all practical purposes virtually no tumours of this type will be induced at the low doses of interest.

142. In other cases, tumour incidences have been described as having a negative slope in the dose-effect relationship which sets in at the lowest doses and then generally proceeds up to the highest doses tested (700-900 rad). This pattern of response is found for the reticulum cell sarcoma and the non-thymic lymphoma in RF (694, 686, 681, 692, 145, 107) (fig. IV). LAF_1 (688) and $(C57BL \times C3H)F_1$ (438) (fig. IV), for

pulmonary adenoma in RF (692, 145, 107) and LAF_1 (515, 688) and for hepatoma and mammary sarcoma in LAF_1 mice (688). A radiotherapeutic effect on the cells which will eventually give rise to the tumours (in the absence of any significant concomitant induction of new tumours by radiation) is usually invoked to explain the negative slope of the relationship (447, 671). This may well be the case for systemic tumours, where such an interpretation at the single-cell level is supported by ancillary evidence concerning the slope of the inactivation curve of possible target cells (233, 438), but cell inactivation data favouring a similar interpretation in other cases is lacking. A discussion on this point will be found in paragraph 151.

143. In the majority of cases, the dose-effect relationship is of a complex type and shows an initial rise at increasing radiation doses, a peak or a plateau at some intermediate dose levels and in many cases, a final decline of incidence of the type as shown in figure I(f). The relationships for the induction of myeloid leukaemia and thymic lymphoma in RF (694, 671, 684, 692, 145, 107), C57BL (330) and LAF_1 mice (688) (figs. II and III), of ovarian tumours in LAF_1 (514, 688), SAS/4 (385), RF (145, 692, 107) (fig. VI) and BALB/C mice (750), of mammary carcinomas, fibromas and sarcomas in LAF_1 mice (688) and in Sprague-Dawley rats (614, 611, 712) (fig. VII), of kidney tumours in Wistar rats (422) (fig. VIII), of skin tumours in CBA (285) and Swiss mice (7) and in Sprague-Dawley (94) and CD rats (80) (fig. IX), of hepatomas in LAF_1 (688) and SAS/4 females (385), and of lung tumours in RFM (754) (fig. V) and in (C57BL X C3H)F_1 mice (135), conform to this general pattern. Systemic and non-systemic, benign and malignant neoplasms, mostly with rather low spontaneous incidences are included in this category. Although a large variability of this typical pattern is observed according to the various systems tested and to the quality of radiation, the doses at which the initial rise becomes detectable and the shape of this rise, the dose range where the peak incidence is observed and the height of the peak, and the presence and slope of the final negative part of the curve may usefully serve to characterize the various responses.

144. Regarding the shape of the incidence curves at low doses, myeloid leukaemia has been tested down to the level of 25 rad of x rays in the RF mouse; if one considers the observed points from that dose up to the peak incidence, the shape may be described as curvilinear (671) (possibly quadratic (233)) without excluding a linear component (685). There are however quite substantial variations in x ray inducibility between male and female RF mice (685), and neutron doses have not been tested below 50 rad in the female, which is less inducible (145), or below 130 rad in the male (692). Judging from these series, it would appear possible that the initial rise in incidence with dose may be more prompt after neutron irradiation than after x or gamma rays in both sexes. The dose-incidence curve for thymic lymphoma, up to the peak incidence, may be described as being of a curvilinear or possibly quasi-threshold type, but there appears to be considerable variation between strains, with a faster rise between 300 and 500 rad of x rays in the C57BL (330), a more gradual increase between 25 and 300 rad of low-LET radiation in the RF (694, 686, 692, 107) and a very slow rise up to 700 rad in LAF_1 mice (688). Where neutrons have been tested (688, 692, 145) (in these cases the observations do not extend below 50 rad) the curve might possibly be described as becoming more linear.

145. The incidence of ovarian tumours is greatly increased with respect to controls by a dose as low as 50 rad in RF mice, and for this reason it appears difficult to attribute any shape to the response curve at lower doses (692, 108). In the only instance where the effect of 25-rad gamma radiation was estimated, the point did not appear significantly different, although lower, than the control value (692) and a plateau was already apparent at 100 rad. Neutrons yielded conflicting results: 50 rad of 14-MeV neutrons produced a substantial increase in incidence, but a beam of 5-MeV neutrons seemed rather inefficient in producing ovarian tumours in the same strain of animals.

146. The only instance in which a linear dose-effect relationship has been reported in the interval of 17-250 rad is the early-appearing mammary neoplasia of the Sprague-Dawley rat (611) although, even in that case, some departure from linearity was apparent at the lowest doses (575). In the same system, but on late-appearing tumours, the hypothesis of linearity has been questioned (714) at least for neutron irradiation with doses as low as 5 rad. This observation does not exclude, however, linearity of the response below this limit, although it would indicate a much steeper rise of the induction curve upon neutron treatment. In the case of kidney, skin and lung tumours after local sparsely ionizing irradiation (422, 285, 80, 7, 754), the response at low doses would be termed in general to be of the curvilinear type, while alpha-particle irradiation data show less curvature than the electron irradiation curve in the same system (80).

147. To the extent that simple biophysical models could be applied to a biologically complex phenomenon like tumour induction, the above conclusions would appear to be in general agreement with the observations made for a variety of radiation effects on cellular and subcellular structures, according to which the dose-effect data at low doses (delivered at high dose rate) can be fitted by power functions of the dose, with lower exponents for high-LET radiation than for sparsely ionizing radiation (13). They are also in agreement with the arguments of Kellerer and Rossi (340), according to which the interplay of primary biophysical events produced by at least two low-LET particles is required to initiate biological effects, whilst one single densely ionizing particle might suffice to produce these effects. Such a hypothesis implies predominant quadratic kinetics as a function of dose in the case of low-LET radiation and linear kinetics in the case of high-LET radiation. Actually, an analysis of mammary tumour induction in the Sprague-Dawley rat (575)—the only case where a linear relationship has been claimed down to very low dose levels of low-LET radiation—suggests that linearity, although consistent with the data points, may be fortuitous and that more than one cell may be involved in the origination of these tumours.

148. In the most complete set of data reported for transformation of hamster cells *in vitro* by x rays (57), the power function which would best fit the

experimental points in the interval 1-10 rad would have an exponent of less than one, although a linear dependence of induction on dose would not fall outside one standard deviation of the data. Thus, even at this very simple level, the expected quadratic shape of the response to x rays cannot be confirmed, probably due to heterogeneity of the cell population to transformation (an inherent characteristic of the cell system used). Population heterogeneity might also explain the paradoxical results of dose fractionation in this same system (58), where dose splitting is shown to enhance rather than depress (hypothesis of a quadratic relationship) or leave unaltered (hypothesis of linearity) the transformation phenomenon. These data emphasize the difficulties in the interpretation of the transformation effect even at the rather simple level of *in vitro* cells and therefore indirectly point to the conclusion that similar analyses in *in vivo* systems may at present be unwarranted.

149. Concerning the doses at which the maximum incidences in the dose-effect relationships of reticular systemic tumours are found, the peak incidence for myeloid leukaemia is generally observed at doses of 200-300 rad with both high- and low-LET radiation in the RF mouse; at higher doses, a declining incidence is usually observed. For thymic lymphomas the peak appears at somewhat higher doses (300-700 rad) and a subsequent negative slope is rarely seen, probably because of the post-irradiation bone-marrow syndrome which can reduce substanstially the survival of the animals at these high doses (694). The peak incidence seems to occur generally at lower doses with densely ionizing radiation. This feature is compatible with the theory of dual radiation action and with the model of two competing processes discussed in paragraphs 50 to 66. Peak incidences of between 40 and 60 per cent at 100-200 rad have been reported for ovarian tumours in the most sensitive RF and BALB/c strains, and within each strain there appears to be no special tendency for the maximum to occur at lower doses with fast-neutrons or alpha particles than with x or gamma irradiation. This phenomenon seems, on the contrary, well documented for mammary and skin tumours in the rat, in spite of the great diversity of the doses at which the peak incidence occurs (400-500 rad and 3000 rad of low-LET radiation, respectively). Maximum incidences in the dose range of 1500-1700 rad are found for lung and kidney tumour induction by local x-ray treatment.

150. In conclusion, there appears to be no obviously identifiable correlation between the susceptibility to tumour induction and the character of the dose-effect relationships resulting from low- or high-LET irradiation; neutrons and alpha-particles have a tendency to produce peaks at lower doses than x or gamma rays in all systems. The height of the peak is also not clearly influenced by the radiation quality but may rather be regarded as an intrinsic biological characteristic of the particular system, having little correlation with radiation quality.

151. The declining trend in tumour incidence at high doses of radiation could be qualitatively explained by taking into account two concomitant dose-dependent phenomena: on the one hand, the effect of transformation tending to increase with increasing doses according to some linear or curvilinear function (see paragraphs 144-146; and, on the other hand, the inactivation of the reproductive integrity of potentially transformed cells, which also increases with dose following complex kinetics which in mammalian cells are usually described by a multi-target one-event type of equation (170).

152. A quantitative analysis of this hypothesis was carried out by Gray (233), who tested data on the incidence of myeloid leukaemia in RF mice (671) and more recently by Mole (459) and by Mayneord and Clarke (430). Gray found that at the low doses the induction of tumours would proceed in this system with the 2.28 power of the dose; the loss of reproductive integrity of the transformed cells at high doses could reasonably be described by a survival curve having an extrapolation number of 2 and a D_0 of 120 rad.

153. However, a similar model fitted to the skin tumour data of Hulse (285) by Hulse *et al.* (288) showed that a dose-squared function would adequately describe the initial rise, but the D_0 resulting for potentially tumorous cells from the declining portion of the curve would be 20 times greater than the 135 rad reported by Withers (741) as the sensitivity of the clonogenic cells in irradiated mouse skin. Fitting other linear or two-hit kinetics to the induction process did not essentially change the conclusions of the analysis, nor could the high D_0 be explained on the basis of cell migration from non-irradiated areas of the skin. Very similar arguments have also been developed by Barendsen (25) for his system of tumour induction in the skin and might also be easily applied to other results on kidney carcinogenesis (422). It might further be added that if the negative slope at high doses does in any way reflect the sensitivity to killing of the potentially transformed cells, one should expect a steeper decline after high-LET radiation than after x or gamma rays in the same system, which is by no means an obvious or a consistent finding in all the data reviewed.

154. Finally, the data of Borek and Hall (57) indicate that the plateau and the decline in incidence of the transformed clones with dose is independent of the killing of potentially transformed cells, since it is observed also after correcting for loss of reproductive integrity. This would imply, therefore, that transformed cells have a higher sensitivity to radiation with respect to normal cells in the same population. On the basis of these data (which are anyway of doubtful applicability *in vivo:* see paragraphs 147 to 148) the hypothesis of a balance between transformation and killing of potentially tumorous cells should therefore be considered under a different perspective. Granted that tumours must by definition arise from cells which have retained their reproductive ability, the peculiar shape of the induction curve would show that at the highest carcinogeneic doses an excessive amount of damage may render the transformed cells more sensitive than their normal counterparts to radiation-induced loss of mitotic integrity. In this respect, the plateau and the declining portion of the curve would not reflect the intrinsic sensitivity to killing of the transformed cells, but rather the differential sensitivity of these cells with respect to the normal clonogenic population.

C. RADIATION QUALITY AND THE EFFECTS OF DOSE RATE AND DOSE FRACTIONATION IN CARCINOGENESIS

1. The concept of RBE

155. In addition to absorbed dose, the quality of radiation, sometimes specified as the linear energy transfer (LET) of the charged particles (primary or secondary) in the medium of interest, is also an important physical factor in radiation carcinogenesis. This factor was discussed in the 1972 report of the Committee (670). In experimental work the concept of relative biological effectiveness (RBE) is commonly used to characterize the quantitative differences of effect brought about by different types and energies of radiation. For this purpose, the RBE of one kind of radiation compared to another is defined as the inverse ratio of the doses of the two kinds of radiation that produce the same biological effect (563), under the stipulations that *(a)* the basis for comparison should be the absorbed doses, and *(b)* other radiological or biological factors known, or suspected, to influence the response of the irradiated system should be the same.

156. It is clear however that since the nature of the biological effect, the nature and physiological conditions of the irradiated system, the dose level, the distribution of the dose in time and within the irradiated system affect the RBE estimates, the strict definition given above would imply a very detailed knowledge of the exposure conditions and of the system and effect under study before reference could be made to true RBE values. Short of this knowledge, an "equal-effect ratio" could be derived, defined as the ratio of two doses producing equal responses, when undetermined factors, other than the LET of the two radiations compared, would affect the biological response (563).

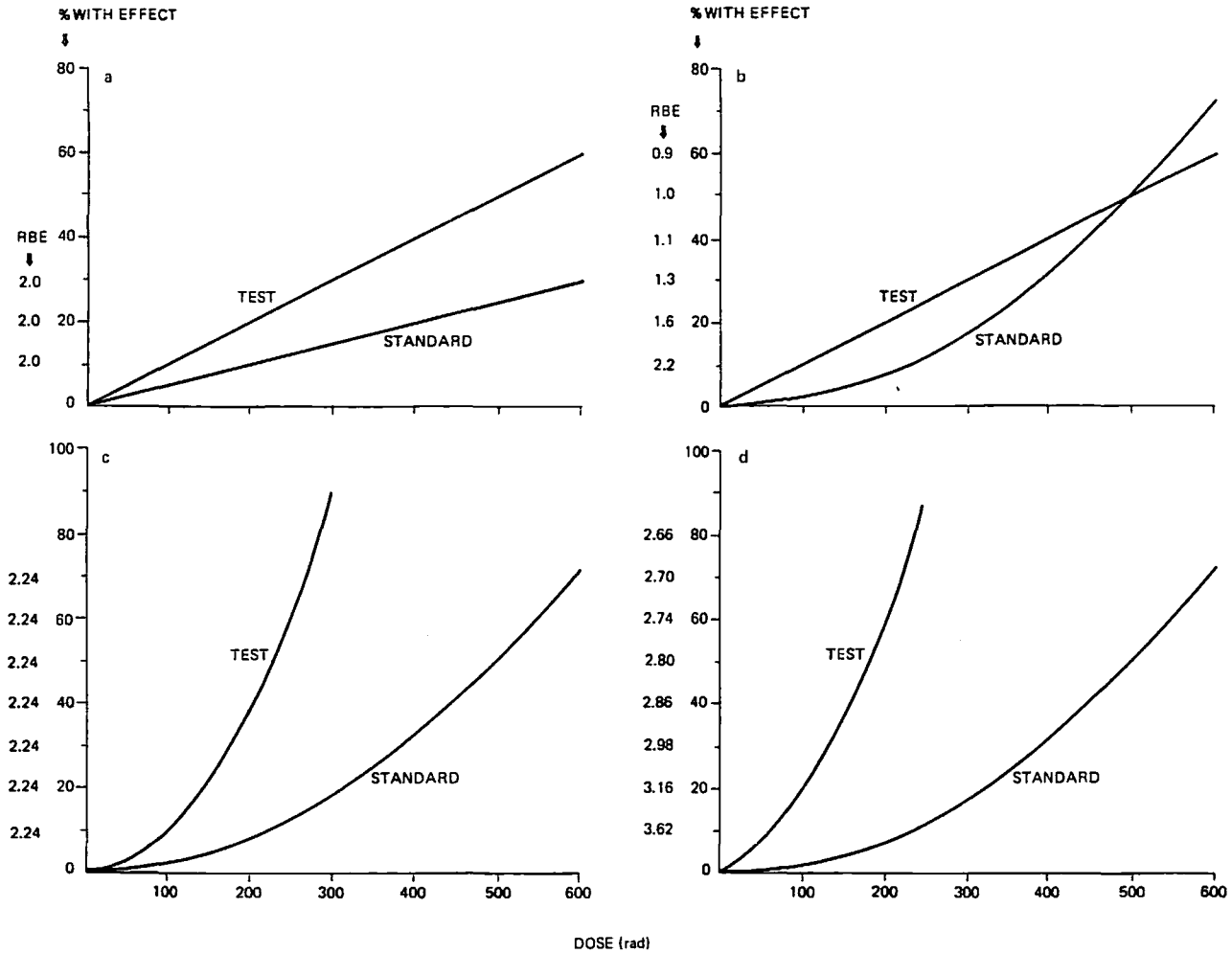
157. Actually, the vast majority of the so-called RBE values for tumour induction published in the literature and reviewed in the present report fall into this latter category of estimate, since only seldom have the physical parameters of exposure and the biological characteristics of tumour system studied been determined or reported with the necessary degree of precision. This observation refers especially to the use of inappropriate end-points or of uncorrected estimates of tumour incidence for the calculation of the dose ratios and to the lack of a systematic exploration of the dose-effect relationships within a large range of doses in most of the systems studied. All this might largely account for the scatter of the values reported. Chapter I of this Annex discussed the appropriate methodology for RBE studies. The influence of the shape of the dose-effect relationship on the RBE values, especially at the low doses of interest in radiation protection, was already discussed in the 1972 report of the Committee (670), where the rationale for the interpretation of the relevant RBE changes was reviewed. Although additional experimental data have since become available, these concepts have not been sufficiently considered in general terms (except in references 340 and 430) and need review and systematization in the light of the most recent theoretical acquisitions.

2. Dose-RBE relationships

158. Figure X, taken from the 1972 report of the Committee (670), illustrates schematically the influence of the shape of the dose-effect relationships on the change of RBE values with dose. It appears that when the effects brought about by the two radiations under comparison follow simple linear (case *a*) or second-order (quadratic) polynomial kinetics with different second-order coefficients (case *c*), there is no reason why the RBE should differ at different levels of dose and/or effect. However, when the effect of the standard radiation follows a curvilinear shape and the test radiation produces a linear dose-effect relationship (case *b*), the RBE will tend to increase at very low doses; at higher doses the RBE would gradually decrease and might in principle even become less than 1 above the intersection of the two curves. However, as was mentioned in paragraphs 91 to 103, simple polynomial approximations are only valid at the lower doses. A similar increase of RBE values at low doses, but without a tendency for inversion at high doses, will take place when the effect of the standard radiation follows a second-order polynomial relationship and the test radiation produces a dose-effect relationship with an appreciable first-order component in addition to the quadratic term (case *d*).

159. The most recent theoretical analysis of the concept of RBE has been carried out in the context of the theory of dual radiation action (340) which leads to rigorous mathematical formulations and, even for complex effects such as tumour induction, may account for the shape of the dose-RBE relationships. Concerning the RBE changes as a function of dose rate, it is customary to explain the experimental data on the assumption that high- and low-LET radiation can operate through single-track and multi-track mechanisms, with a very high probability of multi-track phenoma in the case of the low-LET radiation. As the dose rate decreases, the probability of simultaneous or near simultaneous multi-track events for sparsely ionizing radiation also decreases and only the single-track component remains effective. The RBE would then tend to a high limiting value which is the same as the limiting value of the ratio of the initial slopes of the dose-effect curves (563). The loss of efficiency at very low dose rate is comparatively smaller for the high-LET than for the low-LET radiation, and therefore the RBE increases towards a limiting value that would correspond to the RBE at low doses.

160. The mathematical formalism for the dependence of effect on dose and on RBE in the presence of inter-track phenomena, as a function of the irradiation time and of the recovery time of the irradiated system, has been recently worked out on the basis of the theory of dual radiation action (340). The relations holding for constant irradiation times and for constant dose rates are given, and the pitfalls in interpreting RBE values at constant low dose rates as being due exclusively to single-event mechanisms are also discussed. Data on RBE of different radiations in various tumour model systems are examined in the following paragraphs. The values of RBE pertaining to high and low dose rate will be considered separately for those systems where sufficient data are available.



(a) First-order (linear) polynomial curves with the same intercept but with different slopes

(b) Standard radiation, second-order (quadratic) polynomial; test radiation, first-order polynomial

(c) Second-order polynomial curves defined by only two terms, the intercept a (which in this case equals 0) and the second-order term cx^2, but with different second-order coefficients c

(d) Standard radiation, second-order polynomial defined by only the intercept and the second-order term; test radiation, second-order polynomial defined by the intercept, and the first- and second-order terms, $y = a + bx + cx^2$

Figure X. Influence of character of dose-effect curves on RBE (670)

161. Concerning the induction of tumours of the reticular tissues, when myeloid leukaemia was induced in RF mice, the RBE of fast neutrons (1, 5 and 14 MeV) compared with x and gamma rays was shown to vary with dose and dose rate. For acute exposure in the dose range of 25-450 rad, the neutron RBE was estimated to be not appreciably different from 1 (145, 693, 692), while at low dose rates an unequivocal increased relative effectiveness of the neutron treatment (perhaps by a factor of 10) was reported, owing to the greatly reduced yield of tumours in the animal groups irradiated with sparsely ionizing radiations (692). Treatment of the same strain of mouse with 60-MeV protons appeared slightly less effective than irradiation with 300-kV x rays in the interval of 50-200 rad, but at higher doses the effectiveness of the two radiations was very similar (107).

162. Thymic lymphoma incidence was also examined in the course of the same experimental series (145, 692, 107). At the highest dose rates, the RBE of neutrons of all energies was not significantly greater than 1 at all doses tested, but 60-MeV protons tended to be less effective than x rays at doses of 300 and 400 rad. At low dose rates the efficiency of the low-LET radiation treatments decreased by two to three times and a corresponding increase of the neutron RBE was observed (692). As already pointed out (see paragraph 142), other reticular tissue neoplasms such as non-thymic lymphoma and reticulum cell sarcoma show an inverse relationship of incidence with dose, with x, gamma, neutron and proton irradiation. In view of the inhibitory effect of the radiation treatment and due to very pronounced variability introduced by biological factors (see paragraphs 80-82) the RBE calculation would be here of limited interest.

163. The different shape of the dose-incidence curves for the various classes of leukaemia seen in the rodent, the different times at which the leukaemic syndromes occur, the distortions introduced on the final incidence estimates of the late-appearing leukaemic syndromes by the early-appearing ones, and the frequent lack of appropriately corrected incidence data account for the

difficulties in generalizing meaningful RBE values for all leukaemias considered together. In cases where such comprehensive analyses have been attempted, 60-MeV protons appeared slightly but consistently less effective (0.80-0.65) than 300-kV x rays in the interval 100-400 rad, but microdosimetric and biological considerations could not account for this difference and would not permit in any case extrapolation of such data to larger animals (107).

164. Observations on the mortality and pathology at death were carried out on hybrid mice irradiated with 200-kVp x rays (0-200 rad) or with 400-MeV neutrons (0-84 rad) at comparable dose rates. No differences were observed in the longevity, which would suggest an upper limit to the RBE for life-span shortening of approximately 2.5. Similar conclusions were also drawn with respect to the induction of all types of leukaemias and of other solid tumours (136). Preliminary data on a large RBE experiment on C57BL mice have been published by Mewissen and Rust (442). The dose range was between 3.2 and 47.2 rad of reactor fast neutrons and between 18 and 141 rad of ^{60}Co gamma rays. A spontaneous spectrum of tumours including a major proportion of reticular tissue was established in control animals and modulation of this spectrum by the radiation treatment was observed, particularly in the reticular tumours. Dose-effect relationships for tumour appearance were non-linear and the radiation-induced changes in tumour spectra seemed to be related more to different intercompetitive processes, rather than to probabilistic random events. No numerical RBE factors were however provided. In conclusion therefore, as far as neutrons are concerned, their RBE appears to be about 1 in the range of a few tens to a few hundred rad at high dose rates; at low dose rates the tendency is towards an increase of the RBE by a factor of 2-10, according to the particular type of leukaemia and the particular dose rate examined.

165. In RF mice, the incidence of lung adenomas has a negative trend with dose which is not appreciably different in groups irradiated with 300-kVp x rays or 60-MeV protons (107); fast neutrons at various doses and dose rates caused a greater reduction in incidence of these neoplasms than gamma rays (692).

166. The RBE for the induction of ovarian tumours by neutrons in the RF strain cannot be established with certainty: in one series (145) 14-MeV neutrons appeared no less effective than x or gamma rays, whilst in other experiments (693) lower energy neutrons appeared to be very inefficient for the induction of ovarian neoplasia. In a more recent report by the same group of workers (692), RBE was studied as a function of dose and dose rate, and similar results were found, with the exception that tumours appeared in a significantly increased number after only 2 rad of neutron irradiation delivered at the dose rate of 0.004 rad/day. If this observation is a spurious one, then the RBE for neutron carcinogenesis of the ovary could be low; but if it were confirmed, it might imply that the absence of tumours at higher doses and dose rates (neutrons) could be due to excessive injury or life-span shortening due to the treatment. The latter would be then in favour of a very high RBE value for ovarian carcinogenesis by 1-MeV and 5-MeV neutrons. The RBE for x rays and fast protons for this same effect was rather similar at all doses tested, with a possible higher efficiency between 100 and 400 rad for protons. However, for both radiations the maximum incidence was seen already at 50 rad, suggesting that down to this dose level the efficiency of the two radiations under comparison is not appreciably different from unity.

167. The RBE for the induction of mammary neoplasia in the rat following acute irradiation has been the object of considerable attention. The 1972 report of the Committee (670), in examining the older RBE data for this tumour, commented on their technical heterogeneity. Actually, although the same animal strain was used in all the experiments, the most extensive results on low-LET irradiation were obtained in one laboratory on 40-day-old rats by scoring the neoplastic response at about one year post-irradiation (for a comprehensive analysis of the low–LET data see Shellabarger (611)). The neutron irradiations, on the other hand, were performed in another laboratory on animals 2-3 months old, with lifelong observations (708, 712). The differences in the scoring technique account for the fact that the background incidence of mammary neoplasia in non-irradiated rats is negligible in the first case and approaches 50 per cent in the other. In addition, the use of data uncorrected for competing risks, probably did not alter greatly the final estimates of tumour induction in the first case, since only 4 per cent of the rats had died at all doses within the observation time of one year (611), while in the neutron series it seems likely that the calculation of appropriate final incidence values might have changed the conclusions to some extent.

168. There is no doubt that if one considers the data produced by the ^{60}Co gamma treatment, which are reported as being linear in the interval of 16-250 rad (611), and the data of the fission neutron series (where a dose as low as 5 rad produced a near-maximum effect (714), and one calculates the ratio of doses producing the same neoplastic effect, one finds very high values of the RBE. However, comparing the results of 5 rad of fission neutrons and 100 or 300 rad of x rays by the same lifelong technique of scoring shows that at all times from irradiation to death the curve describing the percentage of rats bearing tumours for the neutron-irradiated group is intermediate between the curves following 100 and 300 rad of x rays (714). Thus, RBE values of between 20 and 60 could be applicable to the data.

169. The problem of RBE for breast tumour induction in the rat was discussed recently at the Symposium on Biological Effects of Neutron Irradiation (43), where the results of the two groups of scientists active in the field were updated and compared. Long-term observations on animals irradiated with neutron doses of about 2 rad were matched by the results of 100 rad of x rays, implying an RBE of about 50. A non-linear "step function" of the neutron dose-effect relationship between 2 and 20 rad was also reported, the explanation of which, except for the possibility of statistical fluctuations, seems rather obscure (709), especially since no such trend was found by the second group of workers in an experimental series extending down to 0.1 rad of neutrons (613).

170. These latter data were thoroughly analyzed by means of dose-effect relationships based on the time-integral of the tumour incidence rate *P(t)* (see paragraph 103) for the two radiations under comparison (0.43-MeV neutrons and 250-kVp x rays). In good agreement with previous analyses (575), the neutron dose-effect relationship showed an effect proportional to a dose power of less than 1, an observation interpreted to imply that the induction of neoplasia in this particular animal system might be due to the interaction of a number of cells, rather than to the transformation of an individual cell developing into a tumorous clone. The RBE approached values of 100 at the lowest neutron dose of 0.1 rad and of about 10 at the highest dose used, 6.4 rad. Thus, the earlier discrepancies found in the analysis of the breast tumour system by the two laboratories were apparently reconciled, at least to the extent that at the very low neutron doses the RBE would attain extremely high values, as the theory of dual radiation action (340) would predict.

171. However, the biological peculiarity of this tumour system should be emphasized, since radiation acts in this case essentially through an acceleration of tumour appearance, rather than by the induction of new neoplasms. There seems to be agreement about increasing values of the RBE with decreasing doses, but whether the above conclusions would also apply quantitatively to all other tumour systems remains to be established by new experimental evidence. An equal effect ratio of 1.5 between ^{60}Co gamma rays and 2.2-GeV protons for the induction of breast neoplasia has also been reported (620), following a pattern qualitatively similar to the induction of this tumour by other low-LET radiations and well within a range of RBE values reported for different cellular and functional end-points. Finally, the RBE of ^{3}H administered internally as compared to gamma rays from ^{137}Cs given externally at similar dose rates was found to be around 1.8 for the yield of mammary tumours in rats between 13 and 19 months after exposure (475).

172. No data are available for the breast tumour system on the changes of RBE as a function of the dose rate, except for the facts that after gamma irradiation at exposure rates of 10 R/min or of 0.03 R/min there is no sparing effect of the low dose rate in the incidence of mammary fibroadenoma, but a lower incidence of adeno-carcinoma. The total breast tumour response is however unaffected (612). Thus, since at the relatively high doses used the overall low-LET radiation effect is not changed, one should not expect consistent changes in the RBE because the predominantly linear component in the neutron dose-effect relationship would not be expected to change with dose protraction. Similarly, at the very low dose rates, for which, according to the theory (340), the inter-track interaction is negligible by comparison with the intra-track effects, one should not expect the RBE values to exceed those which apply for the acutely delivered very low doses.

173. Another tumour system where there appears to be enough data for some analysis of RBE is the skin tumour. Scattered information on the induction of this neoplasia by neutrons and x rays in the rat has been reported by Jones *et al.* (312) and in the mouse by Lippincott *et al.* (394) after proton and alpha-particle irradiation, but this information is unsuitable for deriving RBE values. A fairly complete dose series in the rat has, however, been reported (80) following irradiation with cyclotron-accelerated helium nuclei or with monoenergetic electrons, which allows some estimate of an RBE for skin tumour induction. If the RBE is calculated in this system (see figure IX) according to the displacement of the rising portion of the two curves, then a value of 2.9 is obtained. Since there is the suggestion that the initial slope of the alpha-particle curve is greater than that of the electrons, at very low tumour incidences of between 0.1 and 0.2 tumour/rat appreciably higher values (possibly about 5) might be calculated. The authors themselves point out, however, that the significance of the experimental points at these low levels of induction is questionable in view of the very low number of tumours involved. A range of RBE values dependent on dose and dose rate can be estimated from the data of Fry *et al.* (206) on harderian gland tumours. By comparing the irradiations with fission neutrons and ^{60}Co gamma rays, an RBE value of about 12 may be inferred.

174. A number of values have been obtained from other improperly called RBE studies in various animals and tumour systems, and they are reported here mainly for the sake of completeness. It should be pointed out, however, that in these cases the effectiveness ratio of the radiation is often obtained by dividing the level of effect induced by similar doses, instead of dividing the doses for equal effect. In addition, these data refer mainly to single acutely delivered doses in the range of some hundreds of rads and therefore they do not allow any generalization relating to the changes of RBE with dose and dose rate.

175. In the mouse, RBEs of between 2 and 3 were obtained between 250-kVp x rays and fission-spectrum neutrons for the induction of kidney tumours (118), gastro-intestinal carcinoma (514) and hepatomas (118). Mean after-survival and tumour incidence were the same for BAF_1 mice irradiated with acute whole-body doses of 250, 135 and 80-kVp x rays (229). In the rat, a comparison between fission neutrons and x rays yielded a ratio of about 2 for skin tumour induction (312). In the rabbit, 2.5-MeV gamma rays and 0.7-MeV neutrons gave a ratio of effectiveness of about 3 for the production osteosarcomas, fibrosarcomas and basal-cell carcinomas (286).

3. Conclusions

176. The number of tumour systems for which analyses of the RBE of different radiation can be performed with any degree of accuracy is still rather scanty, in spite of the repeatedly pointed out need for such data in radiation protection (563, 670, 564). From the fragmentary information available it appears that the efficiency of high-LET radiation is greater than that of low-LET radiation for the induction of tumours of various kinds. In those systems where complete dose-effect relationships for both types of radiation are available, the RBE appears to change with the dose, according to patterns dictated by the shapes of the dose-incidence curves. At high sublethal dose levels, RBE

values as low as 1 may be found, but for various tumours the pattern is that of an increasing RBE toward the lower doses. Values of up to 10 have been reported at doses of 25-100 rad, according to the various tumour systems studied.

177. When doses of the order of 0.1 rad of neutrons were tested in the rat breast-tumour system, RBE values approaching 100 were reported. Although such high values conform to the theory of dual radiation action (207) and have previously been reported for acute and delayed somatic effects in irradiated plants and animals, they remain unique in the field of tumour induction. Even though such high RBEs "cannot be used to predict the radiation induction of other tumours in other systems" (613) they certainly require further confirmatory work in other appropriately selected tumour-model systems.

178. An increase of the RBE is generally to be expected also at low dose rates, mainly due to a decreased efficiency of low-LET radiation. Data in this respect however are even more fragmentary and do not allow precise quantitative evaluation, except perhaps in the case of mouse leukaemia where chronic, as compared to acute, treatment could decrease the efficacy of the low-LET radiation by factors of 2-10, with a corresponding increase in the RBE of the high-LET radiation.

4. Effects of temporal distribution of irradiation

179. A physical variable of great relevance in radiation carcinogenesis is the dose rate. The most recent theoretical treatment of the dose-rate effect has been presented within the framework of the theory of dual radiation action (340, 574). According to the general foundations of this theory, a wide range of radiobiological effects in higher organisms (including the induction of tumours) may be visualized as the end-result of elementary lesions taking place in the cells at the subnuclear level.

180. The relationship of these effects with dose may be considered as the sum of two components, a linear and a quadratic one. The former predominates in the case of densely ionizing radiation and is essentially independent of the dose rate since it is associated with the interaction of the lesions produced by one single-particle track. The quadratic component is more clear for low-LET radiation: it is very dependent on the dose rate because it reflects the interaction of lesions produced by different charged particles. Lowering the dose rate in irradiation with sparsely ionizing particles causes a reduction of the inter-track effects because of the spontaneous recovery processes of the elementary lesions and consequently reduces the probability of effects resulting from the interaction of lesions produced by different tracks. In very general terms, the reduction of the inter-track effect will depend on the ratio between the characteristic recovery time of the system and the exposure time; therefore when the latter becomes long compared to the recovery time (i.e. at progressively lower dose rates) the final effect of a given dose will decrease through a reduction of the quadratic component. The case of dose fractionation may be analyzed in a manner which is qualitatively similar to that of continuous irradiation.

181. A further consequence of the postulated model is that correct dose-effect relationship determinations at different dose rates require the use of dose rates proportional to the total dose (constant irradiation time) in order that equal recovery apply at all dose levels. This technique appears to have been followed only rarely in the work reviewed, since the vast majority of the experiments have been performed at constant dose rates for different dose levels, a procedure which makes the analysis of the data very complicated, due to the need of applying to the effect reduction factors inversely proportional to the total dose.

182. It should be pointed out in addition that the preceding theoretical analysis, although valid in principle for any biological effect including carcinogenesis, is based essentially on arguments stemming from the theory of dual radiation action which are applicable only at the subnuclear level; the extrapolation of such formal treatments to the level of cell population, tissues or the whole animal is subject to the methodological difficulties discussed in chapter I and is further complicated by intercellular and physiological effects not easily amenable to generalization. Among these effects one should consider the kinetics of target-cell population for the induction of any particular tumour type (compartment size, cell turnover rates and intercompartment transit times), the phenomena of cellular inactivation, intracellular recovery and compartment repopulation induced by the radiation treatment (which have variable dependencies on the dose rate) and also the modifying factors discussed in chapter II and the biological variables to be considered in chapter IV.

183. All these factors have different relevance in the various tumour systems considered and, although included in the overall carcinogenic response of the system, make it impossible to derive a true quantitative analysis of the dose-rate effect. Hug (283) has analyzed several dose-effect relationships in several animals for tumour induction by external whole-body exposure and internal irradiation. He has attempted to link the effects of dose and dose rate on tumour induction with the incidence and latency time of the spontaneous neoplasms, with the purpose of extrapolating the estimates of malignancy induction to man.

5. Dose-rate effects

184. In agreement with the theoretical interpretation given previously, the reviewers who have considered at various times the effect of dose rate on tumour induction have all confirmed the reduction of the yield of tumours with decreasing dose rate and the relatively lower dependence on dose rate of the effect of densely, as compared to sparsely, ionizing radiation (671, 672, 676, 454, 230, 670). The evidence available up to the present on chronic and protracted exposures will be reconsidered in the following paragraphs in view of attempting general qualitative conclusions referring to all

tumour systems examined and of providing, when possible, quantitative parameters to the effect of dose rate. Experiments on fractionated and protracted exposures will also be considered. On the other hand, the cases of lifelong exposure and of split-dose irradiation will be discussed separately for their methodological and/or theoretical peculiarity.

185. Concerning the tumours of the haemo-lymphopoietic system (446, 325, 674, 675, 676, 678, 670), summaries of the state of knowledge have been published on various occasions. The changes of induction of myeloid leukaemia appear to have been studied mainly in the RF mouse. Dose rates of 0.01 rad/min and 0.004 rad/min of ^{60}Co gamma rays induce considerably less of the disease as compared to acute irradiation and also change the characteristic shape of the dose-effect relationship found with acute doses (which has a maximum at about 300 rad) into a flat dose-effect curve with a maximum incidence of about 5 per cent. The ratio of the peak incidences appears to be about 5. Irradiation by neutrons of about 5 MeV mean energy, at a dose rate of 0.0004-0.004 rad/min, compared to irradiation by cyclotron neutrons (mean energy about 1 MeV) at 100 rad/min, had somewhat less leukaemogenic efficiency, probably by a factor of 2-3, at the same peak incidence of 300 rad. If, alternatively, the reduction of the initial slope of the dose-effect relationship is taken as a measure of the reduced effectiveness at low dose rates, it may be estimated that in the case of low-LET radiation the efficiency is possibly reduced by a factor of 2 at the low dose rates. No difference in slope is seen in the case of neutrons (693).

186. In another series of experiments male RF mice were subjected to daily ^{60}Co gamma-ray exposures at 0.007-0.07 R/min and showed a peak incidence of myeloid leukaemia of about 12 per cent at doses of 250 rad, compared to an approximate incidence of 40 per cent after single high-intensity x or gamma ray exposure. A further reduction of the exposure rate from 0.008 to 0.004 R/min resulted in a still lower incidence of less than 5 per cent at the peak (685).

187. Finally, in an exhaustive report, the influence of dose and dose rate on the induction of myeloid leukaemia was tested in male and female RF mice whole-body exposed as young adults to neutrons of 1 and 5 MeV, or to ^{60}Co gamma rays or 250-kVp x rays at dose rates varying from 10^{-6} to 10^{2} rad/min (554, 691, 692). For a given total dose of neutrons, chronic irradiation was found to be as effective as acute irradiation, but with x or gamma rays the reduced dose rate led to a considerably decreased incidence of the disease, so that no leukaemogenic effect above the control level was observed at dose rates of 0.056 to 0.0038 rad/min for total doses of 200-300 rad, whereas the incidence was up to 40 per cent in animals irradiated at 80 rad/min. The loss of effectiveness induced by the low dose rate of gamma rays was about 1/20 and consequently the RBE values for neutrons at low dose rates might be estimated to be of the order of 10-20 (692). A reduced effectiveness of the low dose rate is therefore consistently found in the case of myeloid leukaemia induced by sparsely ionizing radiation. The magnitude of the reduction factor is difficult to evaluate in view of the changes introduced by the low-rate treatment in the character of the dose-effect relationships. Neutron induction appears to be less sensitive to the decrease of the dose rate.

188. The pattern of response of thymic lymphoma to low dose rates appears definitely less uniform. A graded sequence of whole-body x-ray doses in 2, 4, 8 equal fractions at intervals of 1, 4, 8 and 16 days given to C57BL mice of both sexes produced a gradual increase in lymphoma incidence as a function of dose. For a given total dose the induction of tumours did not seem to be affected by daily fractionation, but fractionation at intervals of 4 and 8 days resulted in a higher incidence of tumours appearing at shorter latency times. A further increase of the fractionation interval to 16 days resulted however in a decreased incidence (330). These results appear to be in contrast with those obtained for other immediate effects of irradiation and for the induction of many types of neoplasia, indicating that different pathogenetic mechanisms are involved in the induction of thymic lymphoma. According to Kaplan and Brown (330), the presence of optimal rythms of fractionation for lymphoma production is to be related to the optimal sequence of the pathogenetic mechanisms (bone-marrow injury, viremia, thymic regeneration, immunodepression) leading to the transformation of the thymic cells (see paragraphs 46 to 48).

189. An enhanced effect of dose-fractionation at intervals of 5 to 8 days has also been confirmed after neutron irradiation of the RF mouse (689). On the contrary, a change in the dose rate of ^{60}Co gamma rays from 7 to 0.004 rad/min results in a rather shallower slope of the induction curve, while the yield of neutron-induced lymphomas appears to be unchanged by the decreasing dose rate (693). These results were confirmed and enlarged in a subsequent series showing that with decreasing dose rate of neutrons no change in the induction of lymphoma takes place, while chronic daily exposure to gamma rays consistently reduces the effectiveness of the treatment to such an extent that there is no detectable tumourogenic effect on the thymus at dose rates of 0.0038 rad/min (692). In CF1 femal mice with doses of 60 rad of fission neutrons or 300 rads of gamma rays administered at the average rate of 1 rad/min in weekly irradiations given in 1, 3 or 6 equal fractions per week, the incidence of thymic lymphoma increased as the number of weekly fractions increased from 1 to 6, whilst at 3 fraction/week a decreased incidence was noted (688).

190. In conclusion, while a difference of behaviour among different strains cannot be excluded, it appears that dose-rate reduction by continuous or by fractionated exposure acts in the case of thymic lymphoma through quite different mechanisms. A decreased rate of exposure rate on a continuous treatment leads to a reduced tumour induction in the case of x or gamma rays but not in the case of neutron irradiation. Dose fractionation, on the contrary, tends to enhance the incidence of tumours and the optimum weekly fractionation schedules may be related to the pathogenetic mechanisms discussed in paragraphs 46 to 48.

191. The incidence of reticular tumours other than those previously discussed is also variable with the dose rate, reflecting probably the heterogeneity of the syndromes included in this class of malignancies. Mice of the CBA and C57BL strains given limited periods of daily x irradiation at an average dose rate of 81-1.3 rad/hour up to total doses of 900-1000 rad and then followed for the rest of their lives, showed that the degree of life-span shortening and of lymphoid leukaemia incidence (on which life-span shortening was primarily dependent in these strains) were markedly dose-rate dependent. The uncorrected incidence of leukaemia in the highest dose-rate group was found to be 39 per cent (average between the two strains) and fell to 5 per cent in continuously irradiated animals. These figures should be compared to a 2-per-cent incidence in control animals (448).

192. In contrast, fractionation of a dose of 690 rad of x rays into 2, 4 and 8 equal fractions given in 8 weeks resulted in an increased incidence of non-thymic lymphoma in LAF_1 mice, with respect to animals receiving a single dose of the same total magnitude (122). Fractionation of x irradiation has also been reported to increase the incidence of leukaemia in CAF_1 mice (115). Finally, it has been reported that in RF mice the incidence of reticular tumours other than myeloid leukaemia or thymic lymphoma has a negative trend with single doses of both neutrons and x rays (see paragraphs 117 and 118). With decreasing dose rates the inhibitory effect of the gamma rays decreases markedly, and at a dose rate of 5 rad/day, there is an actual increase of the incidence in males. Chronic irradiation with neutrons has different effects depending on the sex (since in females no change is found with respect of acute irradiation but in males a failure of the inhibitory effect is found), resembling in this respect the pattern seen with gamma rays (692).

193. In the RF mouse the induction of ovarian tumours by ^{60}Co gamma rays is decreased by a reduction of the dose rate from 7 to 0.04 rad/min. The dose-effect relationship obtained after acutely delivered single doses is also very different, the maximum incidence being obtained at higher total doses; this difference makes it very difficult to specify a numerical value for the reduction factor. In the case of neutrons a very shallow dose-effect relationship is seen at all doses with a very slight increase at low dose rates (about 5 per cent) over the spontaneous incidence (about 1 per cent). For comparison, the maximum incidence obtained in the range of 100 rad/min is of the order of 15 per cent (693).

194. In a more recent report the effectiveness of gamma-ray irradiation decreased with smaller dose rate, even though tumour induction was evident down to dose rates of 10^{-4}-10^{-5} rad/min. Neutrons at 0.004 rad/day significantly increased the induction of ovarian tumours after a total dose of only 2 rad, but no such effect was seen at higher dose-rates. This result clearly needs further confirmation to verify whether the low incidence at higher dose rates could be attributable to excess of damage (692). In sharp contrast with the above data, the incidence of ovarian adenoma was increased to 80 per cent after 618-1335 rad of ^{60}Co gamma rays at 1.45 rad/hour in the LAF_1 mouse (515) starting from a background incidence of about 6 per cent. Animals irradiated previously with comparable doses at 28-30 rad/min had shown an incidence of ovarian neoplasia of 35 per cent (514).

195. A detailed quantitative analysis of ovarian tumour induction in Balb/C mice as a function of dose rate has also been reported recently (750). Animals were exposed to graded doses of ^{137}Cs gamma rays in the range of 49-392 rad at dose rates from 1.75 to 112 rad/day, and it was shown that the incidence of neoplasms was a decreasing function of the exposure time. At variable dose rate, i.e. at constant exposure time, the incidence of ovarian turmours appeared to follow a square function of dose, and when the exposure time was variable, the incidence seemed to be inversely related to the 0.69 power of the exposure time. It was found, in addition, that about one third of this exposure-time factor could be accounted for by an age-related loss of sensitivity of the tumour system, while the rest was attributable to recovery phenomena at the intra- or intercellular level. In summary, therefore, the most complete studies available have confirmed on two different strains the presence of a significant dose-rate effect for the induction of ovarian tumours by x and gamma rays. The neutron data are, on the contrary, inconclusive.

196. Some experiments are available concerning the effect of dose rate and fractionation on the mammary tumour system of the Sprague-Dawley female rats. A dose of 500 rad given in one single exposure at 40 days of age, or divided into 4 equal fractions given over 2 weeks or 8 fractions in 4 weeks, or 16 or 32 fractions for a total treatment time of 8 or 16 weeks, respectively, did not appreciably change either the percentage of tumour-bearing rats or the total number of tumours observed over the entire life span. The susceptibility of the system to tumour induction by a single dose remained constant during the time the experiment was performed. As regards the histological type of tumours, a decreased yield of adenofibromas and a relatively increased yield of adeno-carcinomas was found in the irradiated animals: in this strain adeno-carcinoma is observed particularly in old age and appears to be shifted forward in time after all fractionation schedules (618).

197. The results of the change in dose rate were somewhat similar, in that an inversion of the time of appearance of the two histotypes seemed to be operating. Animals given ^{60}Co gamma irradiation at 0.03 rad/min or at 10 rad/min and followed for about one year had an overall tumour incidence of 37 per cent and 40 per cent after 88 rad given at the lower and higher dose rate, respectively. After 265 rad the total incidence of tumours was 57 per cent at 0.03 R/min and 60 per cent at 10 R/min. However, while the adeno-carcinomas showed a reduced incidence at low dose rate, the fibroadenomas were not reduced (612). Considering the peculiarity of the mammary tumour system, these results are not incompatible with the data obtained in many other tumour systems. In fact, the decrease in dose rate and the dose fractionation act by reducing the yield of the tumour type which is actually induced.

which is the adeno-carcinoma, and the effect is manifested through a relative increase of the induction time by comparison with the acute irradiation.

198. In the case of lung tumours the data on the effect of dose rate and fractionation are few and uncertain. It has been reported that in male LAF_1 mice, urethane alone in appropriate doses produces 16 per cent tumour incidence within 25-26 weeks, while a dose of 300 rad of x rays results in 12.5-per-cent incidence; the two treatments combined give 50 per cent animals with tumours. Fractionation of the x-ray dose into 6 equal fractions of 50 rad daily followed by urethane elicits a higher tumour response than observed in several appropriate groups of control animals (116). In RF mice whole-body irradiated with mid-lethal doses of radiation, the neoplastic response of the lung shows in general a decreased trend with dose, but, paradoxically, gamma rays at a low dose rate cause an increased incidence. To explain these data, it has been postulated that a tumourogenic effect on the lung may result at all dose rates, but may be masked at high dose rates by life-span shortening caused by other forms of injury. Neutrons, for any given dose, generally yield a greater reduction than gamma rays at all dose rates (692).

199. In the $B6CF_1$ mouse the incidence of mammary tumours is around 1 per cent and shows little increase with either single or fractionated exposures to ^{60}Co and fission neutrons (206). Ainsworth *et al.* (3) reported a greater life-span shortening in hybrid in $B6CF_1$ mice with fractionated doses than with single doses (80 or 240 rad of neutrons in a single dose or in 24 doses given over 23 weeks), associated in part with the appearance of pulmonary tumours. Less killing of potentially neoplastic cells because of fractionation, the possibility that acceleration rather than true induction could be operating and changes in age-dependent susceptibility during irradiation are explanations that have been invoked to account for these findings.

200. Some results are also available on dose-fractionation effects on skin tumour induction by beta particles. A sparing effect of fractionation has been reported in the rat by Henshaw *et al.* (262) and by Zackhaim *et al.* (755). CBA mice irradiated with 6 000 or 12 000 rad of ^{204}Tl beta particles in 4, 12 or 20 doses over a maximum fractionation time of three months showed little evidence of change in skin tumour incidence with respect to animals receiving single exposures to the same total doses. However, the yield of epidermal and dermal tumours after extreme fractionation and protraction (20 fractions in 25 days) was reduced to 50 per cent with respect to other groups receiving fractions of bigger size. It was noted that this relative insensitivity to fractionation is in sharp contrast with the great dependence of the acute and chronic skin damage on the fractionation regime, which would indicate that the induction of skin tumours has little correlation with acute skin damage (287, 25).

201. Vanderlaan *et al.* (696) reported a model to account for dose and dose-rate effects on skin carcinogenesis in rats. The model assumes that tumours can arise as a result of either one or two dose-dependent events and predicts that the one-step mode of tumour induction is very small, if at all present. For the two-step mechanism, the first step is visualized as reversible with a recovery time constant estimated to be of the order of 0.17 $hour^{-1}$.

202. In contrast with what would be predicted by the study of chromosomal damage in partially hepatectomized mice (142), an increased incidence of hepatoma (32 per cent) has been reported in LAF_1 mice irradiated with ^{60}Co at 1.45 rad/h (515) with respect to animals irradiated with x rays at 30 rad/min (2 per cent) (514). Control incidence of hepatoma in this strain is of the order of 6 per cent.

203. The incidence of gastro-intestinal carcinoma is also increased above control level in LAF_1 mice by whole-body irradiation with 690 rad of x rays. Fractionation of this dose into 2, 4 and 8 fractions over a total time of eight weeks resulted in a definitely reduced incidence. It has been pointed out that the effect is not dependent on life-span shortening since comparisons between the same age groups show a similar reduction (122). Scattered observations on the effect of dose rate, fractionation and protraction on miscellaneous tumours can also be found in Reincke *et al.* (558), Bustad *et al.* (85), Upton, Randolph and Conklin (692), Vesselinovitch *et al.* (706) and Ainsworth *et al.* (2).

204. Tumours of the thyroid have also been reported after chronic administrations of ^{131}I. Jorno and Zapolskaya (316) have treated mongrel rats with activities of 0.015-0.0015 μCi ^{131}I/day for cumulative thyroid doses up to 4500 rad for the highest dose group. The incidence of neoplasia in these animals was about 10 per cent in the two years after the treatment. No tumours were found in the low-dose group. In another paper (84) a significant increase of malignant (up to 20 per cent) and non-malignant (41-44 per cent) tumours of the thyroid was reported following chronic intake of ^{131}I in drinking water at 0.07 μCi/day for 180 days. However, short-term (10 days up to an activity of 0.1 μCi/rat) versus long-term (6 months up to 1.6 μCi/rat) administration of ^{131}I produced similar carcinogenic effects in the thyroid (15-18 per cent tumour incidence) and the yield of tumours was in both cases higher than in controls (8 per cent) (702). Morphological and ultrastructural data were also reported in the same publication in the thyroid of ^{131}I-treated animals.

6. Lifetime irradiation

205. A number of experiments have been reported on the effect of dose rate on animals irradiated continuously during their lifetimes. They should be considered separately as a rather uniform group, interpretation of which is very difficult, both conceptually and because of problems of technique. It has, in fact, been pointed out (445) that the radiation received during the last part of a duration-of-life exposure is less effective than that received earlier. The difference in efficiency per unit dose between a short-term and a lifelong exposure has been referred to as "wasted radiation" that is, radiation given in excess of that required to elicit the effect. In the present context,

the concept of wasted radiation applies to the dose in excess of that strictly required to induce a tumour, namely, the dose received during the tumour latency time plus that received between the clinical appearance of the tumour and the death of the animal. When dealing with an effect characterized by its late manifestation in time, not allowing for wasted radiation may lead to very important alterations of the determined dose-effect relationship.

206. Groups of LAF_1 mice of both sexes were submitted to lifelong ^{60}Co gamma irradiation starting at 100 days of age with daily exposures from $2\ 10^{-5}$ to 5 R. The survival data were analyzed in terms of accumulated lethality per unit daily dose, and four distinct phases of early lethality corresponding to different types of damage were thus identified. Coefficients of life-span shortening for after-survival in excess of 60 days were also worked out (582). The induction of tumours as a function of daily dose, age and sex at dose rates below 56 rad/day were reported in a subsequent publication (370), and tumour incidence data were obtained both after serial sacrifice and after lifelong observation.

207. Concerning thymic lymphoma, the slope of the cumulative incidence curves increased with daily dose up to 32 rad/day and remained constant thereafter. There was no evidence that lymphoma incidence was higher than control in the 5-rad/day group, but 12 rad/day gave rise to an abrupt increase in incidence in both sexes and to a marked shortening of the latency time. Pulmonary tumours were above control values only in females irradiated at 5 rad/day but otherwise declined with increasing dose in all other dose groups; above 12 rad/day there was a shift forward in the time of appearance of these neoplasms. Hepatomas were only found in the control and in the irradiated groups with long survival times; radiation had little effect on their incidence in both sexes. The incidence of ovarian tumours rose sharply in the irradiated groups but rapidly decreased above 12 rad/day, suggesting that the most effective carcinogenic dose for this organ is to be set at some dose rate below this limit.

208. Comparison of these data with the tumour incidences reported for the same strain with single terminated exposures led to the conclusion that the duration-of-life exposure is considerably less carcinogenic per unit of accumulated dose. The duration-of-life experiment was later extended to mice of six different genotypes. Evidence at dose rates below 6 rad/day, where life-span shortening is less than 15 per cent, indicated that all of this life-span shortening could be associated with neoplastic diseases (227, 228). The pattern of age-specific mortality rate for reticular tissue tumours indicated a maximum in the incidence-rate curve at daily doses from 6 to 43 rad/day, with total accumulated doses of about 3000 rad. Pulmonary tumours, hepatomas and ovarian tumours showed, on the contrary, a modest increase in incidence at 6 rad/day or less, followed by a sharp decline at higher daily dosages. A possible model accounting for the observed life-span shortening due to causes other than reticular tissue tumour has been also proposed (583). Lifetime periodic gamma-ray exposure experiments have also been reported in other mouse strains, with special regard to leukaemia and life-span shortening on five successive generations (735) and in the guinea-pig (581).

209. Yakovleva (744) reported data on tumour development in 150 dogs exposed for six years to chronic (21, 63 and 125 rad/year at dose rates of 0.06, 0.17 and 0.34 rad/day) or to combined chronic and acute gamma irradiation. Various types of benign and malignant tumours of various organs were seen at autopsy and the majority of them were seen in animals exposed chronically at the highest dose rate and at the highest total dose.

210. Of special interest is an experiment being performed on beagles irradiated continuously in a ^{60}Co field at daily doses varying from 5 to 300 rad, delivered over 22 hours (205). In this experiment the causes of death appear to be related to the dose rate and total accumulated doses; septicaemia, anaemia and myeloproliferative disorders usually under the form of myeloid leukaemia appear to be the haemopoietic syndromes most common in these animals (204, 203). At 35 rad/day or higher the dogs die with septicaemia, but not at 10 rad/day or less. At 17 rad/day all three syndromes appear; at 10 and 5 rad/day only anaemia and leukaemia are seen, the latter at longer exposure times. Two out of 13 animals dying at 17 rad/day developed leukaemia after 1038 days; 6 of 13 at 10 rad/day after 719 days, and 4 of 6 at 5 rad had leukaemia at an average time of 1063 days. Thus, lower dose rates produced leukaemia in equal or shorter exposure times, so that the optimum rate of exposure for leukaemia induction would appear to be around 10 rad/day, and higher rates might be inhibitory (205).

7. Split-dose irradiation

211. Attempts to utilize the split-dose methodology (170) to evaluate the time-course and the extent of recovery processes in the case of tumour induction have been reported. The data are extremely few and scattered so far, although our knowledge of the kinetics and of the nature of the recovery from late damage could be considerably expanded by the use of such methodology, which has proven to be very fruitful in the case of short-term radiation effects. Split doses of radiation given at various intervals from 4 to 48 hours have resulted in increased long-term mouse survival following a kinetics which is reminiscent of the recovery curves for the survival of single cells (628). The pathological observations performed on these animals were not very satisfactory but showed clear evidence of a decreased tumour incidence even at such short fractionation intervals (439).

212. Split-dose experiments with a 24-hour interval in the mouse lung-tumour system were reported by Yuhas (751), showing significant recovery when the total dose was well in the curvilinear part of the dose-effect relationship (1500 rad), while no recovery was apparent when the total dose fell on the linear portion of the induction curve (750 rad). The split-dose method applied to the mammary tumour system of the Sprague-Dawley rat yielded negative results (605). These latter findings might be explained on account of the linearity of the

dose-effect relationship in this particular experimental model. Recovery with respect to skin tumour induction in the rat was measured by split-dose methodology at a fixed 31-day fractionation interval after a conditioning dose of 750 rad (surface dose of fast electrons) (81). The difference in dose between the fractionated and the non-fractionated treatment to obtain the same level of skin tumour induction was found to be about 650 rad, in good agreement with the 600-rad value found for hair follicle atrophy. More recently the same group (82) reported on the tumour incidence and the lethality of hair follicles in rat skin following several single doses of fast electrons (1000-4000 rad) and split doses (1000 and 1000-4000 rad) with a 24-hour interval. The number of tumours per rat 70 weeks after single doses showed the usual peak at 2000 rad (fig. IX) followed by a decline at higher doses. With split radiation the peak was displaced by at least 70 per cent of the initial conditioning dose. Since the interval of 24 hours is too short for any significant cell repopulation, it was concluded that the effect could be best explained by a rapid process of recovery, similar to the intracellular recovery described by Elkind (170).

213. Split-dose data are, in conclusion, very incomplete and inadequate to resolve between the intracellular component of the recovery and the component due to cell repopulation; the approach seems, however, well founded and should be pursued in the future in view of the essential need for information on recovery from neoplastic damage. In this context, *in vitro* techniques of cell transformation could also be very valuable for the interpretation of experiments on *in vivo* systems. Experiments *in vitro* have already been reported at a 5-hour fractionation time (58) and they deserve further attention since they have shown an increased yield of transformed clones by fractionation, which would appear to be the exception, rather than the rule, in all the *in vivo* systems examined.

8. Conclusions

214. The following conclusions may be drawn from an analysis of the effects of dose rate and fractionation on the induction of tumours in various animal systems. When methodological and technical difficulties are conveniently accounted for, a decrease in the dose rate of low-LET irradiation results in general in a decrease of tumourogenic effect, following some inverse function of the exposure time. The form of the dose-effect relationship applicable to acute irradiation is often greatly altered by the change in the dose rate, and therefore precise values of the reduction factor have so far been estimated only for very few tumour-model systems. Reduction factors of 2-20 have been reported between the highest and the lowest dose rates tested (10^{2}-10^{-6} rad/min) and between single and extremely fractionated and protracted doses, for various systems and different end-points.

215. In the few cases where high-LET radiation has been tested for tumourogenic effects (essentially the haemo-lymphoreticular neoplasms of the rodent) the reduced effectiveness of the low dose rate appears to be quantitatively less important than that induced by a corresponding decrease of dose rate of x or gamma radiation, or it may even be absent. Departures from this very general pattern are found in special cases (the lymphoma, for example); rather than exceptions to the fundamental radiobiological mechanisms they may be regarded as special cases due to the pathogenetic mechanisms of these tumour systems. There are well founded theories accounting for the decrease in effect of low dose rate and fractionation, which may be conceptually ascribed to repair of the elementary biophysical lesions responsible for tumour induction. It seems reasonable to postulate, in addition, that intra- and intercellular mechanisms of recovery may be operating in this case as in the case of short-term radiobiological effects. But the kinetics and the nature of these repair phenomena are still essentially unknown and urgently require elucidation.

IV. CARCINOGENESIS BY INTERNAL EMITTERS

A. GENERAL

216. In reviewing the data on tumour induction by incorporated radionuclides each nuclide will be dealt with separately in this report, the specific distribution of a nuclide being by far the most significant variable. The general problems posed by internal irradiation are in principle the same as for external irradiation, though the presentation by nuclide requires a different format than that used in chapter III. One special aspect referred to in the 1972 report of the Committee (670) is the inhomogeneity of the dose in relation to space and time in the case of internally administered nuclides. The physical and chemical characteristics of the nuclides and the anatomo-physiological characteristics of the target tissues in different animal species give rise to widely different patterns of deposition, retention and excretion. The route and schedule of administration and also biological variables related to the genetic make-up, the sex, the age of the animals, add to the complexity of the main problem, which is the establishment of reliable dose estimates for evaluation of the neoplastic effects.

217. Any meaningful comparison of effects and risks between various animal species requires in fact that the dose delivered by the nuclides to the cells at risk be known with reasonable certainty. In spite of the efforts that have been made to refine the dose estimates (for reviews on dosimetry, see (634) and (635) for beta particles and (704) for alpha particles), there are still considerable uncertainties which render any comparison between nuclides and between species at best semi-quantitative. Data for interspecies comparisons may be found in a monograph edited by Moskalev (469). The criterion for comparison used in many studies of bone-seeking radionuclides, namely the "mean accumulated skeletal dose" is calculated differently by different authors, which increases the uncertainties of the comparisons. Since the object of the present report is to discuss specifically the neoplastic response, the reader is referred to more specialized publications for the above problems (431, 703). There are, however, some problems that must be dealt with and that appear to be

relevant for all nuclides; they refer specifically to the establishment of dose-effect relationships and to the concept of RBE in internal radiation carcinogenesis.

218. In regard to dose-effect relationships for internal irradiation, it should be realized that the effect of dose cannot be readily tested independently from the effect of the rate at which it is delivered, that the dose rate is changing in the course of the exposure period, and that internal irradiation is often extended until the death of the animal and therefore the concept of "wasted radiation" (445, 185, 46) is intrinsic to the analysis of the dose-effect relationships. It is possible to take this factor into account by computing the dose accumulated by the tissues at risk up to the time of first appearance of the tumour or to some such extrapolated time (185, 433, 434). Secondly, although in external radiation carcinogenesis the concept of RBE may be reasonably defined, at least operationally (see paragraphs 155-157, in the case of internal emitters it is difficult to compare nuclides which, in addition to LET differences, have very peculiar types of distribution, retention and translocation to various tissues. These concepts are mentioned in order to stress the need of extreme caution in interpreting statements abstracted from the context of the reviewed experiments.

219. It is customary to divide the bone-seeking nuclides into volume and surface seekers (426). The volume seekers include the alkaline earths, calcium, strontium and radium, the atoms of which can occupy the same sites in bone mineral. They are initially deposited in high concentrations on the surface of the mineral bone and slowly migrate into deeper sites by chemical exchange. This process plus the continuous apposition of newly formed bone mineral eventually buries most of the radioactivity within the mineralized structures of the skeleton. Other radionuclides like plutonium, thorium and americium are surface seekers and deposit on the periosteal and endosteal surfaces in the immediate vicinity of the capillary vessels, after which they may be removed by bone resorption or buried by the apposition of new bone. Added to the physical characteristics of their radioactive decay, this different behaviour has of course the most direct consequences on the distribution of dose to the target cells. Volume seekers with short half-lives (like, for example, ^{224}Ra having a half-life of 3.64 days) represent special cases since they decay almost entirely on the bone surfaces before being buried in the mineral part of the bone.

B. BONE-SEEKING BETA EMITTERS

1. Bone tumours

220. Strontium-90 has a half-life of 28 years: it decays to ^{90}Y by beta emission with maximum energy of 0.54 MeV. The ^{90}Y has in turn a half-life of 64 hours and decays to stable zirconium by beta emission with a maximum energy of 2.27 MeV. The range of soft tissues of the ^{90}Sr + ^{90}Y beta radiation is about 10 mm. Strontium-89 has a half-life of 51 days and a beta-particle maximum energy of 1.46 MeV with a 7-mm range in soft tissue. Strontium nuclides are volume seekers. The data available on single administration of ^{90}Sr are more of theoretical than of practical interest, but have been reported in a number of animal species. Small rodents are particularly suitable to this type of experimentation, since they may be treated in large numbers, thus providing better statistics. Their body size however is very small and therefore not particularly appropriate to mimic the geometrical conditions of exposure of man, without adequate corrections.

221. The data on the incidence of bone tumours obtained in CF1 female mice injected with ^{90}Sr at 70 days of age by Finkel and Biskis (183) (nine dose levels between 1.3 and 2200 μCi/kg), have been updated, re-evaluated and statistically analyzed by Mays and Lloyd (434). When the average skeletal doses, calculated up to the estimated start of tumour growth and ranging in this experiment between 0 and 12 000 rad, were plotted against the percentage incidence of osteosarcomas, the dose-effect relationship was found to be highly non-linear. Furthermore, a decrease in incidence from 91 per cent to 73 per cent was seen after an accumulated dose between 6630 and 12 000 rad. The incidences found at low doses appeared consistently less than those which would be predicted from an assumed linear dose response extrapolated to the control incidence value and fitting the data up to the peak incidence. Median life spans decreased rather regularly from the lowest (1.3 μCi/kg) to the highest (2200 μCi/kg) dose injected.

222. Dose-related data on radiostrontium intoxication of CBA X C57BL female mice injected at two levels (0.2 and 1.0 μCi/g) were also reported by Van Putten (699) and Van Putten and De Vries (700). Incidences of bone sarcoma of 19 per cent and 82 per cent were found respectively in the two groups, to be compared with a 0 per cent incidence of the control mice. In another series, two malignant bone tumours were found in 102 RF male animals injected once with 0.2 μCi/g and one in 75 animals receiving 0.04 μCi/g. No tumours occurred in controls or in animals given 0.51 μCi/g (128). In a more recent series of papers, Nilsson (497, 499, 502), reported dose-related data for CBA mice injected with ^{90}Sr at levels of 1.6, 0.8, 0.4 and 0.2 μCi/g. The spontaneous incidence of osteosarcoma was low in these mice. Bone tumours were found in all groups but the highest number (292 tumours in 120 mice) was observed in the 0.8 μCi/g group. A tendency to multiple tumours was also found, except in the 0.2 μCi/g group. The dose-effect relationship has been analyzed by Mays and Lloyd (434) and found to be non-linear. Latency time of bone sarcoma was shorter (from 485 days to 268 days) as the dose increased.

223. Single dose experiments with ^{90}Sr were carried out by Moskalev, Streltsova and Buldakov (470) on Wistar rats injected intraperitoneal (IP) at three months of age with activities ranging from 0.005 to 500 μCi/kg. The dose to the bone at 170 days before death were calculated by Mays and Lloyd (434) to range between 0.2 and 5760 rad. The incidence of osteosarcoma in these animals was up to 51 per cent in the two highest dose ranges and the average time from injection to death tended to lengthen as the dose decreased. The dose-effect relationship found did not appear to support a linear non-threshold hypothesis.

224. Brooks *et al.* (64) reported data on hamsters injected with ^{90}Sr (0.2 to 5.0 μCi/g, given IP). An activity-related shortening of life-span was observed. No animal survived within the first two weeks with 3.0 and 5.0 μCi/g. The 50 per cent survival times ranged from 90 days with 2.0 μCi/g to 1100 days at 0.2 μCi/g. With 1.0 μCi/g, an activity known to produce a high incidence of bone tumours in mice, only a few osteosarcomas were observed. Myeloproliferative diseases were, on the contrary, very common in the controls and in injected animals. ^{90}Sr was also injected into rabbits of various ages (from 2 days to 165 weeks). Osteosarcoma was found in animals receiving 500 μCi/kg at 6 weeks of age and occasional bone tumours were also found at 50-200 μCi/kg (705). Two bone sarcomas were observed in 15 miniature pigs with single injections of 64 μCi/kg (281).

225. The latest published data (April 1970) on the Utah experiment on beagle dogs given at 1.4 years of age single IP injections of 0.57 to 97 μCi ^{90}Sr/kg (corresponding to doses of 105-9100 rad at one year before death) were reported by Mays and Lloyd (434). Eight out of 14 (57 per cent) dogs that died at the highest dose level had bone sarcoma. Two of 12 dogs injected with 63.6 μCi/kg, which died, had osteoscarcoma. No bone tumours have yet been observed in the lower dose groups. Data are far from complete and no firm dose-effect relationship can yet be established, but the results so far would not support a linear response. Other interim data on ^{90}Sr toxicity in dogs (the Argonne Study), in relation to age effects and dose pattern, were reported by Finkel, Biskis, Greco *et al.* (188). Finally, acute inhalation studies with $^{90}SrCl_2$ were also performed and reported by Boecher *et al.* (49) and by McLellan *et al.* (414). Seventy-two dogs were exposed to aerosols which resulted in long-term body burdens of 1-120 μCi/kg. In the animals already dead, hemangiosarcomas, osteosarcomas and chondrosarcomas were observed.

226. Another volume seeker is ^{45}Ca, a beta emitter with a half-life of 165 days decaying to stable Sc. The radiation emitted is weaker than that of ^{90}Sr and has a maximum energy of 0.254 MeV and a maximum range in soft tissue of ~ 0.7 mm. A dose-effect relationship for single injections of ^{45}Ca in 70-day-old female CF1 mice has been reported by Finkel and Biskis (183), and these data have been reanalyzed by Mays and Lloyd (434). The activity range extended from 16 to 49 600 μCi/kg, corresponding to average skeletal doses from 63 to 111 000 rad. The highest incidence of bone sarcoma (96 per cent) occurred at 26 400 rad, after which a pronounced decrease in incidence was observed. Median survival time from injection to death decreased regularly with dose. Seven cases of bone sarcoma were observed in the dose interval 63-4700 rad, while a linear model would have predicted 26 cases. The chance that the linear extrapolation would actually be valid in the low dose region, appears to be less than one in 10^5. Kuzma and Zander (361) have also carried out a comparison of the neoplastic effects of ^{89}Sr and ^{45}Ca in rats and have established that the carcinogenic effect of calcium per unit activity administered is lower. A number of benign osteomas were found after its administration. Histologic and histochemical studies were also reported on ^{45}Ca-induced autochtonous and transplanted osteosarcomas in Donryu rats (257).

227. A single treatment with ^{90}Sr results in an uneven distribution of the dose both as a function of time and within the bone. The dose rate is bound to be very high at the time of injection, after which dose will accumulate at a progressively slower rate. In addition, the nuclide will be deposited initially only in those bone zones which are actively laying down bone mineral at the time of treatment, thus producing a non-uniform irradiation of the osteogenic and haemopoietic tissues. Repeated administration, on the contrary, is likely to result in a more even distribution of the dose within the bone tissue. Also, by injecting the nuclide in different fractions or by continuous administration, it is possible to deliver the same dose at various average dose rates, which may give indications about the role of the temporal distribution of dose in internal irradiation. Following this idea (185), experiments on fractional and on continuous exposure to ^{90}Sr have been carried out in various animal species.

228. Seventy-day-old female mice of the CF1 strain were injected with three different activities of ^{90}Sr (250, 500 and 1000 μCi/kg), once or five times in 5 weeks or 20 times in 4 weeks. It was found that for the same total dose the tumourogenic response (both as tumour incidence or as tumour expectancy) was highest when the nuclide was delivered in one injection and lowest when the dose was divided into twenty fractions. This experiment shows that the distribution in time of the same dose reduces its carcinogenic effect and that immediate high dose rate is more important for bone tumour production than the dose from the isotope retained in the skeleton (194). Similar data with ^{45}Ca gave a maximum yield of tumours at five injections in five weeks and lower responses at 1 or 20 injections. The data were explained on the basis of the lower energy and of the non-uniformity of deposition of ^{45}Ca with respect to ^{90}Sr (185).

229. ^{90}Sr was also incorporated into food, and female CF1 mice were kept on this contaminated diet from three days before mating until death, together with their offspring. A ^{90}Sr level of 15 μCi/g of stable calcium produced bone tumours in adult females, but at lower levels the tumour expectancy was within control limits. Females on ^{90}Sr diet since conception had osteogenic tumours at dietary levels of ^{90}Sr from 15 to 5 μCi/g of calcium, but not at lower levels. Males, on the other hand, developed three times fewer tumours than the female siblings. A careful analysis of body burdens in these animals and comparisons with the results of single injections, suggested that the activity accumulated in the skeleton was a valid indicator of the absorbed radiation responsible for oncogenesis (185). Preliminary data on the dose-rate effect following continuous ingestion of ^{89}Sr in Balb/C, C57BL and RFM mice have been reported for both haemopoietic and osteogenic tumours (742). It has also been shown that the incidence of ^{90}Sr-induced malignancies in CBA mice decreased after gestation and lactation, by comparison with unmated controls (495), and that this effect results from a decreased dose rate to the bones of the lactating females owing to a higher excretion rate of the nuclide (503).

230. In the rat, data on short-term administration (from 10 to 30 days) of ^{90}Sr in the drinking water were reported by Casarett *et al.* (93) and reanalyzed by Sundaram (746). Myeloid leukaemias, angiosarcomas and osteosarcomas were observed at total activities of ^{90}Sr of 330-464 μCi. There was an indication that at low dose levels the primary effect might be leukaemia and that at high levels osteosarcoma might be prevailing. 718 miniature swine representing three generations were kept on a continuous ^{90}Sr diet at levels from 1 to 3100 μCi/day; some animals were also sacrificed for dosimetric and histological studies. The experiments are still in progress and the data have been reviewed in various reports (280, 110, 281, 278, 109). Tumours of the bone (giant cell tumours, osteosarcomas) have been found at bone doses of 6300 rad (434), corresponding to an intake of 125 μCi/day of the nuclide. The chance that a linear non-threshold model for bone-tumour induction may correctly apply to these data has been estimated to be about 16 per cent (434). However, the high competing risk of leukaemia and other proliferative disorders and the non-completion of the study render these calculations very uncertain.

231. A study on chronic feeding of ^{90}Sr has been set up at the Davis campus of the University of California on several hundred **beagle dogs** treated from mid-gestation (onset of foetal ossification) up to 1.5 years of age with the purpose of labelling uniformly the skeleton of these animals. Average levels of ingestion range from 0.03 to 12 μCi/day. Metabolic and dosimetric parameters are evaluated in parallel experiments (217, 218) as well as non-neoplastic skeletal changes like endosteal or periosteal sclerosis, fractures, osteolytic lesions and trabecular coarsening (462). Up to 1972, osteosarcomas and other tumours were seen at the highest intakes of 12 and 4 μCi/day, after accumulated doses to the skeleton of 8000-11 000 rad (166, 543, 87). In a most recent report of these experiments (463), the delay period between exposure and bone sarcoma incidence was estimated to be 1.5, 5.1 and 9.4 years with activities of 36, 12, and 4 μCi respectively, starting from birth. The interplay of dose, dose rate and age were analyzed in this experiment in order to attempt extrapolation to low doses. Other data on dogs given fractional injections of ^{90}Sr during one year have been reported by Finkel, Biskis and Greco (188). Malignant bone tumours occurred in this case at 150 μCi/kg but none was seen after 10-100 μCi/kg.

232. Chronic feeding studies with ^{90}Sr in dogs were also reported by Burykina (83) at levels of 0.2 to 0.0004 μCi/kg per day, yielding average skeletal dose rates from 0.4 to 0.004 rad/day. Treatment lasted from 2 to 4 years. The tumours observed were mainly in the soft tissues (16 cases out of 51 dogs in all treatment groups) but 1 out of 15 and 2 out of 15 dogs at the highest dose levels developed osteosarcoma and leukaemia, respectively. The latency period of all tumours decreased with increasing dose. The data show that marrow and soft-tissue neoplasms are more readily induced than tumours of the bone for chronic irradiation.

233. A detailed statistical analysis of the dose-effect relationship for bone sarcoma induction, in ^{90}Sr and ^{45}Ca treated animals of various species, has been made by Mays and Lloyd (434), and it seems relevant here to report the main conclusions. They have normalized the data analyzed to a common quantity, the "average skeletal dose" (i.e., the dose from the time of treatment initiation to the time of initial tumour growth), which has been estimated differently in the various animal species. They have found that in all analysed cases the number of bone tumours appearing at low doses is considerably lower than the number that would be predicted from a linear model of the dose-induction relationship. The probability that a linear dose-induction relationship might adequately fit the data, ranges from 10^{-13} in the case of ^{90}Sr-injected rats (470) to $1.6\,10^{-1}$ in the case of continuously treated swine (281). In their opinion, the data at low doses would strongly support a "practical threshold" model with extremely low incidences below a few hundred to 1000 rad spread over the lifetime. At very low doses this model would not be distinguishable from a "sigmoid" model where the dose-incidence curve would first be very shallow, then would rise steeply and eventually would reach the plateau or bend down at extremely high doses. Mays and Lloyd have ascribed the sigmoid trend of the data to the efficient recovery from low-LET radiation damage at sufficiently low dose rates.

234. Extrapolating from the analysed data, the authors have inferred estimates for the 50-year risk from ^{90}Sr-induced bone sarcoma in man, which are $(1 \pm 1)\ 10^{-6}$ tumour per man rad for average skeletal doses below 1000 rad, according to a linear model, and $(4 \pm 4)\ 10^{-10}$ tumour per man rad^2 for average doses below 1000 rad according to the dose-squared model. These figures should be compared with the natural incidence of bone tumours, which is of the order of $5\ 10^{-4}$. Vaughan (703) has however pointed out some of the difficulties in accepting these conclusions, which extrapolate single-injection and continous-treatment data between species, while it is clear (see paragraphs 236 to 240) that different types of neoplasia may be relevant under the two exposure conditions. In addition, the dose estimates should be treated with caution in view of the differences in bone structure in various species.

235. It is of some interest to report, for comparative purposes, that the lowest estimated average skeletal doses proven to induce bone sarcomas in various animal species after intravenous (IV), IP and oral administration of ^{90}Sr range, according to Mays and Lloyd (434), from 2500 to 6300 rad. Concerning the effect of dose rate, the data available suggest a reduction of bone sarcoma incidence at low dose rates. Dynamic studies of the growth of osteosarcomas produced in beagle dogs by various IV-injectod nuclides have been reported (662) together with comparative studies on the skeletal location of naturally occurring or radiation-induced tumours in the dog and in man (544, 663).

2. Myeloproliferative diseases and other tumours

236. Tumours of the bone are not the only form of neoplasia found after radiostrontium intoxication. Another important neoplastic disease is leukaemia. The general problems concerning the induction of this

disease in animals and in man after ^{90}Sr contamination have been discussed by Loutit (404), especially in relation to the risk of osteosarcoma. Concerning the experience with laboratory animals, a high incidence of reticular tumours by comparison with the controls was noted by Finkel (182) in the mouse (CF1) given ^{90}Sr in a single injection or in fractionated administration. In another report, an activity of 0.2 μCi/g in intact or splenectomized RF male animals increased the incidence of thymic lymphoma; other forms of leukaemia and non-thymic lyphoma also increased in number and occurred earlier (128).

237. Continuing reported experiments on the effects of various levels of ^{90}Sr on the haemopoietic system (marrow, spleen, thymus) of four groups of mice at the 0.2-1.6 μCi/g level (498), Nilsson reported more recently (501) on a complete series in which 1430 CBA mice were administered graded activities of ^{90}Sr (0.2-1.2 μCi/g), in order to investigate the site of origin, the development and the dose-effect relationship of leukaemia induction. The significance of the bone marrow in the thoracic vertebrae as the site of origin of the leukaemia and the relations among marrow, spleen and thymus in leukaemogenesis were also studied. The highest frequency of leukaemia developed among animals in the 0.2-μCi/g group and the incidence of the disease decreased with activities of the nuclide. The latency time did not vary greatly among the different groups. In a comparative study of the leukaemogenic action of x rays and ^{90}Sr in mice it was found that 680 rad of fractionated x rays produced 77.3 per cent of mostly thymic leukaemia, while 1.0 μCi/g of ^{90}Sr gave 61.8 per cent of lymphoblastic, reticulum cell or stem cell leukaemia. Thymectomy inhibited the development of the x-ray-induced but not of the ^{90}Sr-induced disease (298).

238. In a recent and yet incomplete study, CBA mice of a low-tumour strain were given from 6.7 to 20.0 μCi per mouse. The predominant tumours found were not osteosarcomas but haemangial and lymphoreticular sarcomas, presumably arising in the bone marrow. In this case also, the highest incidence was more likely to be at the lowest dose (405). The effect of ^{90}Sr (0.4 or 0.8 μCi/g) and of combined ^{90}Sr (0.2 μCi/g) and fractionated x irradiation on the thymus and other haemopoietic tissues of CBA mice were also studied by Järplid (305, 306) with serial sacrifice and long-term studies. Following the ^{90}Sr irradiation changes of the weight and cellularity of the thymus, spleen and marrow were reported. In the case of combined irradiation, the administration of ^{90}Sr delays the haemopoietic regeneration that takes place after an x irradiation, resulting in an increased incidence of thymic lymphoma. The induction of non-thymic lymphomas by ^{90}Sr was also enhanced by small doses of external x rays.

239. In the rat, myeloid leukaemias were reported after chronic administration of ^{90}Sr in drinking water, suggesting that at low dose levels the primary effect might be leukaemia and not bone tumours (93, 646). An incidence of 6.1 per cent of leukaemia (reticulosis, haemocytoblastosis and myeloid) was noted in 82 rats given 10 μCi/kg, corresponding to a marrow dose of 530 rad. These data should be compared with a spontaneous incidence in the controls of 1.7 per cent (470). Marrow changes, but no leukaemia, were also reported in rabbits given 600 μCi of ^{90}Sr per kg (703). In miniature swine fed on a ^{90}Sr diet (1 to 3100 μCi/day) for three generations a large number of myeloproliferative disorders were described, including myeloid, lymphoid and stem cell leukaemia, the incidence of which seemed to be in general relationship with dose and to have latent periods shorter than those of bone sarcoma (280, 110, 277, 278, 109, 551).

240. Haemopoietic changes (leukocyte depression, erythrokinetic disturbance, formation of ectopic haemopoietic centers) were described in beagle dogs chronically fed ^{90}Sr at dose levels of 12 and 4 μCi/kg (86). At later times, myeloproliferative disorders became apparent (166, 218, 165, 543). In these animals there was a continuous spectrum of diseases ranging from myeloid metaplasia to neoplastic proliferation of the granulocytic series. The main feature of these lesions consisted of an infiltration of the haemopoietic sites by mixtures of stem cells and granulocytes in various stages of development, rather than an increased blood leucocytosis. Infiltrations of the subendothelial and perivascular spaces of various organs (liver, lung, etc.) were also found. Finally, lymphosarcomas, myeloid leukaemias and reticulum cell sarcomas were also observed in the Argonne dog experiment (188). Other tumour types found in various mammalian species with single or continuous treatment with ^{90}Sr included haemangioendoteliomas and angiosarcomas of the bone marrow (195, 431, 49, 498, 499, 405), carcinomas of the mucous membranes of the head (496, 652), squamous cell carcinomas of the external ear or of the skin (705, 500, 502, 474), epidermoid carcinomas of the oral cavity (195, 652) and tumours of the mammary gland (474). In most of these cases (including leukaemia) the observations were too few to allow the derivation of complete dose-effect relationships.

3. Conclusions

241. The general picture drawn from the reviewed data cannot yet be very detailed and systematic, but appears in any case sufficient to support some inferences. It will have of course to be refined in the future by other data, either becoming already available or in progress, concerning the deposition, excretion and dosimetry of ^{90}Sr in the many species tested, for the various routes and schedules of administration. A detailed discussion of all these problems is clearly not within the scope of the present report and more specialized publications have dealt with them extensively (703).

242. Even if qualified by the uncertainties mentioned above, some important conclusions seem to emerge from the reviewed data. Firstly, the incidence of bone tumours, especially osteosarcoma, increases with dose in all the experiments examined, the form of the dose-effect relationship is probably sigmoid, and a dose-rate effect can be found if adequately looked for. Secondly, in most animal species tumours of the haemopoietic tissues are also found, sometimes in fairly high numbers. Thirdly, bone tumours predominate at high total doses and dose rates, while the incidence of

haemopoietic neoplasms follows in general gross haematological disturbances and is particularly high at low doses or with continuous exposure (415, 703). Fourthly, it seems possible that the neoplastic syndrome that will kill the animal may be determined by the different latency periods of the various forms of leukaemia and of bone tumours which are species-specific, and which depend on the dose and dose rate delivered by the nuclide. These variables, however, have not yet been incorporated into a comprehensive model. Finally, vascular and epithelial tumours may appear in some cases.

C. BONE-SEEKING ALPHA EMITTERS

1. Radium isotopes

243. Radium-226 has a half-life of 1620 years and decays to ^{222}Rn with the emission of alpha particles of 4.6 MeV having ranges in soft tissue of 31-70 μm. Radon-222 is in turn, as are several of its decay products, an alpha emitter, with a half-life of 3.82 days. Since radon is an inert gas, it does not become fixed in tissues and tends to escape at a rate that is different in different species and depends on the tissue characteristics. Radium-226 follows the metabolism of calcium and is therefore a volume-seeking isotope. Since information on ^{226}Ra is available in man (578), it is regarded as the standard bone-seeking nuclide and a basis for deriving estimates of risks for other bone-seeking nuclides in man by comparing radium and these other nuclides in the experimental animal (185). Earlier animal studies with ^{226}Ra have been summarized by Chiacchierini *et al.* (101).

244. In a report comprising 3210 femal CF1 mice (191), 70-day-old animals were injected singly with 14 different amounts of the nuclide, ranging from 0.05 to 120 μCi/kg. In these experiments, bone sarcoma was found to be the most sensitive indicator of damage, since it was induced even at dose levels where histological evidence of damage was not apparent. When the average tumour expectancy (the number of tumours still to appear divided by the number of animals still alive) was plotted against dose, the effect was shown to increase linearly between the control and the 2.5-μCi/kg level. At higher activities, up to 20 μCi/kg, another linear response having a lower slope was obtained; still higher activities produced no further increase in tumour response. According to the authors, the change in slope at around 20 μCi/kg would reflect severe damage and possibly the interplay of several carcinogenic factors, the relative importance of which would change at that turning point. Tumour expectancy is an unusual end-point in carcinogenesis and one rarely to be found in the analysis of dose-effect relationships; the above data are therefore not directly comparable with other experimental series.

245. Actually, when a more conventional end-point such as the (uncorrected) percentage incidence of tumours was employed, a different dose-effect relationship could be generated (433), and the incidence of radiation-induced bone tumours was shown to increase linearly with the average skeletal dose up to about 1000 rad. In the low-dose region (below 300 rad), the cases of bone sarcoma observed were in good agreement with those predicted by a linear dose-effect relationship. Other tumours, such as osteomas, hemangioendoteliomas and reticular tissue neoplasms, were also observed, in no obvious relation with dose (191). Radium-226-induced osteosarcomas were also reported in H strain mice (511) and (648).

246. Two still incomplete experiments on dogs injected with ^{226}Ra are also available. In the Utah study (163) beagles were given single injections of the nuclide at 9 levels from 0.0074 to 10.4 μCi/kg, corresponding to cumulative average skeletal doses at one year before death of up to 10 900 rad. Osteosarcomas were found (433) down to the 0.166-μCi/kg level (458 rad). At the three highest dose levels (1.07-10.4 μCi/kg), 32 of 35 animals died with osteosarcoma. At 0.339 μCi/kg and at 0.166 μCi/kg respectively, 5 out of 13 and 1 out of 9 of the dogs that died had osteosarcoma. No bone tumours were found in 13 out of 22 animals dead at the lower levels or in the 12 out of 22 animals dead in the control group. A progressive decrease of the survival time of the animals who died with bone tumours was noticeable with increasing dose. Some more recent data from this experiment were analyzed in terms of dose effect by Mays and Lloyd (433), and it was observed that a linear relationship fitted through the data would predict 0.7 sarcoma cases at a dose level of 147 rad, while up to that time no case had been observed. It was also noticed that the slope of the linear dose-effect relationship (0.043 per cent incidence per rad) is remarkably similar to the slope found for the previously considered experiment on mice (191).

247. In the Davis study (218), ^{226}Ra was administered to beagles in 8 injections at 14-day intervals. Retention and distribution studies were carefully performed (461). The data on late effects are still incomplete, but osteosarcomas have appeared, the number being roughly related to dose. Acute haemopoietic effects (leukopenia and ensuing anaemia) have been described in these animals, but no myleoproliferative disorder has yet been found. Eye melanomas were also reported in the dog (651). A comparison of the toxicity of ^{90}Sr and ^{226}Ra, on the basis of injected activities causing bone cancer in equal times, has been performed by Blair (47) showing that the ratio of ^{226}Ra to ^{90}Sr is about 40 to 1.

248. Radium-228 is a beta emitter that decays (half-life 5.7 years) to radiothorium or ^{228}Th, an alpha emitter (energy 5.4-8.8 MeV, particle tissue range 39-88 μm) with a half-life of 1.9 years. Thorium-228 concentrates on the endosteal surfaces and is therefore to be considered a surface seeker. With this nuclide, experiments have been carried out on dogs given a single IV injection (163). It appears from the results (433), that at 8.49 μCi/kg, 1 of 4 dogs had died with bone tumours; at the 2.62-μCi/kg level, 4 of 5 dogs; and at the 0.973-μCi/kg level, 3 of 9 dogs had developed osteosarcomas. There appeared to be a shorter induction period at increasing doses. A relative carcinogenic potency of about 2.5 for ^{228}Ra compared to ^{226}Ra has been computed for the average skeletal doses accumulated to the mean time of death with bone tumours. This high figure has been ascribed to the longer alpha-particle

range of the ^{228}Th daughter and to the redeposition of ^{228}Ra, ^{228}Th and ^{224}Ra (163). The dose-effect relationship up to the peak incidence (corresponding to an average skeletal dose of 485 rad calculated at one year before death), has been reanalysed by Mays and Lloyd (433), and it appears that many functions could be fitted to such data. However, a linear function passing through the origin would predict at least one case of bone sarcoma among the four dogs that had died already at an average skeletal dose of 226 rad. Six dogs at that dose level were still alive and it cannot be excluded that bone sarcomas might develop among them. Until the conclusion of the experiments, therefore, no firm statement can be made.

249. Radium-224 (thorium X) has a half-life of 3.64 days. The decay scheme of the isotope is complex, but essentially it is an alpha emitter with energies of 5.4-8.8 MeV. Radium-224 is not a surface seeker, but its short half-life results in its decaying almost entirely on the bone surface. When IP-injected into Neuherberg mice of both sexes 20-30 days old in single administrations of 5-200 μCi/kg at weekly intervals, it induced bone tumours very efficiently (284). Even at 5 μCi/kg, about 13 per cent of the females developed osteosarcoma and a further increase up to 50 μCi/kg did not result in a higher incidence. At still higher levels, the incidence decreases owing to a high acute-mortality. Differences in induction between males and females were conspicuous. The monthly tumour rates and the integral of tumour rates in males increased with increasing doses up to 100 μCi/kg. Tumours of other tissues and organs were also observed but, with one exception, not in higher incidences than controls. The microscopic distribution of the ^{224}Ra and its relationship to tumour induction in various bones were reported on by Hendringer and Gössner (261).

250. The observations on sarcoma induction in these animals were also reported by Gössner *et al.* (222) and, supplemented by further data, provided the basis of an analysis of the dose-effect relationship for the induction of osteogenic tumours at low doses, carried out by Mays and Lloyd (433). In the female, a mean skeletal dose of 150 rad (5 μCi/kg) already produced a peak incidence of 17 per cent; in the male, 1500 rad (50 μCi/kg) were needed for an incidence of 7.6 per cent. Spontaneous incidence was zero in 259 males and 1.3 per cent among 460 females. The experimental points agreed better with the hypothesis of linearity than with the threshold model. On a "per rad" basis, females would appear to be 15-20 times more sensitive to the induction of bone sarcoma than males. Whether this phenomenon is related to the higher spontaneous incidence of bone tumours in females or to other reasons, such as more active bone remodelling by oestrogen stimulation in the female (507), it would, in the opinion of Mays and Lloyd (433), give cause to question the hypothesis of Mole (456) that radiosensitivity to tumour induction by alpha and beta emitters is the same in all species.

251. In more recent work, single injections of ^{224}Ra (1-100 μCi/kg, corresponding to skeletal doses of 70-3000 rad) produced incidences of osteosarcomas from 7 per cent to 22 per cent in female mice. In contrast with other data with beta emitters (185), dose protraction by fractionation (twice weekly up to 36 weeks) resulted in increasing incidence (up to 90 per cent) of osteosarcoma with protraction time and total dose. This phenomenon might be related to cell kinetics or disturbed cell turnover (478, 479, 223). Similar experiments in rats (5-40 μCi/kg) produced an incidence of osteosarcoma of about 19 per cent. The radionuclide appeared to be slightly more effective than in mice, for the same activity injected. A comparison between ^{226}Ra and ^{224}Ra data in mice on a μCi-to-μCi basis showed that ^{224}Ra might be 10 times less effective in the low and medium dose range, taking the life-span shortening effect of the two nuclides as the basis for comparison (284).

2. Thorium isotopes

252. Another series of beagles was injected in the Utah experiment with ^{228}Th in single IV injections of a monomeric solution (163). From the latest published data it would appear that the peak incidence (83 per cent of animals with bone sarcoma) occurs already at the 0.0302-μCi/kg level (corresponding to an average skeletal dose of 249 rad accumulated until one year before death). There is, as in other cases, a good inverse relationship between the dose and the time to death with osteosarcoma. At lower levels some departure from linearity is observed, in that one case of sarcoma would have been predicted by a linear model among the six dogs dead without tumours at doses of 16 and 47 rad. However, the experiment is not yet complete and more than 20 animals are still alive at the lowest doses. Thorium-228 was evaluated to be 9 times more carcinogenic than ^{226}Ra on the basis of the average time to death with osteosarcoma (163). On the basis of incidence per unit dose (433) the efficiency would seem to be 6-7 times that of ^{226}Ra.

253. Thorium-232 has received attention because colloidal thorium dioxide has been used as a contrast medium in radiological practice. The content of ^{232}Th in Thorotrast (the commercial name of the medium) is about 25 nCi/ml. Thorium-232 has a half-life of $1.4\ 10^{10}$ years and emits alpha particles with an energy of about 4 MeV. Upon IV injection it is taken up by the reticulo-endothelial cells and becomes encapsulated in fibrotic lesions of the liver and spleen, from where some daughter products, ^{224}Ra, ^{228}Ra and ^{228}Th, may escape to reach bone. However, the characteristic lesions of Thorotrast in the human are liver tumours and myeloproliferative diseases. Information on the distribution, retention and late effects of Thorotrast is to be found in 151 and an up-to-date collection of papers, mainly on human Thorotrast cases, has recently become available (549). Studies in animals are relatively few. Guimaraes and Lamerton (240) found concentration of Thorotrast in the liver, spleen and lung of injected mice. Bensted (31) described late-occurring vascular spleen tumours, anaemias and a high incidence of leukaemias in mice injected with Thorotrast, but questioned its carcinogenic activity as being due to the radioactivity of the injected compound. Nodular adenomatous hyperplasia, adenomas and parenchymal cell carcinomas of the liver have been observed, and a dose-effect curve for lung tumour induction in the rat has been obtained (231,

232). Spindle cell sarcoma of the cheek pouch and liver cholangiosarcomas were also reported in Syrian hamsters (465).

254. Thorium-227 has a half-life of 18.7 days, decaying to a relatively long-lived nuclide (^{223}Ra) that can enter mineral bone. Dose-effect curves for the induction of bone sarcoma in mice were reported for single administrations of this nuclide (410, 411, 223) in the range 0.1-50 μCi/kg, corresponding to average skeletal doses of 20-10 000 rad. A peak incidence of osteosarcomas (60 per cent) was observed with 5 μCi/kg, with a median time for appearance of these tumours of about 17 months. Some differences in the anatomical location of the tumours with low and high activities of the nuclide and with similar activities of ^{227}Th and ^{224}Ra were also reported. Metabolic and dosimetric studies were performed by Muller *et al.* (480) with rats inhaling solutions of ^{227}Th in nitrate form. These authors showed that an initial deposition of 100 nCi in the lung resulted in alpha-ray doses of 150 rad in this organ, 76 rad in bone, 2 rad in the kidney and 0.1 rad in the liver.

3. Plutonium

255. Although there are many isotopes of plutonium, ^{238}Pu and ^{239}Pu are the most widely used in radiobiological research. They are both alpha emitters, with half-lives of 87.8 and 24 390 years, respectively. Plutonium may exist in many valency states, but tetravalent Pu is the most important for biology. Plutonium tends to form complexes very easily and its deposition and toxicology are greatly influenced by the chemical form in which it is injected: monomeric plutonium is taken up preferentially by the skeleton, polymeric plutonium by the liver. Long-term exchanges between liver, skeleton and other deposition sites take place. Uptake through wounds and by inhalation are the most frequent routes of contamination in occupationally exposed workers. Animal experiments (292) suggest that bone and lung tumours are likely to be the most important risks of uptake by these routes. In the skeleton, Pu concentrates characteristically on the endosteal surfaces; it may however be found in the marrow, especially when administered in the polymeric form.

256. A thorough comparative discussion of the distribution, excretion and effects of Pu as a bone seeker has been published by Vaughan *et al.* (704). Updated reviews on the uptake, clearance, translocation and excretion of inhaled Pu can be found in Sanders (585) and Bair *et al.* (21). The deposition, retention and metabolism in the liver of various animal species has been reviewed by Lindenbaum and Rosenthal (381). The concentration of plutonium in gonads of five mammalian species and man was investigated by Richmond and Thomas (565). References and details on the radiation biology and radiotoxicology of Pu and other transuranium elements can be found in the extensive reviews by Stover and Jee (645), Hodge *et al.* (269), Medical Research Council (436), Bair (20) and Thompson (661). A review of experimental data obtained by investigators in the Union of Soviet Socialist Republics in 1971-1975 on the carcinogenic action of radiation and dealing mainly with plutonium and other actinides was also obtained by the Committee (477). Additional data will also be found in a chapter by Buldakov *et al.* in (72).

257. The available experimental studies concerning the induction of bone and bone-marrow tumours show that CF1 female mice of about 70 days of age given a single IV injection of (probably) polymeric ^{239}Pu in the range 0.04-15.6 μCi/kg developed a number of osteosarcomas (184, 185). As in other cases reported by the same authors, the carcinogenic effect was analyzed in terms of tumour expectancy, and it was found that this variable was reasonably linear with dose. A reanalysis of these data by Mays and Lloyd (433) shows that the highest percentage incidence of bone tumours (77 per cent) occurs at 3.1 μCi/kg, corresponding to an average skeletal dose of 560 rad at 140 days before death. No bone tumours were found in 195 mice injected with 0.04 and 0.08 μCi/kg, while a linear relationship of percentage incidence to dose including all points up to the peak would have predicted about 3 Pu-induced tumours in this range, in addition to about 2 spontaneous tumours. The probability of observing no tumour against the predicted 5 would be about 0.5. In these same mice, the low-dose groups had an incidence of lung tumours up to 68 per cent, and the decreased incidence at higher doses was attributed to life-span shortening. The frequency of tumours of the reticular tissues was highest at 0.16 μCi/kg and decreased thereafter, probably owing to the same cause. Liver changes (mainly degeneration and a few hepatomas) were also noted in a number of cases, but their significance could not be attributed with certainty to the nuclide, in view of the poor state of health of the colony (184). Monomeric ^{239}Pu (0.0058-0.025 μCi) and polymeric ^{239}Pu (0.0087 and 0.015 μCi) in solution was injected intravenously into other CF1 female mice. When the induction of bone sarcoma was compared on the basis of equal amounts of the nuclide in bone, mice given the monomeric solution appeared to develop twice as many tumours with a shorter induction time. The higher concentration of the monomeric nuclide on bone surfaces was primarily responsible for the difference (572).

258. In a small study of the toxicity of ^{239}Pu (2.95 μCi/kg) injected into (Marshall X August)F_1 rats 6-8 weeks old, Bensted *et al.* (33) reported the occurrence of osteogenic tumours and myelogenous leukaemia. Fractionation of the radionuclide into 5 injections given at two-week intervals seemed to increase the leukaemia incidence. In the same strain of rats, fractionation of the administration did not significantly alter the incidence of bone tumours but shortened the latency interval (177). Plutonium-239 citrate administered intraperitoneally to three-month-old rats (in the range 0.65-5.0 μCi/kg corresponding to an estimated accumulated bone dose of 700-4300 rad) (460) produced a high incidence of bone tumours; the time from injection to tumour death decreased with increasing doses. The incidence data were said to be inconsistent with a linear non-threshold hypothesis. As reported in the same publication, ^{239}Pu was also administered orally in daily fractions that gave an estimated dose to the bone of 33-57 rad. Osteosarcomas, leukaemia and other soft-tissue tumours appeared in a relatively high percentage of rats.

259. Buldakov and Lubchansky (73) studied the induction of bone tumours in Wistar-derived rats by ^{239}Pu administered in various chemical forms (citrate, nitrate, ammonium pentacarbonate), various routes of administration (inhalation, intratracheal, oral, intracutaneous, subcutaneous, intraperitoneal) and at various concentrations. All these data were analysed by Mays and Lloyd (381) by plotting computed (non-corrected) average skeletal doses against the percentage tumour incidence. Within the large scatter of the experimental points (to be expected from such a heterogeneous set of data) a linear function was fitted, corresponding to an induction rate of 0.06 per cent per rad. This value might increase to 0.1 per cent per rad if dose corrections for wasted radiation were applied.

260. Chronic oral administration of ^{239}Pu citrate in activities of 0.1 to 1.0 μCi per rat (average skeletal dose of 1-10 rad) also resulted in an increased incidence of osteosarcoma, leukaemia and marrow aplasia. Life-span changes were minimal in the treated animals (74). Malignant and non-malignant tumours of the skin and of subcutaneous tissues were also described by Buldakov *et al.* (75) after intracutaneous and subcutaneous injection of ^{239}Pu in various chemical forms. Finally, albino rats injected IP with 2.8 μCi submicron-sized $^{239}PuO_2$ particles developed mesotheliomas and sarcomas of the omentum in great number (591). Other data on ^{239}Pu-induced sarcomas of the skeleton in rats were given by James (300) and by Pesternikov and Bukhtoyarova (531).

261. The Utah study on beagle dogs injected intravenously at 1.4 years of age with monomeric ^{239}Pu citrate has been summarized by Mays and Lloyd in 1972 (433, 432), and more definitive data on the completed injection groups were recently presented by Stover (644) and by Jee *et al.* (308). Plutonium-239 levels ranged from 0.016 to 2.9 μCi/kg. The dose-effect relationship for bone sarcoma induction up to the peak level of 69 per cent at 0.048 μCi/kg (corresponding to an estimated average skeletal dose of 191 rad at one year before death) was analysed in one of the papers (433). The two low-dose points (0.0157 and 0.0477 μCi/kg) and the control point fitted a straight line reasonably well. Five further injection levels (between 0.00064 and 0.016 μCi/kg) were added to this experiment in 1973 but no data are yet available. In terms of injected activity the carcinogeneic potency of ^{239}Pu in dogs was evaluated by Hems and Mole (260) to be 10-20 times that of ^{226}Ra. The efficiency of ^{239}Pu relative to ^{226}Ra for life-span shortening was estimated to be 6:1 (163). On a "per rad" basis of average skeletal dose, and for the induction of bone tumours in beagles, this ratio would appear to be of the order of 9:1 (433). It has however been pointed out (397) that the relative toxicity of ^{239}Pu to ^{226}Ra in adult man may be expected to be higher than in dogs.

4. Other actinides

262. Some data on the distribution and carcinogenic effects of other actinides have also been reported. An indexed bibliography of works up to July 1976 includes most of this information (661). In the present context only the most significant data on tumour induction will be briefly reviewed for each nuclide tested.

263. *Neptunium-237* (alpha emitter; half-life, 2.14 10^6 years). This nuclide was injected IV as nitrate and oxalate into rats in doses ranging from 0.017 to 2.0 μCi/kg. Osteosarcomas were produced with incidences ranging from 9 to 58 per cent after average skeletal doses from 5 to 520 rad, respectively (373). In other experiments (371) ^{237}Np oxalate was given IV in activities of 0.00083 to 0.0021 μCi/kg, yielding corresponding bone doses of 110 and 270 rad. Osteosarcomas were seen in 23 per cent of the animals receiving the highest dose. Activities of 0.0001-0.005 μCi/g (100-3100 rad average skeletal dose) of ^{237}Np citrate were also injected into rats by the same route. Tumour incidence was highest in the animals receiving the highest doses, but results were not considered statistically significant when compared with control tumour incidence (472). At injected activities resulting in average skeletal doses higher than 100 rad a more frequent occurrence of soft-tissue tumours has been reported, together with an accelerated ageing. Leukaemia and malignant tumours of the liver and kidney are also consequences of single and chronic administration (372).

264. *Americium-241* (alpha emitter; half-life, 458 years). The distribution and retention of this nuclide were studied in adult mice by autoradiography after a single IV injection of 1 μCi of the nitrate compound (242), and in the developing teeth of rats after IP injection of the same activity (243). The isotope accumulates mainly in the bone and liver tissues. In rats, 30 μCi/kg of monomeric ^{241}Am citrate injected IV produced some impairment of the metaphyseal bone resorption, manifested as abnormal trabeculation (538). In experiments by Filippova *et al.* (181) on rats, the IP administration of ^{241}Am nitrate in doses of 26-13 330 μCi/kg (7-2099 rad to the skeleton) the incidence of osteosarcoma was increased with a maximum (9.3 per cent) at the average skeletal dose of 376 rad. A somewhat different picture with a maximum (24.5 per cent) at doses around 1660 rad was obtained with the citrate of the same isotope (493). Renal and liver tumours were also reported by Moskalev *et al.* (473) in rats injected with ^{241}Am.

265. The liver and the skeleton were confirmed to be the principal deposition sites also in beagle dogs injected IV with 0.00179-4.49 μCi/kg of the citrate. Some concentration of the nuclide in the thyroid gland and in kidney glomeruli was also noted (398). In the skeleton, americium deposits on bone surfaces more uniformly than plutonium. The endosteal and trabecular deposits of the isotope are 1.5-2 times greater than the periosteal deposits, while for plutonium this ratio varies from 2 to 4 (402). At the University of Utah the carcinogenic effects of ^{241}Am in beagles are being studied with eight activity levels ranging from 0.0018 to 2.8 μCi/kg. Two dogs at the 2.8-μCi/kg level have died with extreme liver degeneration after estimated doses of 5500 and 7600 rad in the organ. At 0.19 μCi/kg, 6 of 10 animals that died had developed osteosarcomas and had damage of the liver, kidney and thyroid. Osteosarcomas have been

observed with activities down to 0.096 μCi/kg, but more definite results are not expected to be available for many years (644). Americium-241 chloride injected IV in dogs at 1 μCi/kg (corresponding to an average skeletal dose of 1660 rad) was reported to induce osteosarcoma in 50 per cent of the treated animals (476).

266. *Curium-244 and 243* (alpha emitters with half-lives of 17.9 and 28 years, respectively). Only data on excretion, retention and distribution of injected curium citrate have been reported, showing that although the liver and skeleton are the major deposition sites, other tissues, particularly thyroid, have significant concentrations of the nuclide (400).

267. *Californium-249 and 252* (alpha emitters with half-lives of 352 and 2.63 years respectively). In the rat the distribution and biological effects of ^{252}Cf nitrate were studied with eight administered activities from 0.0005 to 0.064 μCi/g. One to two days after IV injection, about 70 per cent of the nuclide was found in the liver and about 30 per cent in the skeleton. The $LD_{50/15}$ was estimated to be 0.032 μCi/g, and the $LD_{50/30}$ 0.012 μCi/g. With acute doses the animals developed an agranulocytic syndrome. On the basis of the LD_{50}, ^{252}Cf was shown to be 5 times more toxic than ^{241}Am and 9 times more toxic than ^{244}Cm (757). In the beagle, the excretion and retention of ^{249}Cf and ^{252}Cf citrate were followed during 160 days after IV injection. After one week about 20 per cent of the injected californium was in the liver and about 60 per cent in other tissues, mainly in the skeleton (399).

268. *Einsteinium-253* (alpha emitter; half-life, 20.5 days). A study in beagles covered the early retention, excretion and distribution of ^{253}Es over 8 weeks following IV injections of the citrate. The isotope closely resembled californium in its behaviour and localized mainly in the skeleton, liver and thyroid (401).

5. Conclusions

269. The reviewed information on the incidence of bone sarcoma by alpha-emitting nuclides should be evaluated with great caution since the experimental data available are in general fragmentary and heterogeneous and, in particular, the series on large animal species are still incomplete. The relevant variables on which dose estimates should be based have not yet been identified and measured with any confidence (644); until such data are available, any conclusion could well be regarded as open to doubt. Moreover, even if accurate estimates of the dose and dose rate to osteogenic tissues could be made, the lack of knowledge on the variability among species and on the kinetics of normal and malignant cell populations would still make any projection of the risk to man (301) quite doubtful.

270. However, if some conclusion is to be drawn at the present time, the one arrived at by Mays and Lloyd (300) should probably be offered. Analysing the dose-effect relationships for the induction of bone sarcoma in 10 experimental series performed in man, dog, rat and mouse for a number of nuclides such as ^{224}Ra, ^{226}Ra, ^{228}Ra, ^{228}Th and ^{239}Pu injected by various routes and in various amounts, they observed linear responses with dose in some cases and threshold or sigmoid relationships in others. These conclusions are in sharp contrast with the results of parallel studies with beta emitters (434), where the relationship appears to be in all cases non-linear. The higher probability of linearity in the case of the alpha emitters has been ascribed to lower efficiency, or even the lack of repair processes after high-LET irradiation. An alternative explanation is provided by the theory of dual radiation action. Under the assumption of linearity it would of course be impossible to identify the lowest dose for which osteosarcoma can be demonstrated, as is the case with the "practical threshold" models of the beta emitters.

271. Comparisons of efficiencies among alpha emitters could be justified, and if one accepts at face value the dose estimates (433), it might be concluded from the slope of the fitted relationships that ^{239}Pu and ^{228}Th based on the mean skeletal dose might be about 10 times more carcinogenic to bone than ^{226}Ra, and that ^{226}Ra may be equally carcinogenic in mouse and dog, but an order of magnitude less effective in man. Finally, regarding the effect of dose rate, no clear demonstration of a sparing effect of low dose rate has been provided, and the best-documented case would even give indications in the opposite direction. Information on other types of tumours induced by alpha emitters is definitely too fragmentary for any generalization.

D. INHALED ALPHA EMITTERS

272. In regard to the effects of inhaled alpha emitters, important contributions in the field of lung pathology and oncology are found in the books edited by Hanna *et al.* (244) and Nettesheim *et al.* (409). A detailed account of all toxicological effects of inhaled plutonium is given by Bair *et al.* (21). In regard to the induction of tumours, particularly of the lung, there are a number of studies in various species of animals. Mice (BAF_1 female) were injected intratracheally with 0.003-0.16 μCi $^{239}PuO_2$ (doses estimated at 115-4000 rad to the lung) and developed pulmonary fibrosarcomas and carcinomas with a maximum incidence of 12 per cent at 0.06 μCi (657, 656).

273. Carcinomas and bronchio-alveolar adenocarcinomas were also reported, with a maximum incidence of 25 per cent in three groups of female Sprague-Dawley rats inhaling 0.005-0.207 μCi of $^{238}PuO_2$ (9-375 rad to the lung). Lower incidences were found at lower intakes down to 0.005 μCi deposited in the lung. Tumours of other sites were also found in a significantly higher percentage in Pu-treated animals (586). An increased incidence of mammary tumours in rats injected with $^{239}PuO_2$ was reported, although, in general, the deposition of less than 1 μCi/kg of Pu did not result in an increased incidence of tumours of the breast, irrespective of the method of Pu administration or of the solubility of the compounds (588). The uptake in the lung and the effects of $^{239}PuO_2$ particles injected intraperitoneally (589) or transthoracically in the lung (592) were also reported. Preliminary data on pulmonary carcinogenesis in Wistar rats after inhalation of various transuranic compounds are also available, and

they show an influence of dose and dose distribution on the type and the incidence of neoplasms (590). An experimental study of the effects of inhaled alpha emitters (^{238}Pu, ^{239}Pu and ^{241}Am given as oxide and nitrate) was reported recently (468). The accumulated doses varied between 1 and 10 000 rad, and the spatial and temporal dose distributions depended on the different physico-chemical forms used. Survival times and tumour latency times and tumour frequencies, locations and histotypes were analyzed as a function of dose rate and dose distribution. On the basis of these data a model relating dose and the acceleration of tumour appearance was developed.

274. Two large-scale studies in the USSR are also available in this field. Yerokhin *et al.* (745) carried out an extensive study on 1097 male and female Wistar rats administered intratracheally with 0.00042-1.0 μCi of ^{239}Pu nitrate or 1 μCi plutonyl acetate. The range of doses to the lung in the first study was 3-5855 rad, and in the second the pulmonary dose was 1870 rad. The percentage tumour incidence varied rather regularly from 2.5 per cent in the lowest intake group to 33 per cent at 0.42 μCi. A decrease to 24 per cent was noticed at 1 μCi, while this same activity of plutonyl acetate gave rise to about 40 per cent lung tumours. The histological types observed were squamous cell carcinomas, adeno-carcinomas and hemangiosarcomas. Koshurnikova *et al.* (358) observed up to 27 per cent of pulmonary tumours in rats inhaling ^{239}Pu citrate (0.008-1.030 μCi/g of pulmonary tissue) and up to 48 per cent of tumours after ammonium ^{239}Pu pentacarbonate (0.004-1.46 μCi/g of lung). Squamous cell carcinomas, adeno-carcinomas and hemangio-sarcomas were the most common pathological forms found. In the same study, ammonium ^{239}Pu pentacarbonate and ^{239}Pu nitrate in various amounts produced up to 20 per cent malignant tumours in the rabbit. The induction of lung tumours in rabbits administered intratracheally ^{144}Ce (25 μCi per animal, corresponding to 24 000 rad to the lung) was also described by Ivanov and Kurschakova (299). Comparison of these data with other data on ^{239}Pu (358) would give an RBE of ^{239}Pu as compared to ^{144}Ce of about 12 at this dose level. Data on interspecies comparisons of the efficiency with which tumours are induced by intratracheally administered plutonium in soluble form are reported by Moskalev *et al.* (471).

275. In the dog, Park and Bair (22) produced nearly 90 per cent of bronchio-alveolar carcinomas after inhalation of 0.6 μCi of ^{239}Pu, corresponding to a lung dose of 2922 rad. At higher doses up to 4094 rad, the incidence of tumours and survival time of the dogs decreased. The acute and chronic toxicity of inhaled plutonium in dogs was also described by Park (522), Park *et al.* (523, 525) and Clarke *et al.* (111). In experiments by Moskalev *et al.* (473) the inhalation of ^{241}Am nitrate in dogs (0.14-1.39 μCi/kg, or 344-3320 rad to the skeleton) induced the appearance of osteosarcomas in all cases, while there was no incidence of this tumour in control animals at all. Park *et al.* (524), Levdik *et al.* (373) and Koshurnikova *et al.* (357) reported co-carcinogenic studies on Pu-induced pulmonary neoplasias, and Filippova and Nifatov (180) published data on lung sclerosis and carcinogenesis following intratracheal administration of ^{237}Np and ^{241}Am, respectively. A quantitative assay was recently developed by Nolibé *et al.* (510) for the transplantation of lung fragments from Pu-contaminated rats into immunodepressed mice or genetically compatible rats. In the host animals transplantation of lung tissue from old normal donors resulted in differentiation resembling a tumorous condition. Lung from contaminated rats showed an increased frequency of these lesions with a complex dose-effect relationship.

276. An analysis of the dose-effect relationship for lung cancer induction, derived from some of these experiments, was attempted by Bair *et al.* (22). The plot of the data showed that in the rat, an accumulated dose to the lung of as low as 10 rad might be carcinogenic. The peak incidence in mice and rats probably occurs between 200 and 1000 rad and the few available results in dogs would show an even higher incidence. Special consideration was given in this paper to the problem of tissue distribution of plutonium, and it was concluded that the non-uniformity of the dose distribution does not produce a higher hazard by the nuclide but that on the contrary, a more homogeneous dispersion in the lung can be more hazardous. A similar conclusion was reached by Little *et al.* (396), by Snipes and Brooks (631) and in a recent report (487) by the National Council on Radiation Protection (NCRP).

277. In another review, Baily concludes (155) that radiation from either alpha or beta radioactive materials is usually, but not invariably, more effective than external irradiation for lung tumour induction. The difference in effectiveness is not sufficiently large to abandon the presently accepted concept of average lung dose in evaluating the hazards from radioactive particles in the lung. Lower efficiency for lung cancer induction of inhaled beta-gamma emitters, by a factor of about 10, would confirm the higher RBE of the alpha irradiation by about the same factor (22).

V. BIOLOGICAL VARIABLES IN RADIATION CARCINOGENESIS

A. GENERAL

278. The object of the present chapter is to examine the role of various biological factors in the induction of tumours by ionizing radiation. The most common variables known to alter the neoplastic response of irradiated animals, such as genetic constitution, sex and age, will be reviewed, and additionally a problem of great relevance for radiation protection will be considered, namely the question of the cells and tissues at risk. This question will be considered with the aim of identifying in the tissues susceptible to carcinogenesis, the cellular compartments where tumours originally arise; this identification might allow the quantification of induction phenomena on a cellular basis, and would thus establish a link between information and work *in vitro* and *in vivo*.

B. GENETIC VARIABLES

1. Species

279. Few systematic comparative studies have been made on the influence of the species on the neoplastic response in mammals, and most of the data available have been obtained in the rodent. This problem has been discussed on the basis of the limited available information in previous reports of the Committee (669, 670) and also by various reviews (69, 672, 675, 678). It should be emphasized that the question of species susceptibility to radiation-induced neoplasia has far reaching implications, both theoretical and practical. In fact, it relates not only to the obvious need of extrapolating from one species to another, not only the carcinogenic effect, but also the relationships between latency time and life-span of the species (69). It is also relevant to the relationships between the spontaneous incidence of certain tumour types in certain species *versus* the radiation susceptibility of these animals to the same tumours.

280. Concerning tumours arising after external irradiation, it has often been pointed out (69, 670) that the variation between species appears to be considerable and that in any case, it seems larger than that observed after internal irradiation (456). Although it is true that virtually any type of tumour can be induced in any species by the appropriate doses and administration schedules (670), some species may develop certain tumours after rather low doses, or with relatively shorter latency times than others, so that the spectrum of malignancies found after irradiation in different species is extremely variable.

281. There are numerous examples of such differential effects. By comparison with other species, the mouse ovary is an example of an exceptionally high sensitivity to tumour induction. The rat is reputed to be considerably more susceptible to kidney tumour induction by 500 rad whole-body x irradiation than other species, in particular the mouse (36), but the apparent resistance of the mouse may be attributed to the particularly long latency of these tumours or to different pathogenetic mechanisms operating in the two species (422). Doses of 300-500 rad are definitely carcinogenic for many species, but the burro after single and total multiple doses of 320-545 rad develops an important dose-related shortening of life, without evidence of tumours (67). Lung cancer after 3000 or 4000 rad in the chest occurs in 43 per cent of rats but only in 2 per cent of hamsters (239), and this observation is confirmed by continuous irradiation experiments (734). Rats may develop leukaemia after irradiation, but in a less consistent pattern than mice (683), and so do guinea-pigs (581); Chinese hamsters, on the other hand, appear to be strikingly resistant (450). Data on the incidence of myeloproliferative disorders in animals other than rodents have been reviewed by Nielsen (491).

282. When five different species of rodents were continuously exposed to ^{60}Co radiation, more bone and, especially, lung tumours appeared in rats than in hamsters; other differences in inducibility of lung and oesophageal cancer were also shown to exist between various mouse strains (734). The differences between species found in this latter irradiation experiment appeared, on the whole, to be smaller than the differences in spontaneous tumours. This fact has been interpreted as evidence that radiation is so effectively carcinogenic as to override minor variations in susceptibility (734). Data are still insufficient to draw a comprehensive picture, and it may be concluded that the genetic character of the species is probably the main factor in these variations, to which other physiological and environmental components could add secondary, but by no means unimportant, contributions.

2. Strain

283. The genetic variation of the susceptibility to long-term effects of radiation has been explored, particularly in inbred strains of mouse, and discussed, for example, by Grahn (226, 225) and Grahn *et al.* (227). Data on the spontaneous incidence of various forms of leukaemia in several strains of mice and on their susceptibility to radiation induction have been repeatedly mentioned in this annex (see particularly paragraphs 45 to 49) and will not be examined again. The conclusions drawn by Upton and Cosgrove (683) and Upton (678) are still applicable since, in general, strains having low spontaneous incidence of a particular disease are prone to develop an increased incidence after irradiation, while high-leukaemic strains are not as susceptible. The presence of a viral agent and its vertical transmission may be seen, for some forms of leukaemia, as a necessary condition for interspecies variations of the disease, although the condition is not sufficient since it may be modified to a large extent by the immunological, hormonal and ambient factors discussed in chapter II of this Annex.

284. The analysis of chronic-radiation lethality data from many different mouse strains suggests that all genotypes respond to radiation according to a single primary-injury parameter that can be expressed as life-span shortening. Strain or genotype specific sensitivities to tumour induction are of a secondary genetic nature and may be separated from the basic injury under special conditions of exposure (224). Daily irradiation experiments have indicated, for example, that life-span shortening at doses below 6 rad/day can be associated with specific neoplastic disease, but at higher dose rates a non-specific component of the damage is detectable (227). Such observations agree with the general view that at sufficiently high doses genetic differences tend to disappear (670). Information concerning sex differences in tumour induction by external irradiation, can be found in paragraphs 68 and 73.

3. Internal irradiation

285. Although it is commonly held that the neoplastic response of different animal species is more uniform after internal than after external irradiation (69, 456, 670), differences in the tumour susceptibility in the former case are also quite apparent. For internal exposures, in addition to the genetic factors discussed.

anatomical and physiological factors could modify the neoplastic response through modifications of the dose received by the relevant cells. For example, differences with species and age of the trabeculation pattern of bones are quite substantial (544, 18), and they influence the dose to the osteogenic or haemopoietic target cells in the case of bone-seeking radionuclides. Metabolic differences in the retention and excretion of radionuclides between different animals have also been shown, even for closely related chemical substances, and when operating over a long time they will result in appreciable differences of the accumulated dose in the target tissues (680). Thus, extrapolation to man of metabolic patterns and of the ensuing neoplastic effects only appears possible after careful consideration of several animal species with different life spans. Evaluation of the relative species sensitivity should therefore be made after appropriate corrections for all the factors mentioned above, and on the common basis of the estimated dose to the target cells.

286. Attempts to express sensitivity in terms of tumour induction have been made in the case of certain alpha-emitting radionuclides (433), and it has been concluded, for example, that the dog and the mouse are very similar in their response to ^{226}Ra, but that man appears to be less susceptible by an order of magnitude. After appropriate corrections, mice and dogs seem also to be equally sensitive to the oncogenic effects of ^{90}Sr (188) or ^{226}Ra (219) and, on the basis of the lowest dose of ^{90}Sr proven to be carcinogenic for bone, mice, rats and dogs, would also appear to be very similar in their susceptibilities (434), while the hamster would be more resistant (64). The cat, on the other hand, has been reported as particularly sensitive to ^{89}Sr induction of osteosarcoma (489).

287. Systematic comparisons between species and strains are, however, rather few. In one of them, 70-day-old CF1 and CBA mice were given the same activity of ^{90}Sr and examined every week radiographically for bone tumours. CF1 animals developed the first bone sarcoma at 98 days, and from then on tumour appearance followed a normal distribution with the mode at 27 weeks. The average time from the first scoring of tumours to death was 39 days. In CBA mice, on the other hand, tumours started to appear later and the peak incidence was at 35 weeks. The presence of inhibiting host factors, the higher spontaneous incidence of osteosarcoma in CF1 animals and the different rates of tumour growth in the two strains might account for these effects (185). More recently, four inbred strains of hamster treated with multiple intratracheal administrations of ^{210}Po absorbed onto hematite particles were found to have very different tolerances to the treatment and induction times of the lung tumours. However, the final incidence of the tumours was very similar in the four strains, varying between 33 per cent and 50 per cent (395).

288. Species differences in the response of dogs, rabbits and rats to subcutaneous injections of ^{210}Po were also reported (490). An important difference in susceptibility to osteosarcoma induction by ^{224}Ra between male and female mice of the NMRI strain (284) has already been discussed (paras. 250-252); this observation appears to be in contradiction with what is found in humans (636). Chameaud *et al.* (98) have recently compared the susceptibility to lung tumour induction by radon and its daughters in man and in rat. They have shown that the tumour incidence plotted against the accumulated exposure in working level months (WLM) is similar in experimental studies with animals and in epidemiological surveys in man. They concluded that the rat could be a good model system for analyzing this type of neoplasia. In conclusion, until further progress in the specification of anatomo-physiological characteristics of the various species is made, and until assessments of the dose to the relevant tissues may be carried out with better confidence, the scanty available data appear to be unsuitable for meaningful generalizations.

C. AGE EFFECTS

1. Post-natal irradiation

289. The relationship between age and susceptibility to the induction of tumours has been explored by irradiating animals of different post-natal ages or, in other cases, by comparing animals irradiated *in utero* or after birth. The two cases will be considered separately. It has long been known that life-span shortening in mice and rats after single acutely delivered doses of radiation is frequently associated with tumour induction, even at relatively low doses. Life-span shortening changes considerably with the age at irradiation: it is maximum in juvenile animals, then decreases with increasing age and can rise again in very old animals (383, 384, 385, 386, 387, 451, 349, 313, 130, 682). These variations have been attributed in part to the long latency in the expression of the life-span shortening effect (682) and in part to an intrinsic age-dependent change of the animals' susceptibility (313, 385).

290. Concerning specifically the induction of tumours, only fragmentary data on age-dependent differences in response are available. Mice of the RF strain given whole-body doses of 100-300 rad at several ages from birth to 180 days, showed that their susceptibility to granulocytic leukaemia is minimal shortly after birth, reaches a maximum at about 70 days of age and then slowly declines thereafter. This trend occurs in both sexes, although in the male peak incidence reaches 54 per cent after 300 rad of x rays, while in the female the incidence after the same dose at the same age is only 26 per cent (690). Susceptibility to the induction of thymic lymphoma in the same strain is maximal shortly after birth and declines later in life with natural thymic involution (690). These observations are in good agreement with data on strain A mice, where maximal susceptibility to induction of lymphoid tumours after 1000 rad of x rays (given in 12 days) occurs at the age of 1 month or earlier, with a sharp decrease at 2 months and later (319). They are also in agreement with data on the C57BL mouse given fractionated daily doses of 50 rad of x rays for 12 consecutive days, where the increased incidence in early life is also associated with a shorter mean induction-time (320), and with data on SAS/4 animals, where leukaemia incidence tends to decrease with increasing age at exposure (386).

291. Sensitivity to the induction of ovarian tumours in RF females appears to be high (61 per cent after

300 rad) between 1 and 9 days of age and to decrease progressively up to 70 days (26 per cent for the same dose) (573). A very definite age variation is also found in SAS/4 mice where a dose of 650 rad of 15-MeV x rays produces about a 30 per cent incidence of ovarian tumours at 10-20 weeks of age, whereas in younger and older ages the incidence is smaller and may even be less than the 15-per-cent spontaneous incidence observed in the non-irradiated control mice (386). In another report, the spontaneous incidence of this neoplasia appeared to be different in three different mouse strains (IC, XLII and C3He/A), but a whole-body dose of 300 rad of x rays produced in all strains a higher tumour incidence in mice irradiated at an age of 4-6 weeks than in mice irradiated at an age of 4-6 months (566). In LAF_1 mice the induction of ovarian tumours was likewise lower after irradiation at 1 year than after irradiation at 10 weeks of age (130), but no differences with age, between 5 months and 2 years, were found in CAF_1 mice (349). In Wistar rats, the induction of ovarian tumours was significantly larger when x irradiation was performed at 13 days of age with a single dose of 270 rad (560).

292. A lack of dependence of **mammary tumour** development on age at the time of irradiation, between 40 and 160 days, was observed in Sprague-Dawley females exposed to 500 R of ^{60}Co gamma radiation (610). **Pulmonary tumour** induction tended to increase with age in SAS/4 mice (386), but was unaffected in LAF_1 mice between 10 weeks and 1 year of age (130) and in CAF_1 mice between 5 months and 1 year (349). In the rat the induction of these tumours was significantly higher at 3 months than at 1 or 21 months (95). **Kidney tumours** were found more frequently in mice given 690 rad of x rays at birth than in animals irradiated at 3 months of age (123). Other data on the incidence of miscellaneous tumours as a function of the age at exposure may also be found in Kohn and Guttman (349), Reincke *et al.* (560), Jones, Osborn and Kimeldorf (315), Jones (311) and Castanera, Jones and Kimeldorf (95).

293. It may be concluded that there are quite definite age-dependent changes in the susceptibility to the induction of various types of tumours by external irradiation. The best-documented case is that of leukaemia (both thymic and granulocytic) where data on four different strains of mouse have confirmed the presence of a low susceptibility at birth, followed by a peak incidence in the young mouse and a final decrease of induction with age. The sensitivity of the ovarian tissue tends in general to decrease with post-natal age, while the susceptibility to pulmonary tumours appears to be variable in the different animals examined. Data on other neoplasms are insufficient to allow any conclusion.

2. Pre-natal irradiation

294. Data on the relative susceptibility to tumour induction in animals irradiated before or after birth are relatively scarce compared to the data on pre-natal irradiation in humans. Up-to-date lists of references on this subject have been published (562, 458).

295. When RF mice were irradiated *in utero* 1-3 days before birth with 300 rad of x rays, it was found that the incidence of granulocytic leukaemia was nil, but it increased substantially when irradiation was performed after birth to reach an incidence of 30-50 per cent at 70 days of age. Thymic lymphoma was similarly not induced by irradiation *in utero* but was readily induced after birth. Ovarian tumours were significantly less common in mice irradiated *in utero* than post-natally. There are no data at lower doses, but it could be assumed that 300 rad is too large a dose for effective induction of these tumours, because at doses of this magnitude the dose-effect relationship observed in the adult could be already in the declining portion (see paragraphs 151 to 154) (690). In a study carried out in RF mice irradiated at various pre- and post-natal ages, life-span shortening was found to be minimal in animals exposed pre-natally except for males exposed to 300 rad at 14½ days of gestation, where survival time was very short. Mice exposed pre-natally showed stunting of body growth, microcephaly and premature glomerulosclerosis but no increases in incidence of leukaemia or solid tumours were noted (682). These data appear to be generally in agreement with data on CF1 mice with doses of 100 rad of x rays, where the evidence for any increment in neoplasia following embryonic or foetal irradiation was equivocal. There was, however, much evidence of reduced growth and permanent stunting (580). It may thus be concluded from all these data that the long-term effects of pre-natal irradiation relate more clearly to growth disturbances than to tumourogenesis.

296. From the available data in the rat (560), it would appear that animals irradiated *in utero* with a single dose of 270 rad of x rays had a considerably higher short-term mortality, and the survivors showed growth retardation, microcephaly and micro-opthalmia. Genital tumours in the female increased significantly only after post-natal irradiation, and their relatively low incidence in pre-natally irradiated rats was attributed to hypoplasia of the genital organs. Other data on Wistar rats, irradiated on the 18th day of gestation, have been reported by Piontovski and Kalashnikova (535). The beagle dog foetus responds to continuous irradiation *in utero* in a manner similar to that of the adult dog, but no effects on tumour induction were reported. At a dose rate of 17 rad/day or less of ^{60}Co gamma rays, beagle bitches irradiated continuously from conception delivered apparently normal litters. At 5 rad/day, all female offspring were sterile, and at 10 rad/day, all male pups were sterile (512).

297. From the fragmentary data available, which do not cover specific tumour types in many different strains and species, it could be concluded that pre-natal irradiation affects the growth and differentiation of mammalian systems, rather than their malignant transformation. There is no evidence that irradiation *in utero* of mice and rats may be more carcinogenic than irradiation of young or adult animals.

3. Internal emitters

298. Age-related differences in the susceptibility to the induction of tumours by internal emitters have at times been reported. In the case of radiostrontium intoxica-

tion, the mouse (3-20 weeks) (701), the rat (6-60 weeks) (646) and the dog (new-born to adult) (188) were apparently more sensitive to bone sarcoma induction in youth than in old age. However, when appropriate dosimetric corrections to account for body size and higher retention in the young animals were made, these differences disappeared, showing that there is no major age variation in the intrinsic susceptibility of the cells at risk. Similarly, a larger susceptibility to bone tumours was noted after injection of ^{144}Ce (but not after treatment with ^{239}Pu) in weanling rats than in adults (417).

299. Comparisons of tumour induction between pre- and post-natal ages have been made by Finkel and her group using foetal and infant beagle dogs exposed to ^{89}Sr. At the level of 1.33 μCi/kg *in utero*, ^{89}Sr was not acutely lethal, nor did it produce haematologic disorders and bone sarcoma, however, extremely abnormal skeletal growth was found (186). In a later report (188) on ^{90}Sr, some tumours were seen at higher levels of contamination. Differences in retention were held responsible for differences in tumour induction with respect to post-natal exposures, but it was concluded, on the whole, that pre-natal exposure was not more carcinogenic than post-natal exposures at comparable levels of dose. In the pig, exposure of the foetus to ^{90}Sr ingested by the mother, plays an important role in the development of leukaemia (517). It has been reported that the administration of ^{32}P to pregnant mice produces a significant increase of the incidence of leukaemia in female offspring (272). Finally, the age dependence of metabolism and effects of ^{239}Pu has been studied in the rat by Sikov and Mahlum (626).

300. The relative sensitivity of the thyroid gland to the induction of tumours by ^{131}I was investigated by Walinder and Sjoden (729) in mice exposed *in utero* or at the age of 3 months. They found 3 benign and 4 malignant neoplasms in 109 mice irradiated *in utero* to 7800 rad but no tumours at all after irradiation of 91 animals 3 months old to approximately similar doses. It was therefore concluded that the foetal thyroid gland is more susceptible than the adult thyroid. In analysing other evidence (160, 627), Pochin (537) concluded, however, that the numbers involved are probably too small for any conclusive statement about a higher sensitivity of the foetal thyroid.

D. TISSUES AT RISK

1. General

301. As pointed out in a publication (291) of the International Commission on Radiological Protection (ICRP), no general criteria are available at present to make reasonable predictions of the susceptibility of various tissues to tumour induction by radiation on the basis of known properties of the tissues themselves. Tumour susceptibility is therefore an empirical concept derived from the observed frequencies of cancer in different tissues or organs, following a given radiation dose. In man such a relative scale of sensitivity to tumour induction has been derived, with possible use in establishing dose limits to individual parts of the body (291). An empirical procedure is perfectly adequate for practical purposes such as setting dose limits, but fails to identify and explain biologically the reasons why some tissues or organs are more prone to neoplastic transformation than others, in a manner which is obviously quite independent of the number of cells they contain or of the renewal rate of these cells.

302. In considering this problem, it has to be kept in mind that although the natural occurrence of tumours is a rather common phenomenon in animal populations, the probability that a neoplastic clone would be induced in cells exposed to radiation is quite low. Induced neoplastic transformation may therefore be regarded as a rare phenomenon (70, 429, 459). There are general hypotheses compatible with this fact and also with the extreme variability of cell susceptibility to tumour induction; they have been discussed at some length in chapter II of this Annex. Other basic questions have not yet been discussed in detail, such as whether all the cells in any one tissue or organ, irrespective of their state of differentiation, are susceptible to the induction of neoplasia or only some of them can be transformed, or whether it is possible to identify the cells in a population having a higher risk of neoplastic transformation by radiation. These questions have already been considered in the 1972 report of the Committee (670) with special regard to bone and skin tumours.

303. In a recent publication (430), Mayneord and Clarke have discussed the relevance and importance of the number of cells at risk in studies of radiation carcinogenesis and have developed some biomathematical concepts to relate the transformation of these cells to radiation dose under various conditions of irradiation. Although the authors themselves recognize the limitations of such an approach in view of the complex reality of the biological mechanisms, the formulations proposed and the general consequences to be drawn provide a stimulus for a better definition of the relevant problems. In the following paragraphs the question of the cells at risk will be considered systematically in the light of available information, in an attempt to elucidate the problem of the differential susceptibility of cells to tumour induction and also to provide a rational basis for possible extrapolation of data between species.

304. *Leukaemia.* The comparative aspects of radiation-induced leukaemia in animals have been considered by Upton (678) and Kaplan (328). It is quite apparent that the histological type, the time of onset and the organ distribution of the reticular tissue disorders developing in the experimental animals are extremely variable. In the mouse, which is the species most extensively studied, the inducibility of leukaemia by external or internal irradiation and its type depend primarily on the strain and then on sex, age at irradiation, environmental factors, radiation dose and type of fractionation. All these factors have been considered at some length in this Annex. In this species the tumours of the reticular tissue may frequently take the form of a lymphoma (in the C57BL strain typically) which appears to arise early in life in the thymus and then to spread in some cases to the thoracic lymph nodes or to other lymphatic and haemopoietic districts (326). Alternatively (and more

rarely) a myelogenous granulocytic leukaemia may occur, particularly in the RF strain, involving primarily the marrow, spleen and liver and producing peripheral blood leucocytosis (685).

305. In the mouse another form of non-thymic reticular tumour of complex and still uncertain classification has also been observed, which generally arises late in life, involving primarily the reticular cells of the spleen and of the abdominal lymph node and which may then extend to other organs where reticular tissue is present (683). In addition to anatomo-pathological and epidemiological evidence, there are also radiobiological reasons to keep these tumours separate from the others since radiation appears to depress, rather than enhance, the incidence of the diseases (see paragraphs 117 and 119). In the rat the development of radiation-induced leukaemia is less well documented as to form and induction time and rate, but myeloid leukaemia, leucosarcoma and reticular diseases have been reported (683, 161). In guinea-pigs, leukaemias of a chronic lymphatic type (683) or lymphosarcomas (581) have been described. Swine irradiated chronically with ^{90}Sr develop high incidences of myeloproliferative disorders, including myeloid, lymphatic and stem cell leukaemias (278), while beagle dogs submitted to chronic irradiation by external sources (205) or by ^{90}Sr feeding (166) show highly proliferative infiltrating forms of myeloid leukaemia.

306. In view of the diversity of these syndromes and in the absence of any indication as to whether and to what extent any of them might be akin to the human leukaemias, attempts to identify the nature and the number of the cells at risk on the basis of our present knowledge may only be regarded as an "academic pursuit" (459). For all practical purposes, in fact, reliance must be placed mainly on the few observations made in the cases of human leukaemia (562). The virus-induced thymic lymphoma of the mouse, the complex pathogenesis of which has been sufficiently well documented, may be a good example of the difficulties involved in assessing the cells at risk.

307. As already discussed in paragraphs 46 to 48, anatomo-pathological observations and the effects of thymectomy and thymus reimplantation have shown that thymus is the target organ for the action of the virus. Further experimental evidence has identified the immature lymphoid cells of the thymus as the target cells in this tumour system. However, irradiation of the target organ is not sufficient, as such, to induce lymphoma without irradiation of the haemopoietic system and, in addition, other micro-environmental, humoral, immunological and consitutional factors are essential requirements for the expression of the disease. The relative abundance and the susceptibility of the target cells to the virus are very dependent on their state of differentiation and on the age and constitution of the animal (326, 327). It is clear, however, that since a viral agent is present at the origin of the disease, the problem is primarily one of investigating quantitatively *in vivo* the interactions between target cells and virus, since radiation acts primarily through a change in the host-virus relationships. The evidence on this point has been reviewed by Kaplan (327).

308. The same approach should probably be followed in the case of myeloid leukaemia, although definitely fewer data are available. The anatomo-pathological evidence concerning the site, origin and histological type of the disease, and the fact that it occurs after localized irradiation of the skeleton by bone-seeking nuclides (particularly high-energy beta emitters) point to the bone marrow as the target tissue and, among the great variety of cells of the marrow, to the more immature myeloproliferative elements as the target cells. Since it is now possible to titrate progenitor haemopoietic cells by *in vivo* and *in vitro* assays (629), it should also be possible to study cell-virus interaction in the case of myelogenous leukaemia.

309. Special consideration should be given to the haematological neoplasms occurring in animals (swine and dogs) submitted to chronic external irradiation or to internal irradiation by beta-emitting bone seekers. The character of these diseases is rather heterogenous when compared to other forms of leukaemia in the rodent. They are often preceded by profound disturbances of haemopoiesis, including all the differentiative lines of the marrow. Considerable differences in the invasiveness of the diseases in different species are noticeable. Although they are frequently referred to as myelogenous leukaemias, morphologically all cell types, from the more differentiated ot the "stem cell", are often described. It seems reasonable, therefore, to conclude that the identification of one type of progenitor haemopoietic cell as a possible target and the assumption of a common induction mechanism are probably not justifiable, in view of pathological, epidemiological and clinical variety.

310. For other non-thymic lymphomas, for which there is as yet no definite proof of a viral origin, preliminary data on the relationships between dose and probability of cell transformation have been obtained *in vivo*, in a model system where heavily irradiated animals have been repopulated with a known number of isogenetic bone-marrow cells, intact or irradiated (135, 437). A dose-related excess of leukaemia has been documented in the animals given irradiated marrow and, correcting for radiation cell-killing, some estimates of the probability of leukaemic transformation of the injected bone-marrow stem cells have been obtained. Quite aside from the absolute value of these estimates, which may or may not be relevant, it was shown that the rate of induction per unit dose of leukaemia per surviving cell was higher at 400 than at 200 rad; this would be compatible with the fact that the probability of transformation in this system is not linear (concave) up to the doses tested.

311. It appears, in conclusion, that in order to investigate the relationships between dose and probability of neoplastic transformation of target cells, in cases where radiation is not simply directly acting on the target tissue but through indirect or systemic mechanisms, highly sophisticated techniques of quantitative radiation biology and cellular virology must be developed and applied *in vivo*. Nevertheless, if the data on radiation-induced cell transformation *in vitro* (paras. 53 to 58) should at some stage be applicable to *in*

vivo systems and be useful not only for investigations of mechanisms but also for practical applications (564), suitable *in vivo* models ought to be developed to fill the gap. These models should have under better control the number and the functional characteristics of the cells that appear to be the likely candidates for neoplastic transformation.

312. *Ovary.* Irradiation of the ovary leads in general to a precocious reduction of the number of oocytes and ovarian follicles (14). With the exception of these cells, practically all the other cells forming the organ (lutein and granulosa cells, mesothelial and endothelial cells) appear susceptible to neoplastic transformation by radiation (675). Ovarian tumours are particularly frequent in the mouse, where doses as low as 50-100 rad of low-LET radiation may produce peak incidences of tumours (107). They appear to be responsive to hormonal mediation by the pituitary gonadotropins or by the controlateral non-irradiated ovary, in the case of partial-body irradiation (211). No special cell may be identified as being characteristically at risk in the case of ovarian carcinogenesis.

313. *Lung.* The pulmonary tissue is very complex, both morphologically (633) and functionally (623). A considerable spectrum of tumour types occur spontaneously (492) or are induced in domestic animals after pulmonary deposition of radionuclides. Bronchio-alveolar carcinomas have been reported in dogs (111), squamous cell carcinoma, adeno-carcinoma and hemangiosarcoma in the rat (358, 741) and fibrosarcoma, squamous cell carcinoma and bronchiolar carcinoma in the mouse (657). It is apparent, therefore, that all cells of endodermal origin composing the lung may give rise to neoplasia. With succeeding degrees of anaplasia, the cells may express any of the characteristics of the embryonic pulmonary endoderm (633). Connective and vascular tissues are also capable of neoplastic transformation. The role of non-specific fibrosis of the lung, preceding or accompanying the lung neoplasia, has been discussed (111) and it has been concluded that it may be an important contributing factor when a specific carcinogen is present. Bronchiolar and alveolar proliferation into scarred areas of the lung gives rise to proliferative and metaplastic cells, which are often the primary changes of the lung in the case of inhaled compounds (490). Pulmonary adenomas are frequently found in mice both spontaneously and following whole-body and partial-body irradiation (see paragraphs 119 and 120). They are frequently of alveolar origin, with a variety of histological patterns (641, 642, 65).

314. *Mammary gland.* Most of the studies on the mammary gland are confined to breast tumours of the Sprague-Dawley rat. In this system, irradiation of other tissues except the target tissue is not required to elicit the neoplastic effect (52, 616, 617, 606). The intact function of the ovary is however required for maximum expression of the neoplastic effect (138). By histological and biological criteria, the tumours produced are described as mammary adeno-carcinomas, adeno-fibromas or fibroadenomas, according to the relative abundance of fibrous and adenomatous tissue (611). No information is available on which are the possible cells at risk, although this system, which has good characteristics for oncological studies (614), would appear to be open to quantitative developments on a cellular basis. It is of interest to note that very recently an experimental technique to quantify radiation effects on rat mammary tissue has indeed been developed by Clifton *et al.* (112).

315. *Kidney.* In the Sprague-Dawley and the FAF1 rat, radiation-induced kidney tumours appear to be tubular in origin, while in mice they seem to arise from the glomerular capsule with secondary tubule involvement. Nephrosclerosis and arteriosclerotic changes would appear to play a major role in their pathogenesis (36). In a thorough study of the histogenesis of kidney tumours in rodents (422), Maldague has confirmed that in the absence of radiolesions, leading to renal atrophy and nephrosclerosis, no tumours are found in Wistar rats and in mice of the strain XVII. Concerning the tumour types found in the rat, cortical adenomas originating from cells of the convoluted tubules, carcinomas with various degrees of anaplasia and a few sarcomas were described. In animals locally irradiated in the kidney and then uninephrectomized controlaterally, it was found that focal localized proliferation of the epithelial cells at the junction between cortex and medulla (which are probably the induced cells transformed to malignancy) give rise very frequently to the neoplastic nodules. Cortical adenoma, cortical carcinoma and transitional cell carcinoma were also described in rats (569). In the mouse, tubular adenomas and clear cell carcinomas, similar to the tumours found in rats, were also seen (422). It may therefore be concluded that the available evidence points particularly to the tubular cells as the cells susceptible to neoplastic transformation, but that tumours arise in other degenerative and sclerotic lesions. The role of these pathological components is still unclear.

316. *Skin.* The histopathogenesis of skin tumours after irradiation with low-energy beta particles of the CBA/H mouse has been described by Hulse (421). Epidermal (papilloma and squamous carcinomas), dermal (mainly fibrosarcomas, but also fibromas and hemangioendotheliomas) and subdermal (fibrosarcomas) tumours were found. In spite of the fact that early and late effects on skin and skin annexes were carefully followed and described, it was not possible to find any correlation between the degree of non-neoplastic skin damage (depigmentation, ulceration, scars) and the likelihood of tumour development. It was definitely stated however that, contrary to other reported results, tumours seemed to arise as a direct effect on irradiated cells and in areas of the skin which did not appear to have suffered gross radiation damage. In a later report on dose fractionation, the lack of correlation between skin damage and tumour formation was confirmed and the relative independence of skin tumour production on the mode of exposure to radiation suggested, in the opinion of the authors, the existence of a mechanism of tumour induction of a permanent and cumulative type, such as a somatic mutation (287). It was further argued that the sensitivity of the transformed cells to radiation killing might be exceptionally low compared to the values commonly found in mammalian radiation biology (288). Other results in the mouse are particularly interesting for a discussion of the cells at risk (369). By skin irradiation with helium ions of different energies it was found that

the number of tumours increased with increasing penetration of the beam, in agreement with other data relating to the rat to be discussed below. The dependence of tumour formation on acute skin damage was in this case partially confirmed.

317. The situation in respect to skin tumour induction in the rat appears to be quite different, in the sense that in the skin of this rodent there is an association between hair follicle damage and the magnitude of tumour response. The incidence of atrophic follicles reaches a peak at about the same dose at which maximum tumour yield is found, and also there is good correspondence between the shape of the dose-effect relationships for the two types of damage (6). In a study performed with electrons of several energies it was established that, when the dose delivered with all energies is normalized at a depth of 0.27 mm, the dose-incidence curves coincide, indicating that the cells located at this depth from the surface (identified as the cells at the bottom of the resting hair follicle) are to be considered as the cells at risk for this type of tumour in the rat. In recent experiments (7), a comparison of the skin tumour response of mice and rats showed that the markedly lower susceptibility of the mouse was due to the failure to develop adnexal tumours, which are the predominant type of neoplasia in the rat. Marked differences in hair follicle injury in the two species were noted. In particular, the mouse develops relatively little follicular atrophy, and hair follicles appear to be either intact or destroyed; in addition, the mouse hair follicle appears to be more sensitive by a factor of about 2. The susceptibility to the induction of connective-tissue tumours, on the contrary, is roughly similar in the two species.

318. *Bone.* Detailed descriptions of the histopathological changes observed in bone after irradiation by bone-seeking nuclides have been provided by Nilsson (499, 509, 647, 494) and Vaughan (703). It is doubtful, however (459), whether the described microscopic damages have any relation with tumour induction since the occurrence of tumours has been shown to be the most sensitive parameter and indicator of radiation damage to the bone (185, 703). Histopathological evidence points to the following cells as the most important cells at risk in the case of internal irradiation by bone-seeking nuclides: the osteogenic tissues of the bone surfaces giving rise to osteogenic and chondrogenic sarcomas; the bone marrow for all haemopoietic, lymphopoietic and myelopoietic disturbances, and the epithelial cells in close contact with the bone, giving rise to epithelial tumours of the mucous membranes of the head. The case of the marrow has already been discussed in connection with leukaemia (paras. 304 to 311), and it should be pointed out that in rare cases other cells than the haemopoietic elements might be susceptible to neoplastic transformation, as for example in the case of haemangial tumours.

319. Concerning osteogenic tissue tumours, chromosome-marker experiments on chimerized CBA mice have definitely proven that osteosarcomas developing after ^{90}Sr treatment derive from the osteoprogenitive tissues of bone and not from the pluripotent cells of marrow (26, 48). The cells at risk are therefore to be found among the progenitor cells of the bone-forming tissue, namely the pre-osteoblasts and pre-osteoclasts. These cells lie within 10 μm of the endosteal and periosteal surfaces (703) and therefore are at risk in cases of irradiation by both alpha and beta emitters of all energies deposited in bone. These cells are the ones becoming malignant due to an abnormal proliferation following irradiation while maintaining the functional activity of the original progenitors (499, 4). The particular location of these cells explains the observation that bone tumours are more frequently of endosteal than of periosteal origin, on account of the fact that endosteal surfaces are far larger than periosteal. It also accounts for the observation that surface seekers are more effective than volume seekers for bone tumour induction, since the dose delivered to the target cells is higher in the first case.

2. Conclusions

320. It may be concluded that further refinements of our knowledge about cells at risk for neoplastic transformation are of extreme importance, both for elucidation of mechanisms and for better systematization of data. The problem has been tackled so far (and in some cases qualitatively solved) only in those tumour systems where indirect mechanisms of induction and promotion are relatively less important, and for which the direct action of radiation on the tissue at risk appears to be the determining factor for tumour induction. A more quantitative approach seems now required, as well as the development of investigation techniques aiming at the establishment of links between observations *in vivo* and model systems of cell transformation *in vitro*.

VI. SUMMARY AND CONCLUSIONS

A. GENERAL

321. A selective review of experimental radiation carcinogenesis has been carried out in order to set the old information and the newest acquisitions in the more general framework of cancer induction as a biological phenomenon, and with the ultimate aim of identifying mechanisms or regularities which might facilitate the interpretation of human data. The reviewed information is both qualitatively and quantitatively inadequate for numerical prediction of tumour induction rates in man, even though projections between species may be considered as the main objective of animal experimentation. The experimental data are, however, invaluable for understanding mechanisms, for the formulation of useful generalizations applicable to all species, and for the development of models to test specific hypotheses of tumour induction.

B. METHODOLOGY

322. Several methodological approaches have been followed in the past, ranging from the large-scale epidemiological-actuarial analysis to the morphological

and pathological approach, and from biochemical and molecular experimentation to the more recent analysis of model systems of carcinogenesis. All of these have advantages for specific purposes, but each of them appears inadequate for comprehensive solutions of general validity. The long-term nature of the work *in vivo* is such that it requires a careful choice of experimental animals, high standards of animal husbandry and maintenance, advance planning of the size of the experiment, selection of appropriate biological end-points, quantitative observations on the relation of dose and time parameters with the carcinogenic effect, and careful statistical evaluation of the age-specific tumour induction rates. Although continuous improvements on these points are evident in the work reviewed, much could still be done in order to refine the technical requirements for reliable investigations and to standardize the working conditions on an international basis to permit a wider applicability of the individual observations.

C. MECHANISMS

323. The probability of radiation-induced changes in individual cells leading to the appearance of tumours is very low. Neoplastic transformation is presently visualized as the end-result of a complex chain of etiological and pathogenetic events that confer upon the tumorous cell an irreversible and unlimited capacity for proliferation outside the normal control mechanisms. Unlike some chemical carcinogens, radiation can both initiate and promote neoplasia; it may also interact with other physical, chemical or biological carcinogenic agents with variable results under different circumstances.

324. The genetic foundation is common to the currently accepted hypotheses of radiation carcinogenesis, and the recent advances in molecular genetics and virology are gradually closing the gap between the classical "theories" of the "somatic mutation" and "viral" induction of cancer. Vertically transmitted RNA oncoviruses have definitely been shown to be at the origin of some radiation-induced murine tumours, and in the very few cases where the analysis of mechanisms has been carried to a sufficient depth radiation has been found to act through a modification of the host-virus relationships, in a complex interplay of physical, genetic, micro-environmental, hormonal and immunological actions. Attempts to study cell transformation by radiation on cultured cells have been initiated and should be pursued to investigate the mechanisms of cancer induction in the absence of other interactions operating at the whole-body level.

325. There are data to show that a transient non-specific immunosuppression caused by fairly high doses of radiation may have a promoting role in the development of radiation-induced tumours. Moreover, the viral infection *per se*, acting through very specific cellular mechanisms, can cause a depression of the immune reaction in cases where tumour viruses are implicated. Although these effects would only appear to have a secondary role, the questions as to their actual importance and their relevance at low doses and dose rates remain unsolved. Similarly, no definite answer can be given about the role and the mechanisms through which hormones could alter the susceptibility of certain radiation-induced tumour systems *in vivo*, although the animal's hormonal balance may affect the carcinogenic response of some systems. Cellular proliferation is implicit in the notion of a promoting action and is certainly required for tumour progression. Cell division is however a non-specific type of tissue reaction to radiation-induced cell depletion, and it is very difficult to attribute to such an action a primary or a secondary role in tumour induction. Other environmental conditions concerning the host microflora, physical conditions, chemical substances and biological treatments may affect to various extent the neoplastic response to radiation.

326. In conclusion, a variety of biological mechanisms through which radiation can induce tumours have been identified and, in some cases, analysed. The evidence shows that mechanisms that appear very important for a particular tumour system may, under a given set of experimental conditions, be less important or even not relevant for the induction of other neoplasms. Our present knowledge of mechanisms therefore provides partial answers, but it is still insufficient for conclusions of general validity.

D. DOSE, DOSE RATE AND RBE

327. Among the physical parameters affecting tumour induction, the dose, dose rate and quality of radiation have been considered. Concerning the dose, three major patterns of tumour response can be identified. The first refers to those tumours which do not seem to be effectively induced in the usual range of low to midlethal doses but may however be induced at higher doses. The second refers to those tumours for which the dose-effect relationship has a negative trend. The third, and probably the most common pattern, is more complex, showing an initial rise at increasing doses, a peak or a plateau at some intermediate level and, in many cases, a final decline of incidence at sufficiently high doses.

328. The peculiarities of each tumour-model system which have been pointed out repeatedly in this Annex are such as to prevent undue generalizations, particularly when they might apply to all systems. There are also difficulties in interpreting tumour induction curves in the animal on the basis of simple mechanisms of action, in view of the complex interplay of primary and secondary factors, also discussed at length in this Annex. With few exceptions, the existing data come from observations at doses above 50 rad, since lower doses have generally failed to cause an increased tumour incidence large enough to be quanitified in experiments of the usual size involving no more than 100 animals per dose-group. Even in those instances where the incidence of a particular neoplasm has been observed to increase with dose, the data usually do not suffice to define the dose-effect relationship unambiguously in the low- to intermediate-dose region.

329. With one exception, namely the rat mammary tumour, the dose-incidence curves obtained at high dose rates with low-LET radiation generally increase in slope

with increasing dose in the range from 50 to a few hundred rad. The data are not incompatible therefore with the notion that an appreciable dose-squared component might be present in these curves, which would imply that linear interpolation or extrapolation from the observed data would tend to overestimate the risks to be expected at low doses (less than 5 rad) and at low dose rates (less than 10^{-3} rad/min). With high-LET radiation, on the other hand, the dose-effect relationships are more often compatible with a linear non-threshold response, and their slopes vary relatively little with dose and dose rate. Those instances where the tumour induction curves are seen to decrease in slope at high doses and dose rates may be interpreted to result from two independent dose-related phenomena: neoplastic transformation of the susceptible cells, the probability of which increases with increasing dose, and survival of the transformed cells, the probability of which decreases as a function of dose.

330. Detailed analyses of the dependence of the RBE of different ionizing radiations on dose and dose rate are only possible at present for very few experimental tumours. It appears that the efficiency of high-LET radiations for tumour induction is higher than that of low-LET radiations, and the efficiency often changes at different dose ranges. At doses of 100 rad or more the RBE is often about 1, and it shows a rather general tendency to increase at low doses and dose rates, owing probably to the form of the dose-induction relationships, where the linear component prevails in the case of densely ionizing particles, while the quadratic component might prevail, at least at high doses and dose rates, in the case of low-LET radiation. A noteworthy example of this type of effect is seen in the acceleration of breast-tumour development of the Sprague-Dawley female rat, where effects of fast neutrons are detectable at doses of 0.1 rad, with corresponding high values of the RBE.

331. A spreading in time of the delivered dose through a decrease in the rate or through fractionation of the dose results in general in a decrease of the oncogenic effect of radiation, following some inverse function of the exposure time. It is however difficult to assign precise values to this sparing effect, since the shape of the dose-induction relationships is often altered by the change of dose rate. The magnitude of the reduction of carcinogenic effect at low dose rates is often found to be smaller with high-LET radiation. Departures from this general pattern have been documented in some tumour systems but are attributed to the pathogenetic mechanisms of the particular system and not regarded as exceptions to some fundamental radiobiological mechanisms. Recovery processes are responsible for the sparing effect of fractionation and exposure rate; their nature and kinetics in the case of neoplastic induction remain largely unknown.

E. INTERNAL EMITTERS

332. Carcinogenesis by internal emitters has been considered as a special case since, in addition to the general problems of radiation carcinogenesis, it poses other problems related to the inhomogeneity of the dose distribution in time, and also to the concentration of the radionuclides in some organs or tissues. In addition, the comparison of effects of various nuclides is often made uncertain by the difficulties of assessing the dose to the target tissues, because of the peculiar behaviour of nuclides having different physical and chemical characteristics and, therefore, different rates of uptake, retention and tissue localization. The cases considered in detail cover the induction of bone tumours and myeloproliferative diseases by beta- and alpha-emitting bone-seeking radionuclides and the induction of lung tumours following inhalation of alpha emitters in various animal species where data are available. A discussion of the probable form of the dose-induction relationship for the various types of neoplasms has also been included.

333. When the special factors mentioned above are taken into proper account, it appears that the qualitative picture emerging from these data is compatible with the concepts developed from the analysis of the effects of external radiation. The general form of the dose-induction relationships, the fact that at low doses beta emitters tend to produce curvilinear responses and alpha emitters linear ones, the higher efficiency of the alpha emitters, and the sparing effect of low dose rates of sparsely ionizing radiations, are all phenomena that can be documented in the case of internal irradiation. This strongly suggests that, with appropriate corrections, the general knowledge on tumour induction may safely be applied to both irradiation conditions.

F. BIOLOGICAL VARIABLES

334. Among the biological variables influencing radiation carcinogenesis, the effects of species, strain, sex and age at time of irradiation have been reviewed. Even with the lack of systematic data, it is possible to conclude that the genetic character of the species and, within species, of a particular strain, represents a major determinant of the carcinogenic response, to which other physical, physiological and environmental parameters may contribute as secondary variables. Genetic differences in susceptibility to tumour induction by radiation are especially manifest at low doses; with increasing doses and dose rates they tend to be cancelled. There are also quite definite changes in the susceptibility to the induction of various types of tumours as a function of the post-natal age at which animals are irradiated. Irradiation of experimental animals *in utero* would not appear, on the whole, to be more carcinogenic than irradiation during post-natal life.

335. Finally, the existing data on the problem of the tissue and cells at risk for the induction of various tumours have been reviewed. It appears that this subject may have important implications for the elucidation of mechanisms and for possible practical applications. Existing data relate, however, only to those tumour systems where the direct action of radiation on target cells appears to be the determining factor for tumour induction. A better quantitative definition of these problems by development of more sophisticated techniques of analysis at the cellular level is desirable.

VII. NEEDS FOR FURTHER RESEARCH

336. The previous report of the Committee (670), as well as other publications (563, 291, 564, 419), have indicated some topics of special interest for future research. Adequate selection of research topics is particularly necessary in carcinogenesis studies because of their long-term nature and of the major organizational and financial efforts they require. The Committee calls attention to the role of the experiments on animals for the eventual elucidation of the mechanisms involved and therefore for the extrapolation of data to man. Considerably more data would be required to extrapolate the few available data in humans to different conditions of exposure. A systematic analysis of the effects of the main radiobiological variables in experimental systems could make possible the refinement of the risk estimates in man by a considerable factor within the next decade (564).

337. Concerning the strategy of future experiments, special emphasis should be placed on the development and analysis of models of the carcinogenic action, rather than on large-scale experiments. It seems likely that some elucidation of the many factors interacting in carcinogenesis could be obtained through the study in depth of conceptually simplified experiments. A multidisciplinary effort of a quantitative, rather than a descriptive, nature seems to be called for. For example, our present knowledge of some tumour systems *in vivo* makes it possible to select as an indicator the induction of tumours in a definite cell line at risk, rather than the gross appearance of any type of tumours in a population of animals. The use of more relevant end-points may provide a rational basis for possible extrapolations from one species to another.

338. It is generally recognized that the area of greatest applied interest is, and will continue to be, that of the effects of low doses and dose rates. It follows that the experimental efforts should be concentrated in that area. It should also be emphasized that experiments on tumour induction as a function of dose and dose rate in selected animal model systems appear at present to be the type of studies that might best contribute to further advancement. Careful planning and design of the experiments, refined statistical analysis of the data, and also a better standardization of the techniques used in different laboratories would strengthen the validity of the observations.

339. The following are some specialized topics requiring further elucidation, and for which currently available techniques would justify increased efforts with reasonable hope of progress. The topics are given in the same order as they have been discussed in the main text of the report, without any indication of priority.

(a) The somatic mutation hypothesis of tumour induction and its possible relations with the viral hypothesis could be investigated by means of studies of the damage and repair to DNA and genetic structures in transformed cells following irradiation or viral infection. An attempt should be made to clarify the relationships between neoplastic transformation of the cell and its capacity for further reproduction and other possible damage to important cell structures.

(b) On the basis of the data reviewed, it seems that different radiation-induced tumour systems do not have the same etiopathogenetic mechanisms; on the contrary, it seems that the relative importance of each mechanism is different in different systems. By testing this relative importance, better elucidation of the role and relevance of the various inductive and promotive factors in different experimental situations could reasonably be expected. Further experiments of the role of various co-carcinogenic factors with particular relevance to the presence of potentiating effects in regard to tumour induction would also be desirable.

(c) Since viral agents are implicated in the induction of at least some radiation-induced tumours, attempts to demonstrate the viral origin of other tumours should continue together with studies on virus activation and on the immunological mechanisms interacting in such cases.

(d) The development of models of cell transformation *in vitro* should actively be pursued to clarify the kinetics of cell transformation and its relationship to cell inactivation. Several possible models have already been identified (564), and it is not unreasonable to expect that some of the classical radiation-induced tumour systems *in vivo* could also be subjected to more quantitative *in vitro* analysis.

(e) For *in vivo* studies, the identification of the cells at risk would greatly help in identifying the mechanisms and unifying the observations. Quantitative analysis of the capacity for division and differentiation of these cells, in relation to the transformation events, would provide important links between *in vivo* and *in vitro* studies. Furthermore, the period elapsing between the initial transformation of the cell and the clinical manifestation of the tumour should be studied, together with the influence of immunological, hormonal and other promotive factors.

(f) More experimental data are required to establish with precision the dose-effect relationship below 10 rad for many tumour systems. Studies of the relative importance of the linear *versus* quadratic components in dose-induction curves would be very valuable in this context. Better knowledge of the nature of such relationships would considerably improve the confidence in the estimation of the risks of tumour induction in man at low doses and dose rates (see Annex G). The development of model systems *in vitro* and the analysis of the data by means of refined theoretical models could help identify the relevant trends. It should be pointed out, however, that any conclusion will have to be confirmed by data *in vivo*, which are extremely difficult to obtain, particularly in the less susceptible species.

(g) The mechanisms involved in the determination of the nature of the dose-effect relationships at medium to high doses are uncertain. It seems reasonable to assume that the identification of such mechanisms might indirectly help establish the possible shape at very low doses.

(h) There are few studies of RBE for tumour induction. More effort is needed in this direction, particularly with the most sensitive systems which could allow an assessment of the RBE at low doses and dose rates, for which information is definitely insufficient.

(i) The lower efficiency with which irradiation at low dose rates induces tumours, which has been qualitatively described for some systems *in vivo*, should now be explored in other tumour systems and evaluated quantitatively.

(j) Although it seems reasonable to postulate that repair phenomena with various time constants are operating at various levels of the biological organization, the nature and kinetics of such repair mechanisms in the case of low dose-rate irradiation are still essentially unknown and require elucidation.

(k) Further comparative studies of tumour induction in different species and strains would increase our confidence in interspecies extrapolations. In this respect it would be desirable to test in other animals the conclusions reached in rodent experiments about the effect of the main physical and biological variables. However, no large-scale studies should be undertaken without sufficient scientific justification, which could be based on the relevance of the information to be gained for human assessments.

(l) The importance of systematic studies of tumour induction in various animal species and in animals of different size and age should be recognized. These studies should attempt to correlate the induction of neoplasia with the number and functional state of the target cells at risk of malignant transformation in any particular tissue.

(m) The conclusion that irradiation *in utero* is not more carcinogenic than in the young or in the adult animal appears to be based on rather scanty data. A more systematic search covering various tumour types in different strains and species and relating tumour induction with the rate of maturation of the relevant organs would considerably strengthen that preliminary conclusion.

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ANNEX J

Developmental effects of irradiation *in utero*

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Introduction

1. Since its 1962 report (344), the Committee has not comprehensively reviewed the data on pathological and teratological effects induced by irradiation of the mammalian embryo and foetus, with the exception of the effects on the developing central nervous system, which were considered separately in the 1969 report of the Committee (345). Much information has accumulated in the meantime; obtained mainly in animal experiments, it could be of help, if not for the prediction, at least for the interpretation, of the human experience. Additionally, reassessments of earlier observations and some new data in man have become available. This annex therefore reviews the effects observed in various mammalian species following exposure *in utero*, with the aim of extracting information relevant to the assessment of radiation effects in man. It deals exclusively with somatic effects.

2. Radiation exposure of the mammalian conceptus *in utero* gives rise to a large variety of short- and long-term deleterious effects. For many of them, especially those following irradiation during late pregnancy, the pathogenesis is similar to that of lesions seen after irradiation of animals in the extra-uterine life. There are, however, effects which may be viewed as the typical sequelae of irradiation of a developing organism, which is characterized by major processes of differentiation leading to the structural and functional organization of organs and tissues. The complex morphological and physiological events leading to the development of a mature animal may be disturbed or disrupted by radiation, and the consequence is the production of malformations of different nature and degree. Some of these defects are so profound as to be incompatible with the animal's life *in utero*; some can easily be recognized morphologically at birth; others cannot even be scored at the microscopic level and are only manifested at a later stage as functional deficiencies.

A. DEFINITION OF MALFORMATIONS

3. There is some lack of uniformity in the definition of congenital malformations owing to the large variety of these lesions. Brent (27) regards as malformations all permanent defects (morphological, histological or biochemical) which an organism cannot repair during the course of its normal growth and development. Warkany (356), on the other hand, draws a distinction between congenital anomalies and congenital malformations: he regards the first type as a broad category covering all microscopic, biochemical and functional disturbances seen at birth, and reserves the second term only for the gross structural effects in the new-born animal. According to Stevenson (334), the characteristic features of congenital malformations are their production during intra-uterine life (even though they may be recognized only at a later stage) and their macroscopic anatomical nature.

4. It is not surprising that this absence of uniformity in the definition is reflected in different estimates of induction rates as a function of time or radiation dose. It is largely a matter of definition whether growth retardation of an otherwise normal animal should or should not be regarded as a malformation, or whether malformations should comprise changes in the life-span of animal populations, or whether one should include the malformations seen in animals dying *in utero* or in stillborn animals and which therefore are never scored in live animals.

5. There is no doubt that when these problems are approached experimentally the area of concern should be carefully defined, so that the design, execution and interpretation of the work may be carried out properly. However, when reviewing a large body of experimental data, the acceptance *a priori* of firm definitions might lead to the exclusion of important information. Since it is the Committee's intention to consider all evidence at hand which might be of help in interpreting the scanty information available for man, it follows that no information should be disregarded. Data on genetic damage are covered in another section of the Committee's report (Annex H) and data on behavioural effects of irradiation *in utero* have also been reviewed previously (345).

B. PREVIOUS REVIEWS

6. Taking such a wide perspective does not imply that the present contribution attempts to review extensively most of the work in radiation teratogenesis.

which would obviously be an impossible task. It does not consider, for example, much of the early work on animals and man, which made important qualitative contributions but was often limited to very few observations or lacked quantitative definitions of the relevant physical and biological parameters. Nor does it include the work on animals that are phylogenetically far from the mammals, such as birds, amphibia, fishes and marine organisms. The subject of embryonic irradiation has been discussed with great care and scientific authority in many published reviews (52, 260, 262, 264, 362, 295, 230, 27, 109, 39, 127, 121, 370, 136, 170, 303, 92). An updated bibliographic compilation of most published contributions was also made available to the Committee (336), as well as two reports on the teratogenic action of external (178) and internal (178a) radiation sources, summarizing relevant work in the Union of Soviet Socialist Republics. Previous reports of the Committee have also considered general (344) or specialized aspects of radiation teratogenesis (345). All these publications may be consulted for background information.

C. PRESENT REVIEW

7. The developing embryo has some inherent biological characteristics that have always appealed to the radiation biologist (295). Differentiation of major organs and tissues takes place in an orderly sequence at well defined times after copulation or conception, the time of which can be established to a fairly good approximation (see paragraphs 26 and 27). Waves of cell division, differentiation and migration occur during organogenesis at certain times and, since radiation is particularly effective at these times, it is possible to induce selectively malformations in organs or anatomical regions. In addition, the dependence of the mammalian embryo on the mother allows the analysis of abnormalities up to very advanced stages of development that would not be compatible with life in other lower animals.

8. Although radiation-induced malformations are non-specific, in the sense that they can be produced by other teratogenic agents, the use of radiation in experiments offers some advantages over, for example, chemical agents. In fact, radiation from external sources can be administered to the embryo in precisely measurable quantities within very short times, whereas chemical substances must cross the placental barrier, and their kinetics of uptake and clearance result in uneven and less controlled exposures to the effective drug level. Furthermore, there is no selective concentration phenomena since radiation is distributed uniformly over the irradiated embryo; the selectivity of the teratogenic response can therefore be related to the sensitivity of the different structures at the time of irradiation. As with chemical substances, radiation may not be administered to the embryo without concomitant exposure of the mother or, at least, of the pregnant uterus. However, the indirect effects on the embryo, in the case of radiation, are relatively minor (see paragraphs 265-270).

9. For all these reasons the irradiated mammalian conceptus has also been a favourite biological system for the experimental embryologist. It is quite clear that most of the work reviewed has actually been carried out with the ultimate purpose of studying the mechanisms of development, rather than of analyzing the effect of the main radiobiological variables. There is insufficient quantitative information on dose-effect relationships and on the influence of dose rate and radiation quality, not only for the irradiated human embryo, as might be expected, but for experimental mammals as well. Such information lies often buried in large collections of systematic data on kinetics and morphology of malformed tissues.

10. Contrary to most previous reviews, this one will therefore attempt to extract the relevant radiobiological information from the published experimental work, giving particular emphasis to the data of prospective use in the assessment of radiation effects in the human embryo.

I. METHODOLOGY AND TECHNIQUES

A. GENERAL DISCUSSION

11. Before reviewing experimental data in detail it seems appropriate to examine some general questions of methodology and technique relevant to the study of the teratogenic effects of irradiation. Consideration of these questions is essential for the following purposes: *(a)* to illustrate some of the variables or conditions known to influence the induction of malformations and their scoring in laboratory animals; *(b)* to point out the confidence limits and the degree of precision of the data obtainable; *(c)* to warn against generalizations which may not apply to all biological materials and experimental conditions; and *(d)* to set in an appropriate perspective the scanty knowledge available in man.

12. In regard to the animals in which experimentation has been performed, the mouse appears by far the most thoroughly studied, followed by the rat, the rabbit, the hamster and the dog. Data on other species are only occasional. The data in humans represent a separate category and will be treated as such, not only because of their importance but also because little control of the experimental variables can be exerted in this case. Among the biological variables, the embryonic and foetal ages at irradiation have been investigated very extensively in many species. The applicability of these data to man, through a comparative evaluation of the times at which certain important stages of development occur, is also an important issue for discussion. The physical variables affecting the teratogenic effect (dose, dose rate, fractionation, protraction, type and energy of the radiation used) have only been examined in a few special cases. The conditions of exposure which apply to the human case and to animal experimentation should therefore be discussed, in order to ascertain if reasonably uniform sets of data are being compared.

B. BIOLOGICAL FACTORS

1. Genetic homogeneity

13. Certain characteristics are required for the selection of the animals used in embryological experiments. According to Jacobson (136) these are

genetic homogeneity, high fertility, large litter size, and a high degree of sensitivity to the teratogenic agent. These requirements may in some cases be in contrast to each other, so that the optimum experimental condition in any given case is often the best compromise between the various needs.

14. The high fertility and large litter size are conditions obviously favouring the rapid collection of statistically large experimental samples; they are inherent characteristics of the animal species and strains that are desirable choices for experimentation. Concerning genetic homogeneity, even in the absence of knowledge on the relative importance of constitutional and environmental factors in the induction of malformations, there is certainly an advantage in selecting the genetic background as uniform as possible. It follows therefore that the animals should be as homogeneous as possible in their genetic constitution, although some inbred lines may show a high natural incidence of specific malformations. The susceptibility to radiation-induced teratogenic effects is very high in inbred strains, but this advantage is often balanced by decreased reproductive and somatic vigour. In such cases hybrid animals obtained by crossing inbred strains may be the solution of choice to combine vigour and genetic homogeneity. Several approaches to this problem, all equally justifiable, appear to have been followed in the work reviewed.

2. Maternal factors

15. Quite aside from the response of the embryo to any teratogenic agent, there are certain biological characteristics of the animals used that must be taken into account when planning experiments. The quantitative features of reproductive performance and their variability are the most obvious ones, and some data are available on these points. Analyzing the interstrain differences in the breeding capacity of six inbred strains, Ehling (80) has drawn attention to the fact that the intraspecies and interspecies variabilities are of comparable degree. In the mouse, for example, the mean number of offspring per fertile female ranged from 20.5 to 73.4 in various genotypes examined; the embryonic survival varied between 57.1 and 75.6 per cent and the mean number of litters per female between 5.9 and 11.2. Differences in reproductive performance between F_1 hybrid females from reciprocal crosses appearing after irradiation at 50 R[1] have been attributed to a genetically controlled maternal factor (81).

16. But variability in reproductive performance is very high even within the same strain. According to Rugh and Wohlfromm (291), the first litter is always the smallest and the litter size tends to increase in the following three litters. The average litter size is greater among multiparous than among primiparous females of comparable ages and the incidence of abnormal offspring, although never very high in control mothers, tends to increase in successive litters. Many authors therefore tend to standardize experimental conditions by using second-litter animals for analysis of teratogenic responses, since the first litter usually has high mortality and small size. Correlations have been reported (136) between litter size at first delivery and litter size, conceptus number and weight of offspring of the second pregnancy. These correlations could to some extent guide the experimenter in the selection of suitable experimental animals in second litters on the basis of the outcome of the first.

17. Regarding the incidence of malformations after irradiation, the previous reproductive history of the mother appears to be of some importance. Thus, the incidence of intra-uterine deaths and resorptions after 200 rad received at 8.5 days post-conception (p.c.) is almost double among breeders 14 months old than among primiparous young females (287). Similar observations have also been made after doses of 2-32 rad (175). The incidence of gross aberrations of the central nervous system, which is 30 per cent higher in old females, is reduced after correction for *in utero* mortality, but a slight excess of malformations of the order of 3 per cent is still evident in offspring from old mothers (287). In another report (290) primiparous females, even though of the same age as the multiparous, were shown to produce more abnormal embryos. These and other data emphasize the need for careful control of the mother's age and of her past breeding experience in order to ensure good experimental material and uniformity in the teratogenic response. It may be added, however, that in a careful and extensive study by Jacobsen (136) of all these maternal factors, they were assigned a relatively minor influence, in any case not sufficient to result in gross misinterpretations of the dose-effect relationships for the induction of malformations. It may also be mentioned that the radiation history of the female prior to mating may alter some of the reproductive parameters, sometimes with an increase of the litter size (104). Other factors, e.g., immunological incompatibility between the mother and foetus, are known to alter the reproductive performance of mammalian species, but their effect, particularly in regard to the induction of malformations, has not been made the object of special consideration in this Annex.

3. Homozygous and heterozygous animals

18. The influence of genetic constitution in the production of malformations and the relative susceptibility of homozygous *versus* heterozygous animals have received some attention, particularly in mice, where the availability of inbred strains make such analyses easier. Russell and Russell (303) tested the relative sensitivity of three different but genetically uniform mouse populations ((C57 X NB)F_1, BALB/C and 129), taking as the end-point the incidence of animals having 13, more than 13 or less than 13 ribs on each side of the body. They concluded, on the basis of the variation between and within strains of the control animals, that the expression of this character results from a continuous array of variation of the underlying process. They therefore emphasized the need for great caution in drawing conclusions about relative sensitivity with regard to characters having a continuous variability. In fact, particularly under such conditions, a change in the

[1] Throughout this Annex, the radiation units quoted are the roentgen (R) or the rad, as they appear in the papers reviewed. No attempt has been made to express the frequency of radiation effects on a common basis of unit absorbed dose.

end-result would not necessarily indicate a corresponding difference in primary radiation damage (see paragraph 287).

19. Dagg (68) examined the teratogenic response of three strains (BALB/cGn, C57BL/ks and 129/Rr) and some of their hybrids, showing that the differences in malformation response between strains observed after irradiation at 11 days p.c. is not found when the irradiation occurs at 10 days p.c. or when the embryos are irradiated at approximately equal crown-rump length. Thus, the differences observed may be due to different developmental (as opposed to chronological) age of the embryos at the time of exposure rather than to an intrinsic difference in susceptibility.

20. Nash and Gowen (218) followed the post-natal growth response of three inbred strains (Ba, K, and S) and all their hybrids, including reciprocal crosses, at several gestational ages and after various doses. They found evidence that developmental differences are under strong genetic control. These differences may to some extent be related to even minor strain-related changes of the developmental age at the time of irradiation, but they can be exerted in part through the ability of single cells and organs to repair radiation damage. A similar influence of the genetic background was also found with respect to the duration of life-span (219); here again the genotype was shown to condition embryological development at irradiation, and the differences between strains were particularly evident at high irradiation doses given at late pregnancy stages.

21. In a review centred on the question of outbred *versus* inbred animal strains in experimental teratology, Smithberg (327) has considered all relevant problems exhaustively. He concluded that the selection of the most appropriate experimental animals cannot be made on the basis of general principles, but rather depends on the specific aims to which research is directed; in different instances and for different purposes, either genetically pure or outbred animals may be chosen with equally good justification.

22. The available reports almost unanimously show that the heterozygous condition confers a higher degree of resistance to the teratogenic action and to the killing effect of radiation *in utero*. To cite just some of the evidence, Rugh and Wohlfromm (288) have reported an increased radioresistance of hybrid embryos (C57BL/6 X CF1) exposed to 200 R at 8.5 days p.c., by comparison with the parental strains. At 18.5 days, in fact, only 5 per cent of the implants of the C57BL animals were normal, while for the CF1 and the hybrid mice the respective values were 38 and 44 per cent. The small difference between CF1 and hybrids was attributed to heterosis of the hybrids. Dagg (68) reported that hybrids from crosses of C57BL and BALB/C were more resistant to lethal effects and to deforming effects in the foot, palate and tail than homozygous C57BL embryos. Jacobsen (136) refers also to a higher degree of sensitivity of homozygous HC mice relative to (HC X C3H) hybrids. Finally, a differential response between inbred and hybrid mice of three genetic stocks (BALB, K and S) was shown by Nash (217) in regard to both induction of malformations and lethality (neo-natal and early post-natal). In all cases inbred genotypes responded to a greater degree than hybrids.

23. It may thus be concluded that the genetic constitution has an influence on the degree of the observed lethal and teratogenic responses. But just how much of the differential response might be due to intrinsic variation of sensitivity or repair in various species and strains and how much, on the other hand, might be attributed to small variations of the developmental age at irradiation remains unclear. Variations of the rate of development are also genetically controlled, but their effect is indirect and due to rapid changes in embryonic sensitivity in the course of differentiation. The heterozygous conditions seem invariably to result in a higher resistance to lethality and malformations, but the need to irradiate similar developmental stages for meaningful quantitative comparisons remains valid. Finally, the type of effect scored may affect the conclusions about relative sensitivities, especially when it is based on some continuous variable rather than on discrete morphological traits.

24. The position of the implants in the uterus is of relatively minor importance in relation to the occurrence of abnormalities, a question that has been examined by Hashima (114), Trasler (342) and Jacobsen (136). Hashima reported that offspring in the ovarian position of the uterine horn had a significantly reduced weight. Trasler found that embryos in the same position had an incidence of cleft palate which was higher than in all other positions. On the contrary, Jacobsen showed that embyros in the intermediate position were apparently at a disadvantage when the weight of offspring and the placental weight were taken as indicators of the optimal uterine environment. The incidence of skeletal malformations and resorptions were unrelated to the uterine position. These results, although contradictory in the various experimental conditions tested, show nevertheless that the position of the embryos in the uterus may perhaps affect the developmental potentialities and the malformation incidence of the irradiated embryos.

25. Important quantitative differences between experiments performed in summer and in winter were also reported by Jacobsen (136). In the experience of this author, the seasonal variability was so high that it would have masked the effect of doses up to 100 rad had the results not been evaluated separately for the two seasons. In general, summer samples were found to be less radiosensitive. It follows that experimental data must be tested against control groups run at the same time.

4. Timing of pregnancy

26. There is one aspect of breeding technique that requires special attention: the accurate timing of mating and fertilization. In rodents, successful mating is followed by the appearance of the vaginal plug; the time of scoring of this sign is often the starting point for calculations of the embryonic and foetal ages, especially in mice (266). However, many workers consider this time as day 0 and others as day 1 after fertilization, thus

creating inconsistencies among their experimental series. In rats, the presence of sperm in the vaginal canal is also used as an indication of mating (32). Useful and up-to-date information on the reproductive physiology of various experimental animals for an accurate timing of pregnancy may be found in the following references: mouse, 328, 266; rat, 223; rabbit, 109; dog, 6; monkey, 249.

27. Owing to differences in mating techniques used by various laboratories and because of the large time variability between ovulation and fertilization, there are usually differences in the estimation of the conception time and therefore of the gestational age. In some instances, gestational age is measured from the observed or presumed time of coitus and in other cases from the presumed time of fertilization or conception, calculated from the time of coitus or estimated back from the time of scoring the vaginal plug. However, the sacrifice of some experimental animals at irradiation time followed by direct examination of the conceptus, measurements of the length of embryos or observation of external morphological features, affords a better timing of the developmental stage at the time of irradiation (299). Such procedure is, however, carried out only rarely. Owing to the uncertainties referred to above, most estimates of embryonic age should not be taken to be more accurate than about ± 0.5 day, even under the best-controlled conditions. It should also be mentioned that marked differences in apparent age may be seen within embryos of the same litter, especially at the earlier ages (241, 4), and that there is therefore a limit to the improvement of timing control (135).

5. Periods of maximum sensitivity

28. The need for accurate control of the gestational age in experimental radiation teratogenesis stems from the evidence that there are certain well defined "critical periods" in embryonic development when some types of malformations can be produced more readily than others. The concept of critical period was first developed in 1911 from observations on fertilized amphibian eggs (14). Although repeatedly discussed in the following years (337), its importance was not fully and immediately realized. Actually, many of the earliest observations did not sufficiently specify the age at which the embryonic or foetal material had been exposed. The first systematic investigation of this concept in mammals was made by Job *et al.* (139) in 1935. They showed that exposing rats to 90 R at day 9 of gestation produced mainly hydrocephalus, whereas defects of the eye and the jaw were preferentially induced by irradiation on day 10 and 11, respectively. In this work the correlations between teratological effects produced at some specified times and the stage of differentiation of the relevant embryonic tissues at such times were clearly established. It was also pointed out that rather low doses are needed to obtain "specific" teratogenic responses and that "specificity" does not imply that some malformations can only be produced at certain times but rather that a given dose is more effective at some stages.

29. Later experience has shown that some malformations are more likely produced at certain times in pregnancy and that the period of sensitivity may be broadened by raising the dose. These observations have also indicated that susceptibility to malformation induction is not sharply defined in time but extends to a lesser degree before or after the critical period and that accurate mapping of these critical periods cannot be made at high doses (295). The data of Russell (295, 296), Rugh (261) and Rugh and Grupp (278) showed conclusively that these basic concepts hold generally true for many types of abnormalities in the mouse; Warkany and Schraffenberger (357), Wilson (362) and Brent (27) extended this notion to the rat. It is now commonly accepted that there are "stages of maximal sensitivity" in the teratogenic response to radiation (137). This new terminology recognizes that such periods cannot be defined for all doses of radiation and is in agreement with the definition of the "critical period" for teratogenic changes given by Russell (295) as the "developmental interval during which radiation must be applied to produce that change if the dose of radiation is the lowest one that gives a detectable incidence of that change".

C. COMPARATIVE MAMMALIAN EMBRYOLOGY

30. In view of the existence of periods of high sensitivity for the induction of certain malformations, which can be traced back to important stages in the organization of the relevant structures, it is important to study the comparative embryonic development of the different experimental animals. This comparative study is necessary to be able to generalize experimental findings and also to extrapolate results from one species to another. Such an exercise in comparative embryology has been attempted many times but the results are necessarily approximate and imprecise.

31. The general pattern of embryonic differentiation, which is qualitatively similar in all mammals, makes it possible to specify the approximate time of occurrence of certain easily recognizable ontogenic events, as shown in table 1. This table summarizes pre- and post-implantation events in six mammalian species used in radiation teratogenesis on the basis of numerous publications. It will be noted that the occurrence of certain events may be timed rather precisely, especially at the very early embryonic stages. However, as pregnancy proceeds and the structure of the embryo becomes increasingly complex, there is no single embryonic event for which a comparative analysis can be performed on the basis of objective parameters. The number of somites may be used as a possible reference of staging, but it remains true that the time of appearance of each structure in the embryo has a mean that is difficult to measure and a variance that probably increases with the age at which the structure originates (241).

32. Besides the inherent variability of the onset of the various structures, their development in various animal species may be advanced or retarded with respect to the development of the whole embryo. Therefore, the appearance of single structures cannot be accepted as a valid reference. It is instead necessary to make the assessment on the basis of several relative measurements referring to various systems (nervous, digestive, heart and circulatory), a procedure adopted, for example, by

TABLE 1. DEVELOPMENT OF EMBRYOS IN SOME MAMMALIAN SPECIES

Age (days p.c.)	*Mouse*	*Rat*	*Hamster*	*Rabbit*	*Dog*	*Man*
1	2 cells			2 cells		
1.5	4 cells		cleavage	4 cells		2 cells
2	5-8 cells			8 cells		4 cells
2.5	9-16 cells			16 cells		
3		4 cells		morula		5-8 cells
3.5	blastocyst	8 cells	early blastocyst	early blastocyst		9-16 cells
4		morula				
4.5	implantation		late blastocyst	late blastocyst		blastula
5		blastula	implantation			
5.5				implantation		
6	organogenesis	implantation				implantation
6.5	primitive streak		primitive streak			
7	head process		5 somites			proamniotic cavity
7.5			neural groove	neural groove 1-4 somites		
8	first somites	egg cylinder	organogenesis	organogenesis		
8.5			optic vescicle	heart formation	early blastocyst	
9	liver diverticulum	primitive streak	20 somites	neural tube closed		
9.5	anterior limb bud	neural plate		torsion of embryo		
10		first somites	limb bud formation			
10.5	posterior limb bud			anterior limb bud		
11		10 somites				
11.5			open eyelid			
12.5			closed eyelid	forelimb buds	late blastocyst	
13						germ layers, extra-embryonic membranes
14	foetal period					
15				foetal I period		
16		foetal period	birth	separation of digits		primitive streak
17					implantation	
18						head process first somites
19				palpebral fissure closed		
19.5	birth				primitive streak	
20				foetal II period		
20.5						appearance of heart
21					early somites	neural groove
21.5		birth				circulation of blood
22					limb buds	liver diverticulum
22.5						optic sulcus
23					15 somites	
25					tail bud	torsion of heart tube
28					end of major organogenesis	primary brain, G.I. tract and derivatives
30						optic vescicle
31.5				birth		
32						major organization of heart structures, limb buds
34						optic vescicle into optic cup, lens formation, lung buds
35					early foetal stage	
36						thickening of retinal layers
37						arm, forearm and hands recognizable
40						outline of digits (hand)
43						eyelids appear
60						definite limbs established
63					birth	↓

Sources: 3, 6, 22, 59, 92, 102, 105, 108, 195, 223, 225, 241, 245, 247, 262, 266, 295, 328.

Otis and Brent (241). Following such a rationale, these authors have constructed a table and a graph for the estimation of equivalent ages in mouse and human embryos, showing that the rates of development in the two species cannot be related by any simple continuous function. The estimates are certainly affected by substantial uncertainties but provide some average estimate of approximate age equivalence based on the actual developmental stages in various embryos. Rugh (266) has reported some data on the age equivalence of mouse and rat embryos. Using this information, it is possible to establish correlations of embryonic ages

between the species as shown in table 2. It should not be expected that such correlations would apply to minor details of the embryonic development; on the other hand, they certainly serve the useful purpose of allowing rough comparisons of pregnancy stage and embryonic age between these species. The approximate embryonic dimensions of the three species are also given in table 2 for reference purposes.

TABLE 2. EMBRYONIC AGE AND GROWTH DATA IN SOME MAMMALIAN SPECIES

Mouse		*Rat*		*Man*	
Age (days p.c.)	*Length (mm)*	*Age (days p.c.)*	*Length (mm)*	*Age (days p.c.)*	*Length (mm)*
0				1	
1		2		2	
2		3.25			
3		4		3	
4		5	0.13	4	
4.5		6	0.17		
5		6.75		5-6	
5.5		7.25	0.23	7-8	
6		7.5		9-10	
6.5		7.75		11-13	0.15
7		8.5	0.5-0.6	14-17	0.40
7.5		9	0.8	18-20	
8		10		20.5	1.5
8.5	2.0	10.5	2.0	22	
9	2.2			25.5	2.4
9.5	3.3	11	6.0	26	3.0
10	3.8	11.5		27	
10.5	5.2	12.125		28.5	4.2
11	6.2	12.5	12.8	31	4.5
11.5				33.5	7.0
12	7.2	13	14.0	36	
12.5	8.9	13.5		36.5	9.0
13	9.4	14.5	17.6		
13.5	9.8			38	12.0
14.5	11.2	15.5		47	17.0
14		16	19.0		
15.5	13.7			65	40.0
16		17-18	29-32		
16.5	16.1			84.5	
17-19	19.8	19-22			

Sources: Same as table 1.

D. IRRADIATION TECHNIQUES

33. The usual recommended procedures for the experimental irradiation of small and medium-size animals (130) are fully applicable to experiments with pregnant animals. In special instances, irradiation of the pregnant uterus or of a single uterine horn with shielding of the rest of the mother's body or parts of it has been adopted in mice (240) and rats (362, 32), particularly to elucidate the direct action of radiation on the conceptus, as opposed to possible indirect effects mediated by irradiation of the mother. Such procedure allows also a proper comparison between irradiated and control animals belonging to the same litter. Specific problems encountered in the irradiation of the foetus by internal emitters are discussed in chapter V.

E. LETHAL EFFECTS

34. Death of the offspring appears to be one of the most widely reported effects following irradiation *in utero*, and the work reviewed covers embryonic, foetal, and neo-natal mortality in several animal species.

35. Pre-natal mortality has been studied by means of several indicators, including the complete interruption of pregnancy, the percentage of resorbed conceptuses, the percentage of embryos alive pre- or post-partum, and the average litter size before or after birth. In a few instances tentative estimates of the LD_{50} at or just before term have been reported; these estimates can more readily be compared with data on post-natal whole-body irradiation. Neo-natal mortality and in some instances the lethality within the first month of delivery have also been reported. Finally, there are data from animals irradiated *in utero* and followed for the rest of their post-natal life for the purpose of estimating long-term parameters related to the time and mode of death.

36. The present report does not discuss the merits or disadvantages of the different ways of measuring lethality and their possible relationships; they are part of the experimental methodology under which the reviewed observations have been made. It should however be realized that even apparently minor variations of technique may yield quite different numerical estimates, even though they might reflect basically the same end-effect, namely radiation-induced lethality. For example, scoring dead offspring prior to or after birth may lead to quite different conclusions, since parturition trauma and mother cannibalism may modify the results profoundly. When reviewing the experimental data, the above comments should be kept in mind to evaluate correctly the reported death rates.

F. DISTURBANCES OF GROWTH

37. Although there may be doubts as to whether or not abnormal growth or growth retardation should be included among the radiation-induced congenital malformations, these effects have been widely described in animals and man following intra-uterine exposure. As in previous reviews of the Committee (344, 345), these effects are dealt with in the present report.

38. A review of the foetal, maternal and environmental factors that could affect foetal development has been published by Brent and Jensh (37). This publication deals mainly with growth retardations in the human foetus and discusses at some length the applicability to man of data obtained in polytocous experimental animals. It also reviews the relationship between teratogenesis and growth retardation, pointing out that although teratogenesis may be viewed as a differential growth disturbance of some tissues and both effects are often elicited by the same teratogenic agent, there are reasons to consider them separately at the present stage of knowledge. Whatever the etiology or the pathogenesis of growth retardation may be, it can be essentially defined as the failure of the foetus to maintain its normal expected growth potential at any gestational age, as measured by some parameter of foetal growth such as its weight or length. Frequently foetal growth retardation leads to growth defects in the extra-uterine life. This is particularly the case when retardation is induced by radiation.

G. MALFORMATIONS

1. Observation time

39. The time at which teratological effects should be examined is of great methodological relevance and is obviously dependent on the effect under study. There are effects that can only be observed under certain conditions and, in general, the magnitude of the effects is critically related to the observation time.

40. If lethality during the intra-uterine stages (pre- or post-implantation) is the end-point of interest, mortality must definitely be scored before birth. Mortality immediately after birth cannot be expected to reflect mortality *in utero* because the trauma of delivery and cannibalism may seriously affect the estimates. Alternatively, neo-natal, 30-day or long-term mortality may be the relevant end-points, in which case the observations should be conducted at the appropriate times. If growth retardation is the end-point, the selection of suitable conditions of scoring must take into account that the percentage weight reduction increases during the first few days after irradiation (362) and that the time for maximum effect is probably a dose-dependent variable (294, 362).

41. When studying the incidence of malformations, some authors score them after delivery (294, 280), but most workers prefer to sacrifice the mother just before term and to observe the foetuses *in situ*, in order to collect information that would otherwise be lost (position of the foetuses, presence of resorptions, placental form and weight, presence of intra-uterine bleeding etc.). Also, cannibalism practised preferentially on malformed offspring would alter quantitative estimates. The technique of sacrificing the mother before birth is adequate and accurate for the study of most types of malformations. However, there is no general rule for selecting the best observation time, which depends on the particular end-point under study.

2. Techniques of observation

42. Quite different data may result from the experiments, depending on the technique of examining the embryos. For this reason few papers among those reviewed are entirely comparable. Some investigators have examined, in more or less detail, only the external features of the foetus. Others have dealt particularly with special types of malformations (e.g., of the nervous or skeletal system) or have given elaborate morphological descriptions of their findings, sometimes with few numerical incidence data. Others again have been mainly interested in the pathogenesis of malformations and have therefore examined histologically the embryos soon after irradiation, often without relating the histological changes to the induction rate of malformations at later stages.

43. The combined effect of the large variety of experimental techniques, the differences between species and strains, the difference of gestational age at irradiation and the wide range of types of radiation and doses utilized, render any quantitative comparison of all the data virtually impossible. Reviews must therefore rely on the internal consistency of a single experimental series in order to prove certain points of interest. Under these conditions, only generalizations of gross qualitative observations are possible.

44. Detailed procedures for autopsy of irradiated foetuses have been published (294, 297). In general, they involve necropsy of the mother with careful examination of the uterus, foetal membranes and resorptions and examination and weighing of the placenta. The external examination of each foetus consists of a number of morphological characterizations and measurements: foetus shape and length; tail shape and length; morphology of anus and genitalia; abnormal posture of limbs; number, shape and position of digits; shape of head, jaw and mouth; exencephaly; position, size and morphology of ears, eyes, nostrils and nasal septa; presence of spina bifida, exomphalos and ventral hernia; etc. Each foetus is then eviscerated carefully for the macroscopic study of morphology and position of thoracic and abdominal viscera. If needed for examination of skeletal changes, the foetus may subsequently be processed by fixation, staining and clearance of the carcass. A large variety of morphological observations have been carried out on the embryo and foetus, from the simplest measurements of length and weight and conventional light microscopy to the most refined electron microscopical observations.

H. STATISTICAL EVALUATION

45. Statistical treatment of the data obtained in radiation teratology experiments does not usually require sophisticated techniques. Unless subtle questions of correlations between types and degrees of abnormalities are examined, simple statistical techniques for comparison of means and distributions are adequate. The papers reviewed only seldom refer to experiment design on the basis of knowledge of the experimental material or of the previous pilot work in relation to the experimental variables to be examined. In many cases the number of observations is small and, as a consequence, the statistical significance of the data is rather weak. This may be explained by the difficulties in obtaining appropriately timed and controlled embryonic material for irradiation, requiring a special organization of the animal quarters, special training of personnel and highly specialized techniques of observation. But it may also be attributed in part to the predominantly descriptive character of traditional embryological research. Experimental data often include extremely detailed recording of minute abnormalities, reported sometimes without appropriate homogeneous grouping and often compounding major malformations with trivial changes. For these reasons the Committee feels that information of a more gross nature, such as the fractional incidence of grossly malformed foetuses, might often be more informative for the purpose of assessments of the effects of radiation.

I. METHODOLOGY AND TECHNIQUES IN HUMAN INVESTIGATIONS

46. The wealth of information provided by well planned research on experimental animals far outweighs the information derived from observations in man. Many

of the human data are inadequate on account of one or more of the following reasons: *(a)* insufficient knowledge of the developmental stage at irradiation; *(b)* lack of precise estimates of the absorbed dose in the embryo; *(c)* malformations can be scored only after birth and on the basis of medical examinations and laboratory data; *(d)* the numerical limitations of the observed samples, often consisting of single observations, and *(e)* the difficulty in obtaining adequate control groups. For all of these reasons, most of the quantitative conclusions derived from human data are rather uncertain.

47. The embryonic or foetal age at irradiation is only rarely known precisely: the majority of the publications reviewed refer to irradiation performed during the first, second or third trimester of pregnancy, and in very few cases is the age of the sample under study specified by month. In addition, Nishimura *et al.* (226) pointed out a large difference between the developmental ages according to Streeter's horizon and the chronological ages estimated from ovulation in human embryos, showing a remarkable variation of morphological age for a given chronological age. It is therefore difficult to compare the stage sensitivity between man and other species on the basis of developmental scales such as that given in table 2, and this fact greatly limits the usefulness of the available observations. Dealing specifically with malformations, the most interesting period would be the second to the sixth week of the human embryonic life, because the induction rate of malformations is expected to be the highest on the basis of extrapolation from animal data. However, most human surveys refer to the last two trimesters or to the second half of pregnancy, where growth disturbances, rather than teratological defects, are the most common findings (74, 235).

48. The estimation of radiation dose in human investigations is also qualified by large uncertainties. In many cases the doses have been assessed indirectly. The earliest reports on children irradiated *in utero*, in the course of radiotherapeutical treatments of the mothers, are generally of clinical nature; furthermore, the importance of recording the physical parameters of the irradiation was then not fully recognized. Dekaban (71) examined over 200 literature cases of pelvic x irradiation of pregnant women and found that only about 10 per cent of them provided sufficient information (half-value layer, energy, distance, size of fields, current, irradiation time etc.) to allow crude estimation of doses. Even in the most recent and best planned epidemiological surveys (235), where the same apparatus and standardized techniques were involved and the average *per caput* dose in the exposed group was therefore accurately known, the individual doses showed a fairly large variation.

49. Most of the early Hiroshima and Nagasaki data were analyzed in terms of the distance of the irradiated persons from the hypocentre (371, 372) and their location with respect to various types of shielding materials (220). In addition, clinical symptoms of early radiation reaction shown by the mother helped to define the possible range of doses received by the child *in utero* (248, 371, 372). Critical re-evaluations of the doses received by the exposed individuals were performed at various times (8, 115), but only the most recent reports include reasonably satisfactory dose evaluations (196). Other methodological and technical problems encountered in the analysis of the human experience are discussed in other sections of this report.

J. THE MAIN PHASES OF PRE-NATAL DEVELOPMENT

50. The development of the conceptus in mammals is usually divided into three major phases: the pre-implantation phase, the period of major organogenesis and the phase of foetal development. Implantation of the early embryo into the uterine mucosa marks the separation between the first two periods. Although implantation is given in the reports at a certain day p.c., it should be remembered that the complete process, from the initial contact of the blastocyst with the uterine wall to its firm attachment through the erosion and invasion of the uterine epithelium by the trophoblast, may last 1-1.5 days in the mouse (266). In man the whole process may take a few days. A clear-cut separation between the embryonic and the foetal periods is even more difficult since the transition is marked by the end of differentiation and the growth of the newly formed organs in an animal which has attained the characteristic morphological features of the species. Thus, the conventional limits of the three developmental periods, which are given for various species in table 3, are only rough approximations.

TABLE 3. APPROXIMATE TIME OF THE BEGINNING AND END OF THE MAJOR DEVELOPMENTAL PERIODS IN SOME MAMMALIAN SPECIES

(Days p.c.)

Species	*Pre-implantation*	*Major organogenesis*	*Foetal period*
Hamster	0-5	6-12	13-16.5
Mouse	0-5	6-13	14-19.5
Rat	0-7	8-15	16-21.5
Rabbit	0-5	6-15	16-31.5
Guinea-pig	0-8	9-25	26-63
Dog	0-17	18-30	31-63
Man	0-8	9-60	60-270

Sources: Same as table 1.

51. The division in three phases mentioned above corresponds approximately to the most significant developmental events in the embryo and is also suitable for the description of radio-embryological effects, which are very different in nature and degree in the three periods (302, 303). For example, pre-natal death is characteristic of the pre-implantation phase (see chapter II) while neo-natal death and malformations are associated particularly with organogenesis (see chapter III). Irradiation during the foetal stage does not lead to gross malformations but rather to defects of growth, particularly in the central nervous system and gonads, or, at high doses, to post-natal death (see chapter IV). Carcinogenic effects following irradiation *in utero* are considered in Annex I.

52. This Annex deals in turn with the three periods of intra-uterine development. Within each period, it considers the effects observed in different animal species. Many of the experiments reviewed were actually designed to test the comparative effects of irradiation during different developmental stages. In general, these experiments will be described and discussed in the section dealing with the period when the most significant observations were actually made, in order to avoid unnecessary repetition.

II. THE PRE-IMPLANTATION PERIOD

A. LETHAL EFFECTS

1. Intra-uterine death

53. Russell and Russell (300) and Russell (295) have studied the lethal effects in pre-implantation mouse embryos after 200 rad administered each day between 0.5 and 4.5 days p.c. The embryos were observed at 10.5 and 13.5 days after mating, or 6 to 13 days post-irradiation. Embryos at the very early stages (0.5-2.5 days) were found, on the whole, to be more sensitive than those 3.5-4.5 days old. Death occurred long before the time of the first observation, so that any abnormality potentially present in these embryos could not have been recognized. Three modes of death were identified: *(a)* the death of entire litters before implantation, which was inferred from the excess of non-pregnant females over non-irradiated controls at the time of observation. This modality of death was estimated to account for about one third of all irradiated embryos; *(b)* individual deaths, also at the earliest pre-implantation stages, manifested by the decreased number of implants per pregnant female; *(c)* individual post-implantation deaths, assessed from the decreased percentage of living embryos in the irradiated samples.

54. Most of these conclusions were confirmed by the work of Rugh and Wohlfromm (286), giving rough estimates of the intra-uterine LD_{50} for embryos irradiated at various stages of pregnancy and observed at 18 days p.c. The greatest sensitivity was shown to occur at 0, 2 and 3 days p.c. with a relatively resistant phase on day 4 p.c. These early embryos, irradiated prior to implantation, rarely lasted sufficiently long to die as foetuses and were generally resorbed. The estimated LD_{50} for the pre-implantation stage is shown in table 4.

TABLE 4. ESTIMATES OF PRE-NATAL LD_{50} AND POST-NATAL $LD_{50/30}$ FOR IRRADIATION OF MICE AND RATS *IN UTERO*

	Mice					*Rats*					
Age (days p.c.)	*Pre-natal LD_{50} (rad)*				*Post-natal $LD_{50/30}$ (rad)*	*Pre-natal LD_{50} (rad)*			*Post-natal $LD_{50/30}$ (rad)*		
0		100									
1		350									
2		125									
3		140									
4	>200	330					30-120				
5		356									
6		380			400						
7		200			200						
8		165			155	140	120				
9	<200	225			140	150	120				
10		255	~150	80-160	120	215	160				
11	200-300	425	~200		160	250	210	>270			
12		560			175		240				
13		700			235						
14	>300	>700			275				>110		
15		>750			315						185
16		>800			365				110-220	214	
17		>800			500						
18					600				>220		
19											
20											
21										273	
Reference	295	286	68	217	289	362	27	324	212	253	322

55. A very careful analysis of the sensitivity of the mouse embryo to lethal damage during the first 48 hours of development was performed by Russell and Montgomery (299). Within the first 24 hours and with exposures of 100 R, very large variations of sensitivity were observed between developmental stages separated only by a few hours. With exposures of 200 R, the sensitivity, as shown by the pre-implantation loss, was found to be extremely high shortly after sperm entry and during the earlier pronuclear stages. At the two-cell stage it remained lowest to increase again at the beginning of second cleavage. Death occurred at random about the time of implantation and there were no late embryonic or foetal deaths.

56. Rugh and Grupp (278) and Rugh (263) studied the dose-effect relationship for embryonic death in CF1 mice irradiated at 0.5 or 1.5 days p.c., using five exposure levels ranging between 5 and 25 R. Under these conditions, the percentage of resorbed embryos showed

a regular increase at all doses in the 0.5-day series; in the 1.5-day series, the trend with dose was irregular but, on the average, the percentage was higher than in the controls (fig. I). Ohzu and Makino (232) performed a

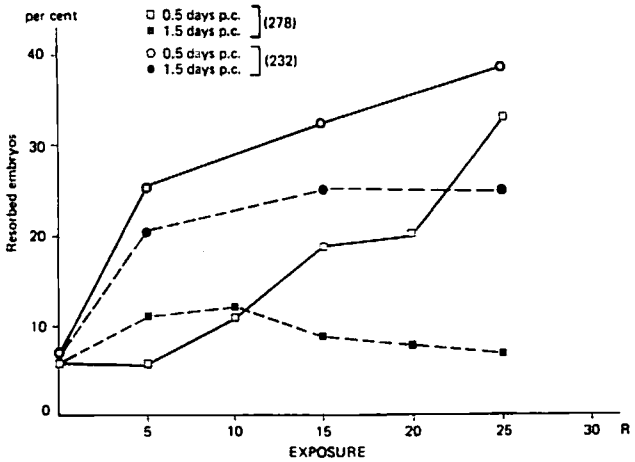

Figure I. Intra-uterine mortality after pre-implantation irradiation (mouse)

similar experiment on (dd X CBA)F_1 mice and also showed, for irradiation at 0.5 days p.c., an increase of the percentage of dead foetuses as a function of dose. Mortality values higher than control, with a plateau between 5 and 25 R, were observed at 1.5 days (fig. I). In a later publication, Ohzu (231) reported the same values for irradiation at 0.5 days, but different ones for irradiation at 1.5 days. Both series show exposure-related increases of the rate of resorption, but the author states that, although the increase of the rate of resorption is statistically significant in both the irradiated groups, the difference between the two groups is short of significance. If a linear regression analysis is carried out for the two sets of data obtained at 0.5 days p.c., the calculated average death increase is found to be 1.06 per cent per roentgen ($P<0.01$) for Rugh and Grupp's series (278) and 1.13 per cent per roentgen ($P<0.10$) for Ohzu and Makino's data (232). The two estimates are therefore in very good agreement.

57. Dose-effect relationships for embryonic death following pre-implantation irradiation were also reported in two recent publications. One publication (91) reports the results of experiments in which several doses of neutrons and x rays were given to pregnant mice, with embryos in the pronuclear zygote stage. Survival data were deduced from the examination of the conceptuses at 16 days p.c. A single exponential relation between the fraction of surviving embryos and absorbed dose was found by the authors to fit the experimental points closely up to a dose of 20 rad of neutrons or 100 rad of x rays. The values of D_0 (the dose necessary to reduce survival to e^{-1} or 37 per cent) were found to be 19 rad for neutrons and 87 rad for x rays. These doses would correspond to an average increase in mortality rate of the order of 0.8 per cent per rad in the x-ray series and of about 3 per cent per rad for the neutron series. The authors concluded that embryonic death could be considered a single-event process for both radiations and that the neutron RBE was about 4.5 (fig. II). The data can also be reasonably fitted by a linear relation, and the

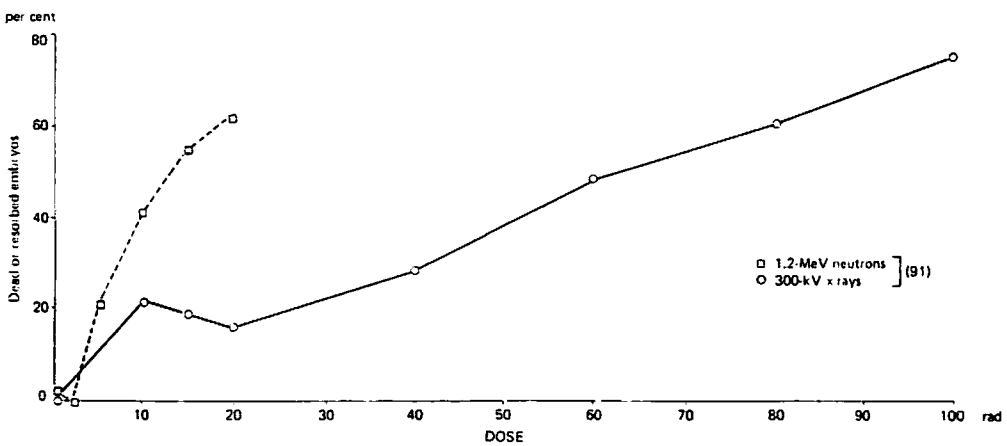

Figure II. Intra-uterine mortality after pre-implantation irradiation (mice exposed to neutrons and x rays)

dose to inactivate 50 per cent of the embryos would be, under this assumption, about 60 rad for x rays and 12 rad for neutrons. The agreement between these estimates of embryonic sensitivity to lethal damage and those discussed previously (278, 232) is indeed remarkable. Other results in the paper concerning the stage at which embryonic death takes place, are in accordance with results already discussed (see paragraph 53). Dose fractionation experiments, which were also reported in this paper, will be discussed in paragraph 311.

58. The other publication, by DuFrain and Casarett (77), reports the results of irradiation *in vitro* of zygotes from superovulated mice, the embryos having been cultured in microdrops of a chemically defined medium. The exposure required to inhibit 50 per cent of the embryos from reaching the two-cell stage was estimated to be about 760 R, and from reaching 50 per cent of the expanded blastocyst stage, about 130 R. As would be expected, the second value is higher than that estimated by Friedberg *et al.* (91) for the development of the embryo up to 16 days. This observation is also consistent with the well established fact that the majority of embryos die at cleavage but some can be lost after implantation has taken place. The *in vitro* culture technique also allows quantification of the cleavage delay observed after irradiation of the zygote. Other

data by Goldstein *et al.* (98) are reviewed in paragraph 69.

59. For the rat there appears to be conflicting evidence in regard to the death of entire litters. Some data show that such an effect may also occur in this species without signs of malformations after exposures of 400 R during the first week of development (123). On the other hand, other findings would question the presence of this phenomenon in the rat (33), though confirming a very high incidence of resorptions and an increased mortality of the implanted embryos after 150 R administered on the first day of pregnancy (32). There is agreement, however, that malformations are not seen in surviving conceptuses irradiated at the pre-implantation stages, even though the possible incidence of malformations in resorbed embryos remains, of course, unknown.

60. In hamsters exposed to 200 R of ^{60}Co gamma rays from the ovulation to the late pronuclear (110), and from the pronuclear to the early blastocyst. stages (0.5-3.5 days p.c. (111)). Harvey and Chang found an increase in pre-implantation lossess only when irradiation was performed at 0.5 day p.c. Post-implantation losses, on the contrary, were increased after irradiations at all times p.c. No malformations were observed. Other data concerning the irradiation of unfertilized ova of mice and hamsters and the subsequent development of embryos can be found in 173, 112, and 113. Female mongolian gerbils x-irradiated with various exposures from 200 to 1200 R on day 2 p.c. (two-cell stage of the fertilized egg) and examined on day 18 suffered severe pre-implantation loss down to 400 R but very few abnormalities were observed in the foetuses (189).

61. From the data of Chang *et al.* (59, 61) it can be concluded that the embryonic rabbit irradiated *in situ* before implantation (day 2-6 p.c.) with 400 R of gamma rays is very sensitive to radiation lethality. Irradiation of the fertilized ova *in vitro* followed by transplantation into recipient animals only resulted in increased mortality at exposures larger than 400 R. Surviving embryos were apparently normal and there was no evidence of differential sensitivity among the various stages of development such as that seen after irradiation *in utero.* In the work of Inman and Markivee (128) rabbit blastocysts of 3.5 days p.c. were exposed to 150 or 200 R of x rays and observed at 9.5 days of pregnancy. These exposures increased pre-implantation mortality from 7 to 18 per cent (average of both groups); post-implantation mortality contributed comparatively little to total mortality.

62. In the dog, irradiation with 150 R of ^{60}Co gamma rays at 5, 15 and 18 days p.c. (early blastocyst, late blastocyst and implantation stages, respectively) resulted in a total pre-natal mortality of 18, 24 and 48 per cent in the stages indicated, while the mortality for non-irradiated embryos was 18 per cent, showing that the dog embryo is most sensitive at implantation. At 8 days p.c., post-implantation mortality was low and it increased with increasing developmental age at which irradiation was carried out (245).

63. Thus, each species appears to have a period of high sensitivity to pre-implantation death in the very early stages. The mouse, rat and hamster are relatively resistant at implantation. The fact that the dog is sensitive at implantation could possibly be attributed to the late occurrence of implantation in this species, and coincides with the formation of the primitive streak, which is another period of high sensitivity in all species.

2. Post-natal death

64. Some data on neo-natal and post-natal death in animals irradiated at the pre-implantation stages are also available, mostly for the mouse. Rugh and Wohlfromm (289) reported that mouse embryos irradiated during the first 5 days of development with exposures from 125 to 400 R of x rays, had a heavy mortality *in utero;* the animals which survived and came to term had good survival during the first 30 days of post-natal life. In another experiment (275), mice irradiated at 0-5 days p.c. with previously determined (289) intra-uterine LD_{50} doses, showed less survival than the controls during the first 30 days of post-natal life. On the other hand, the long-term follow-up of animals surviving later than the first month showed an absence of life-span shortening, indicating that there was little permanent damage after the neo-natal period. Konermann *et al.* (157) performed an experiment in which mice were subjected to daily x-ray exposures of 40, 60 and 80 R during the main phases of pre-natal development. It was shown that irradiation during the period 1-5 days p.c. caused a high incidence of pre-natal death but had no effect (or little effect at the highest daily exposure) on the post-natal (3 weeks) survival of the offspring that were actually born. In dogs exposed to 100 R of x rays at day 13 and 16 p.c., neo-natal mortality increased from 34 per cent (control) to 45 and 57 per cent, respectively. A still higher mortality was observed, however, with irradiations at day 19 and 22 p.c., corresponding to the time of early organogenesis (245).

65. It appears, in conclusion, that pre-implantation death leading to implantation failure is the major mechanism of lethality in all species after irradiation at the early embryonic stages. Pre-implantation death may affect single embryos in polytocous animals or all the members of a litter. Intra-uterine death at later developmental stages is comparatively less important, and the survival of the animals which come to birth is practically unaffected by irradiation during the pre-implantation stages. There are quite substantial variations of the susceptibility to lethal damage, particularly during the early segmentation of the fertilized egg. The sensitivity at the time of implantation is usually lower than at the blastomeric stages, but differences between species can be observed. They may be explained by the different developmental organization reached by the embryos at the time of implantation and may not necessarily reflect intrinsic differences of the susceptibility of the different animal species. Dose-survival experiments in the mouse, in the range 5-100 R, show consistently that the increment in embryonic loss soon after fertilization may be of the order of 10^{-2} R^{-1}. The data on survival at different doses for early segmentation

stages are fitted well by simple linear or exponential relationships, which are not incompatible with relatively simple inactivation kinetics.

3. Mechanisms

66. Concerning the cause of pre-implantation death and the underlying mechanisms, Russell and Russell (302) reported that a high proportion of mouse embryos exposed to 200 R at second cleavage appeared to undergo a rapid disintegration of the nuclei, resulting in lethal damage, whereas irradiation outside cell division allowed further development of the conceptus, often up to implantation. Chromosomal damage in all cells derived from an injured blastomere gave rise to unbalanced chromosome complements. Such damage to the genetic material, together with large radiation sensitivity differences in the cell-division cycle, were confirmed for the first cleavage of mouse embryos (299). After irradiation, a high proportion of embryos showed subnuclei, suggesting that aneuploidy is responsible for most if not all, of the lethal damage. It was also shown that the state of the nucleus at the time of irradiation affects the production of aneuploidy, a fact which would account for the differences in sensitivity as a function of the cell cycle.

67. Rugh and Grupp (276, 277) reported results of extensive morphological studies of the damage induced by low doses of radiation in mouse embryos. Exposures as low as 5 R, at 0.5 or 1.5 days p.c., often resulted in fragmented embryos; the entire egg was broken up into globules, the further development of which appeared doubtful. Anomalies of cytoplasm and of nuclei, pycnosis and complete dissolution of the blastomeres were seen as early as 6 hours after irradiation (281, 282). Other histological studies, performed at 9 or 10 days p.c. on embryos irradiated at several pre- and post-implantation stages, showed that the damage, especially to the mesenchyme, was highest when embryos were irradiated early (310).

68. Kirkpatrick (149) followed the radiation induced morphological anomalies by means of *in vitro* cultures of mouse embryos during the two-cell stage. Also with this technique the irradiated embryos showed fragmentation, disintegration, granulation, nuclear degeneration and pycnosis, or cytoplasmic vacuolization. A distinct correlation was shown to exist between morphological abnormalities and embryonic death. The sensitivity of embryos irradiated *in vivo* or *in vitro* was found to be very similar, the sensitivity having been assessed from the dose required to stop the development of the embryo before the blastocyst in 50 per cent of cases (150, 77).

69. The experiments of Goldstein *et al.* (98) are similar in many respects to those just reported. They analyzed the radiosensitivity of pre-implantation mouse embryos by culturing them *in vitro* up to early post-implantation stages. X-irradiation was also performed *in vitro* at various doses when the embryos were at the 4-cell, 8-cell, morula and blastocyst stages, after which they were returned to culture and scored for the appearance of further events such as the formation of blastocyst, hatching, growth of the trophoblast or of the inner cell mass. Taking blastulation as the end-point, an increase in sensitivity was observed between the 2- and the 4-cell stage, with a decrease at the 8-cell stage. Radiation did not prevent blastulation when administered during the morula stage, but it impaired the occurrence of further events and the efficiency of this impairment was higher the further removed the specific end-point was from the irradiation stage. Growth of the inner cell mass appeared on the whole as the most sensitive indicator of the damage. Up to the 8-cell stage pre- and post-implantation death was responsible for developmental failure, whereas irradiation at the morula and blastocyst stages resulted predominantly in post-implantation lethality. In spite of minor deviations, these findings appear to be in fair agreement with the other data *in vitro* reviewed previously (150, 77) and also with *in vivo* experiments (91, 299, 278, 232). All these data contribute to strengthen our knowledge of sensitivity and mechanisms of damage of the early mammalian embryo.

70. The relationships between the damage to single blastomeres and death of the whole embryo have also been studied. On the assumption that the probability of killing a blastomere is independent of the number of blastomeres in the early pre-implantation embryo, Russell (295) calculated that embryos surviving irradiation at these stages of development included probably some in which one or more blastomeres were injured. Since virtually all surviving embryos appeared to be normal, a considerable degree of totipotency of the blastomeres was inferred. On the other hand, it seems logical to believe that the proportion of damaged blastomeres over the total number present at the various developmental stages, together with their capacity for regulation, may influence the survival of the embryo. It may be of interest in this context that recovery from lethal x-ray damage (300 or 500 R) of the embryonic rat during hormonally induced delayed implantation has been observed by Ward *et al.* (355).

B. DISTURBANCES OF GROWTH

71. The data available on growth disturbances induced by pre-implantation irradiation of mice refer mostly to post-natal observations. Stunting has been reported in the mouse during pre-natal growth (276, 277), but it seems difficult to envisage the existence of a growth disturbance unconnected with other effects, such as lethality or malformations.

72. Regarding post-natal life, an exposure of 100 R of x rays at 0-5 days p.c. did not produce loss of weight or reduction of skeletal size within 4 months of age, while the same exposure at later pregnancy stages produced appreciable stunting (271). Pre-implantation mouse embryos subjected to LD_{50} doses of x rays and which survived to an age of 24 months showed no gross adverse effects on weight. In some instances, the animals with an *in utero* radiation history were even heavier than controls, probably because of the reduced average litter size. These mice also showed no permanent defect of skeletal growth, as determined by radiographs of selected bones performed at the age of 2 months (275).

The offspring at term of mothers exposed daily to 40 to 80 R during the pre-implantation period did not show any loss of weight with respect to controls, but actually showed a significant post-natal overgrowth (157).

73. Brent and Bolden (32) and Brent (31) reported that in the rat the growth of the surviving embryo exposed to 150 R during pre-implantation was not retarded, but this finding contradicted the data of Skreb *et al.* (326), who showed a statistically significant loss of weight in rats irradiated at 5 days p.c. and examined at 15 days of pregnancy. Rabbits irradiated with 150 or 250 R at 3.5 days p.c., and weighed at 9.5 days, showed a reduction of body size observable in spite of the variability of body size among controls, since lighter foetuses in the controls were not as numerous or severely affected as in the irradiated groups (128).

74. It may be concluded that reduction of body growth due to irradiation during the pre-implantation period is not an effect so clearly and universally recognized as embryonic death, even at exposures in excess of 100 R.

C. MALFORMATIONS

75. The appearance of malformations following irradiation of early pre-implantation embryos has been reported in a few instances. Such malformations involve particularly the central nervous system and the skeletal system. In the mouse, a maximum of 6 per cent exencephaly was produced (277) by irradiation with 50 or 200 R of x rays during pre-cleavage, when no organ primordia but only the three primary germ layers are present in an embryo. In another report (278) the dose-effect relationship for this abnormality was examined in embryos of 0.5 or 1.5 days p.c. within the range 5-25 R. The occurrence of the cerebral malformation was confirmed, but no obvious trend with dose was established. The authors believe that damage of the sensitive neuroblasts, which is the cause of exencephaly during organogenesis (see paragraphs 135-140), is not the only possible mechanism of production of this malformation. At early stages of development (gastrula), irradiation could interfere with the cellular movements in a way that alters the process of cephalization of the embryo, causing the appearance of abnormalities of the head structures.

76. The presence of a few cases of exencephaly was also conformed by Ohzu and Makino (232) and Ohzu (231). These authors irradiated fertilized mouse eggs at 0.5 and 1.5 days p.c. and reported, in addition to exencephaly, an average incidence of forelimb polydactilia of 28 per cent and 21 per cent, respectively. The incidence seemed to be unrelated to exposure in the interval 5-25 R. Hind-foot digits were practically unaffected. Since forelimb polydactilia was also observed in 14 per cent of the non-irradiated mice, it was concluded that the increased incidence after irradiation could be indirectly due to an effect on the uterine environment (subsequent, for example, to heavy lethality of the pre-implantation embryos) rather than to a direct radiation effect on the blastocysts. It should be mentioned that exencephaly also occurs in normal mice (in about 1.5 per cent of the embryos of the CD-1 strain), and that irradiation during the mononuclear-zygote stage (91) does not consistently modify its incidence. Also, chromosomal imbalance may frequently lead to exencephaly in the mouse. Therefore, the relationships between an aberrant cytogenic constitution and the appearance of gross malformations could be investigated in greater depth to establish precise pathogenetic mechanisms.

77. Brent and Bolden (32, 33) reported data for embryo rats exposed on the first day of gestation to 150 R, with various combinations of ovary, oviduct and uterine shielding. They were unable to find any malformation in more than 1,000 offspring examined. A small number of irradiated rabbit blastocysts gave rise to embryos that were severely stunted and grossly abnormal in body proportions or retarded in differentiation 9.5 days p.c. The degree of the malformations was such that these animals would probably not have survived long enough to be scored as malformed at birth (128).

78. In the dog (245), developmental malformations were usually not seen following pre-implantation exposure, and the only two cases of severe cranio-facial abnormality seen after an exposure of 150 R at 15 days p.c. were attributed to uncertainty of the foetal age at irradiation.

79. In conclusion, the few reported malformations in mouse foetuses irradiated during the pre-implantation stages (notably exencephaly) represent a very improbable event, particularly in comparison with the frequent occurrence of aberrations during organogenesis. These malformations can be explained embryologically, and their occurrence does not contradict the general view that the death of the embryo, rather than the induction of malformation, is by far the highest risk of irradiation during the pre-implantation stages.

D. OTHER EFFECTS

80. A variety of other effects have been reported, mainly in the mouse, as a result of *in utero* irradiation during the pre-implantation stages. They are mentioned in this report for the sake of completeness but are clearly too scanty for meaningful generalizations. The sex ratio of mice irradiated *in utero* with x rays at different times and doses (289, 292) was equal to that of controls. Similarly, there was no shift of this ratio in the animals dying during the first 30 days post-partum. These observations show that radiation is not selective with respect to sex in inducing mortality.

81. Rugh, Wohlfromm *et al.* (292) reported a significant increase of the incidence of gross lens opacities (sclerosis of the nucleus and overt cataract) particularly in male mice irradiated with 100 R of x rays during the fertilized pre-cleavage stage and followed up to 18 months of age; however this increase was smaller than some values reported earlier (270, 275). It was suggested that the pathogenesis of the radiation-induced cataract might be related to a damage of the developmental processes that was insufficient to be

lethal. Another effect observed in these mice after irradiation prior to implantation and survival for up to two years, was a slight increase in the white-cell count and a small reduction in the red-cell count (275).

82. Data on post-natal fertility of the male mouse x-irradiated at various gestational ages from conception to 18.5 days p.c. were also reported, showing that exposures up to 100 R had little effect (288).

83. Sex-chromosome losses were studied in the progeny of mice irradiated within 48 hours after copulation. Marked changes of sensitivity to this effect were shown to occur within a few hours, in parallel with similar oscillations of sensitivity to lethal damage (299).

III. THE PERIOD OF MAJOR ORGANOGENESIS

A. LETHAL EFFECTS

1. Failure of pregnancy

84. The reduction in the percentage of copulations that result in pregnancy due to irradiation at various stages of pre-natal development is a measure of mortality involving the complete loss of a litter. This indicator is rarely mentioned in the recent literature but was used in the earlier papers (see Russell (295) for a review). In mice, Russell (295) has shown that complete interruption of pregnancy, which is the frequent result of pre-implantation exposure (see paragraph 53), is a comparatively rare event after post-implantation irradiations. As an example, exposures up to 400 R between 9.5 and 13.5 days p.c., when pregnancy may be diagnosed externally, result in almost 100 per cent litter-bearing females, while an exposure of 200 R, between 0.5 and 8.5 days p.c., when pregnancy is not readily apparent, clearly decreases that yield. From these data it also appears that this indicator of lethality is not sensitive for the case of exposures in the post-implantation stages. Such a conclusion is supported by the observations of Jacobsen (136), who noted the variability of the estimates and the absence of effects with exposures of 100 R at 7.5 and 10.5 days p.c.

2. Litter size

85. The decrease in litter size at or just before birth reflects the death of individuals in a litter due to mechanisms which could in principle operate before or after implantation. Jacobsen (136) pointed out that, although this indicator is defined as the ratio between the number of offspring and the number of mothers, its exact specification depends on the choice of which mothers are considered for the ratio: mothers with one or more offspring at the observation time, all pregnant females including those aborting and dead, or mothers that completed pregnancy, including those having offspring or resorptions. With each choice, the indicator has a different biological meaning, but, nevertheless, in all cases essentially similar dose-effect relationships are found.

86. The change in the average litter size has been studied as a function both of developmental age at the time of irradiation (fixed dose) and of dose. This indicator is an easy one to measure and relevant data may be found in many papers. Only some of them are reviewed here. Rugh, Duhamel *et al.* (270) have reported in CF1 mice the values of litter size at birth after exposure to 100 R at different times p.c. The data show (fig. III) a reduction in litter size of the order of 40 per cent with irradiation soon after copulation. For irradiations at a later time, a stabilization of the indicator at about 10 per cent below normal is found, but a further decrease occurs at around 7 days p.c., followed by a return, with oscillations, towards control values. The observations reported by Dekaban (72), obtained by exposing Webster Swiss mice to 200 R at different post-implantation times, are qualitatively similar (fig. III). The average litter size is about 30 per cent of control for irradiation at 7 days p.c.; after irradiation at later times, the indicator reaches the control value by day 12 p.c. and remains unchanged until day 18 p.c. These data consistently show that the

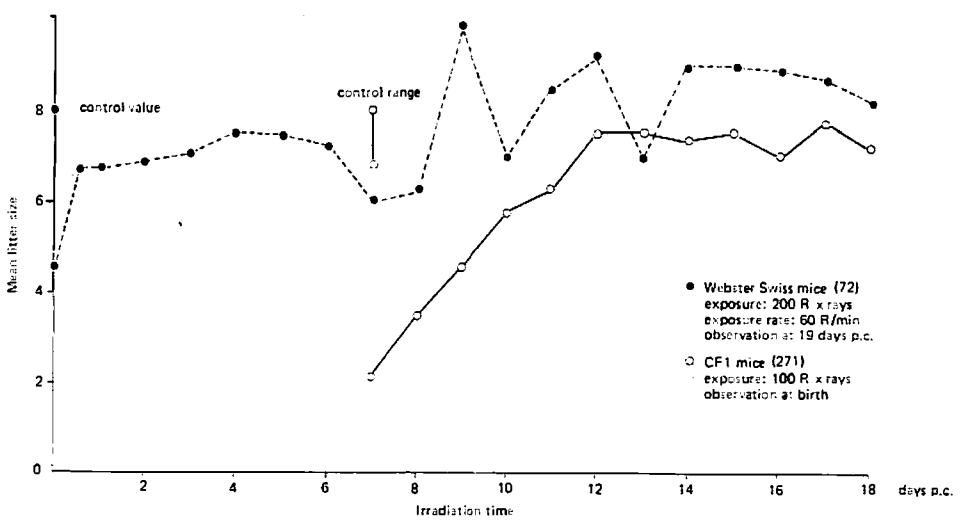

Figure III. Effect of irradiation at various p.c. times on mouse litter size

sensitivity to radiation lethality, as measured by litter size, is maximal immediately after conception and during the early stages of organogenesis and decreases at later times to low and constant values during the foetal stages of development.

87. In the rat, early data by Job *et al.* (139) and more recent data by Murphree and Pace (212) show that exposures of 110 to 220 R in the period 13 to 20 days p.c. have no effect on litter size at birth. The slight changes in litter size in the dog reported by Phemister *et al.* (245) are of doubtful significance with an exposure of 100 R at 16 and 19 days p.c.

88. An analysis of the available data on litter-size reduction as a function of dose shows that different dose-effect relationships are valid in the different embryonal and foetal stages examined. The data of Russell (295) obtained on embryos in the pre-implantation, post-implantation and foetal stages are shown in figure IV. For irradiations in the period 0.5-4.5 days

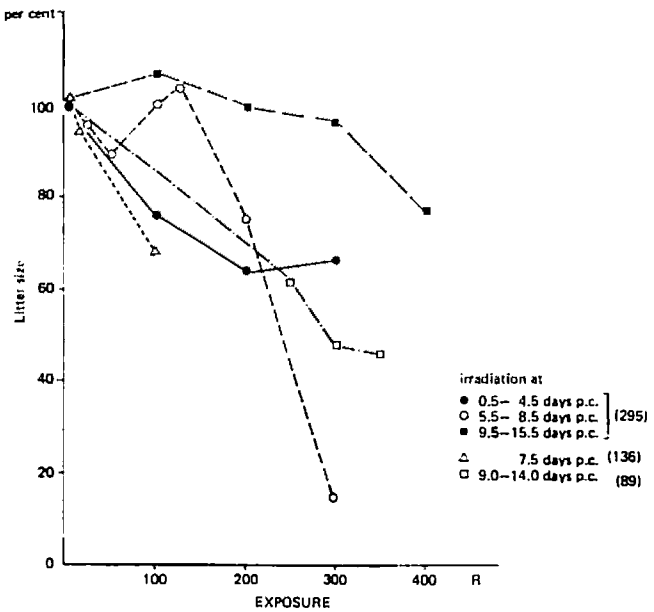

Figure IV. Dose-effect relationships for mouse litter size at birth after irradiation at various p.c. times

p.c., a monetonically decreasing relation is found up to exposures of about 200 R, followed possibly by a constant tail. For irradiation during organogenesis, there seems to be an absence of effect with exposures up to 125 R: at higher exposures, the effect increases substantially with exposure. The relationship for irradiation during the foetal stages show much smaller effects in the same dose range.

89. The data of Fraser and Hall (89), obtained by irradiation during the embryonal and early foetal ages, show a much more important decrease in the litter size at the tested exposures (fig. IV) but are of little help for establishing the form of the relation since they cover only the interval between 250 and 350 R. The low-exposure region is adequately covered by Jacobsen's observations (136), which show an apparently linear exposure-response curve between 5 and 100 R in 7.5-day-old embryos (fig. IV); however, Jacobsen did not consider this effect as a particularly sensitive indicator of lethality in his mouse strain. There is a discrepancy between the linearity of the response found by Jacobsen and the shoulder-type relationships obtained by Russell (295) and by Kriegel *et al.* (160), although the stages of pregnancy at irradiation and the exposure conditions in the two experiments seem to have been comparable. Nash (217) has also studied the litter size at birth in mice of various genetic backgrounds, with four different x-ray exposures (20, 80, 160 and 320 R) at four development ages (6.5, 10.5, 14.5, and 17.5 days p.c.) (fig. V). There appears to be

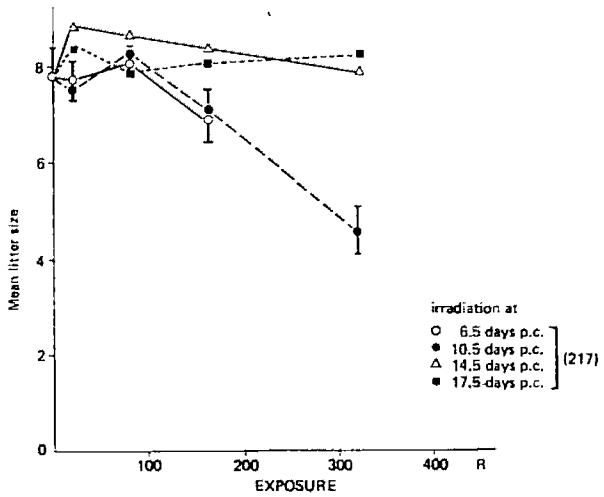

Figure V. Dose-effect relationships for mouse litter size at birth after irradiation at various p.c. times

little or no effect at all ages up to 160 R, and the only point significantly different from the control is that at 320 R in the 10.5 days p.c. series. It should be mentioned, however, that in this series all animals were dead soon after birth.

3. Resorptions

90. Special attention should be paid to the phenomenon of pregnancy resorption, which is rather commonly described in experiments with rodents and observed even during normal pregnancy in a sizeable but variable percentage. As shown by Jacobsen (136) in the mouse, the incidence of resorptions increases drastically with the age of the mother and is very sensitive to seasonal influences and to weak extrinsic teratogenic stimuli, including radiation. Jacobsen (136) broadly classifies the resorption types observed in the mouse. His classification may not be sufficient for an accurate description of mechanisms, but it does make possible broad evaluations of the stage of pregnancy in which resorptions could have occurred. On the basis of the work of Kameyama (142) and his own observations, Jacobsen (136) considers resorption to be a very sensitive indicator in the case of radiation exposure, provided that the conditions under which it is scored are rigorously specified and the strain characteristic and extrinsic factors are properly controlled or allowed for.

91. Since implantation is a prerequisite of resorption, a radiation-induced change in resorption frequency should essentially reflect post-implantation mortality.

There are data on this effect in the mouse covering various days p.c. around the time of implantation or various doses at fixed gestation times. Murakami and Kameyama (204) have reported no change of embryonic loss in mice with exposures up to 50 R at 8 days p.c.; with exposures of 100 R, the fractions of resorbed and missing embyros were about 20 and 30 per cent, respectively, while the control loss was less than 10 per cent. Kriegel *et al.* (160) exposed pregnant mice to 200 R of x rays at different times between 5 and 15 days p.c. and scored resorptions on day 18 p.c. Under those conditions, they were able to show (fig. VI) that

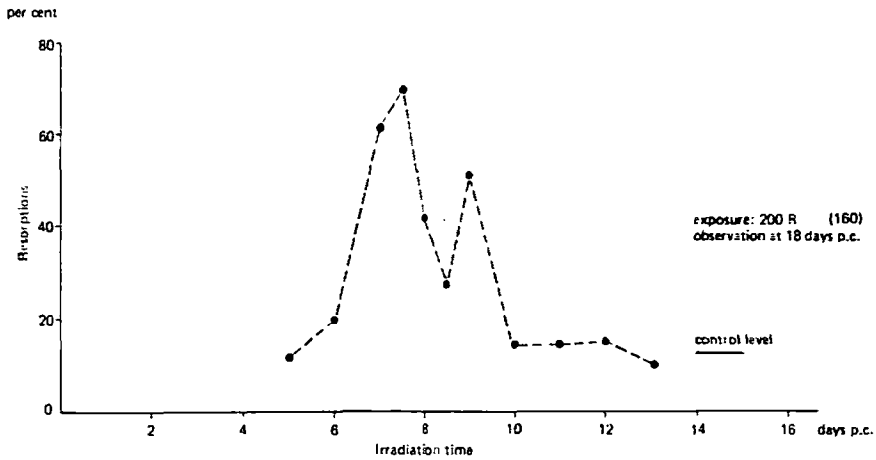

Figure VI. Effect of irradiation at various p.c. times upon resorption incidence in the mouse

the incidence of resorptions, which was around control level (12 per cent) with irradiation at 5 days p.c., increased substantially with developmental age at irradiation, reaching a peak of 70 per cent at 7.5 days p.c.; for older ages at irradiation, the incidence decreased to the control level at about day 10 p.c.. The embryonal lethality was also examined as a function of exposure in

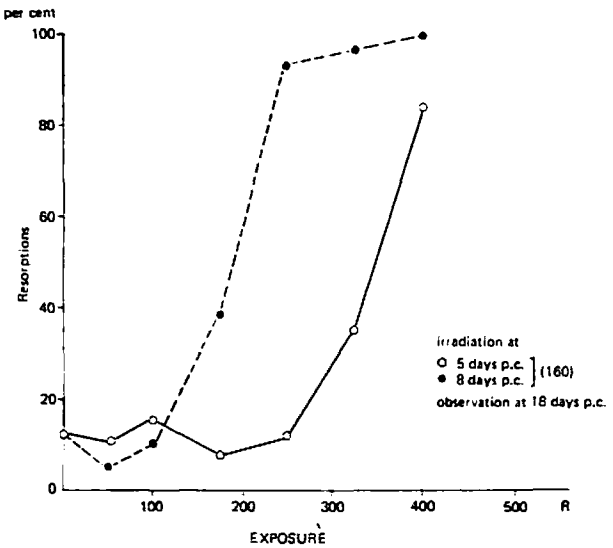

Figure VII. Dose-effect relationships for resorption incidence in the mouse

the range of 50 to 400 R, with two irradiation ages (5 and 8 days p.c.). The curves (fig. VII) show marked differences in that they begin to rise steeply at widely different doses. being fairly parallel from then on; the maximum effect occurs between 250 and 400 R at 5 days p.c. and between 100 and 250 rad at 8 days p.c.

92. These data (160) are at variance with the apparently linear dose-effect relationship between 5 and 100 R reported by Jacobsen (136) for a different strain of mice (fig. VIII), but under comparable experimental

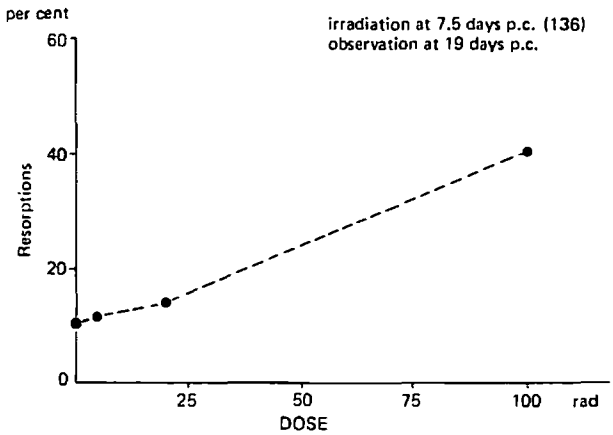

Figure VIII. Dose-effect relationship for resorption incidence in the mouse

conditions (irradiation at 7.5 days p.c., scoring at 19 days p.c.) Even allowing for differences in the technique, the fact that in Jacobsen's experiment (136) an exposure of 100 R increased the incidence of resorptions from the control value of 10 per cent to 40 per cent shows that there is a large variability of sensitivity to radiation among animal strains. Moreover, the different shape of the dose-effect curves (fig. VII) supports the existence of a variation of sensitivity between embryonal stages, as shown already by the timing experiments previously discussed (160).

93. The data of Skreb and Bijelić (325) in the rat (fig. IX) establish the existence of a stage-differential sensitivity to the induction of resorption, with a maximum at 8.5 days, in good agreement with the

mouse data. The work of Skalko (324) with animals of 11 days p.c. exposed to 135 or 270 R confirms that at this gestational age the resorption effects are weakly correlated to the level of exposure.

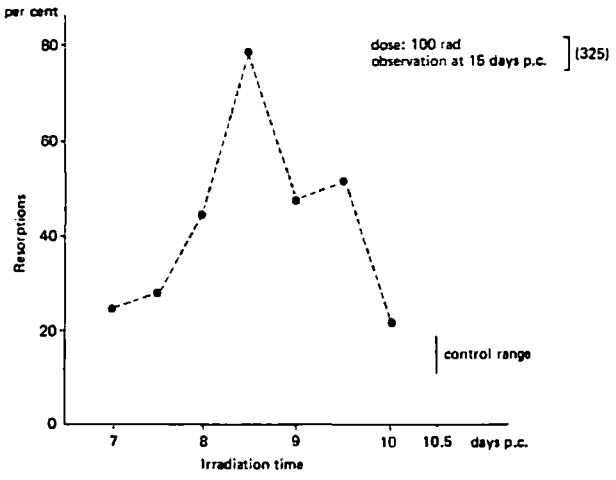

Figure IX. Effect of irradiation at different p.c. times on resorption incidence in the rat

4. Mortality *in utero*

94. The percentage of embryos alive before term is the most straightforward and sensitive indicator for evaluating the lethal action of radiation on single embryos and foetuses. It measures the induced global impairment of the complex sequential process that leads to a fully viable individual. Dagg (68) irradiated inbred strains of mice *in utero* (fig. X) with exposures in the

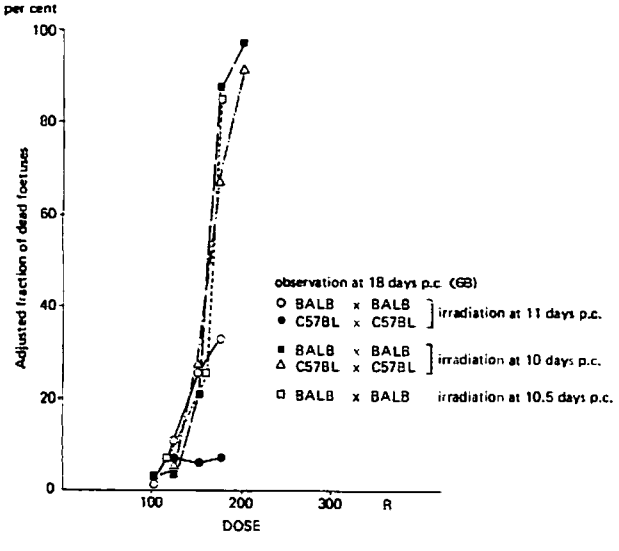

Figure X. Dose-effect relationships for mortality *in utero* for various inbred mouse strains

range of 100 to 200 R and at times between 10 and 11 days p.c. and scored live and dead offspring at 18 days p.c. With irradiation at 11 days p.c., the incidence of dead embryos in the BALB/C strain increased with exposure in the range of 100 to 175 R, for the C57BL strain there was little indication of such a response. However, when irradiation took place at the same developmental age in both strains, both survival curves became similar, even though the BALB/C mice showed a somewhat higher sensitivity. For both strains there was a threshold for the lethal effect of the order of 140 R. The mouse strain 129, on the other hand, was highly resistant to exposures up to 200 R; differences were also seen in hybrid crosses between these inbred strains.

95. Wilson (362) irradiated Wistar rats of 8 to 11 days p.c. with exposures in the range of 12.5 to 600 R. In this experiment (fig. XI) 8-day-old embryos were apparently

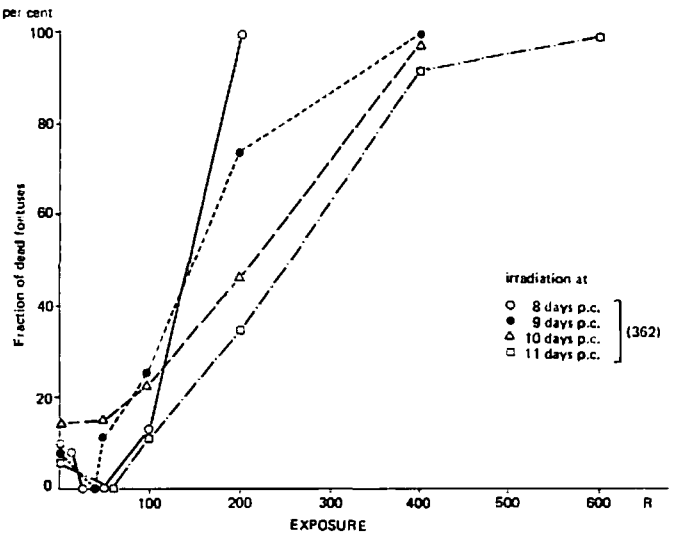

Figure XI. Dose-effect relationships for intra-uterine mortality in the rat

resistant up to 100 R but reached 100 per cent mortality at 200 R. At increasing embryonic age, the sensitivity to radiation lethality tended to decrease, giving rise to mortality curves that were less steep.

96. In the hamster, an exposure of 200 R during pre-implantation causes a moderately high mortality. The same exposure at implantation results in low mortality and at 6.5 days p.c. (time of primitive streak formation), in the highest mortality. At older developmental ages, mortality gradually decreases to the control value during organogenesis and foetal growth (fig. XII). At the time of peak sensitivity, an exposure of only 100 R induces about 70 per cent degenerating foetuses, the 100-per-cent effect being produced by 200 R (111, 59). The data for the rabbit reported by the same authors (59) show that mortality following an exposure of 400 R is 100 per cent if irradiation takes place at the time of implantation and tends to fall if irradiation is carried out later during organogenesis and foetogenesis. There is also a fairly complete experimental series with beagle dogs exposed to 150 R (245), in which pre- and post-implantation mortality has been studied as a function of irradiation time from 8 to 35 days p.c. The results show that post-implantation and total mortality are significantly higher than control values (fig. XIII) for irradiations at a gestational age of 18 to 22 days p.c.

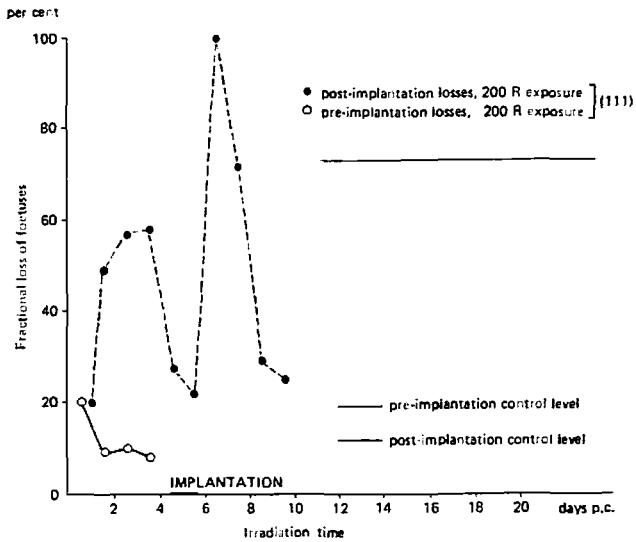

Figure XII. Effect of irradiation at various p.c. times on intra-uterine mortality in the hamster

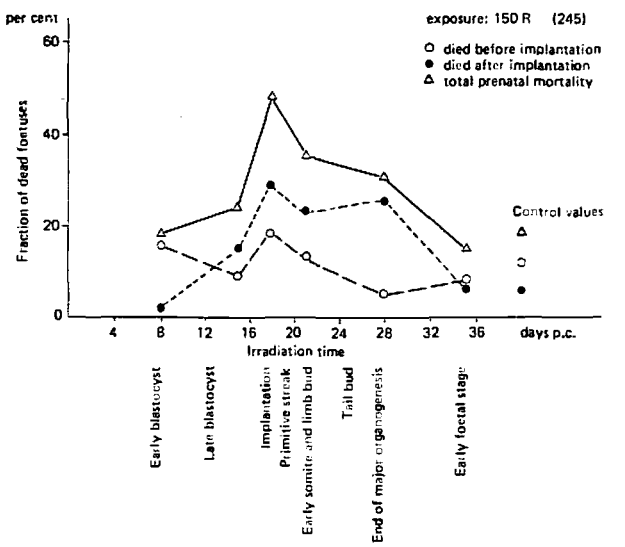

Figure XIII. Effect of irradiation at various p.c. times on intra-uterine mortality in the dog

(during the phases of implantation, primitive streak and early somite formation), in good agreement with the data for rabbits.

97. In conclusion, it appears that pre-natal mortality in many species is highest for irradiations after implantation and during the stages of early organogenesis, and that subsequently mortality decreases with the advancement of embryonic differentiation. From the available data in rats and mice it would appear that the shape of the dose-lethality relationship for *in utero* mortality might change substantially with developmental stage and that, in the large majority of cases, at all post-implantation ages tested a sigmoid relationship would apply with an increase in the slope occurring in the region of a few tens of rads. At the later stages of pregnancy, the decrease of sensitivity is mainly reflected by lower slopes of the mortality curves. There is insufficient information to identify the possible mechanisms of foetal death at these early post-implantation stages.

5. Neo-natal mortality

98. Russell (295) reported data on neo-natal mortality in mice from which it is quite apparent that exposures of 100 R or lower have no effect on survival at birth; 200 R induce a peak of mortality when received between 7.5 and 11.5 days p.c. (early organogenesis); 300 R at the same times induces 100-per-cent mortality, the effect falling off steeply with irradiation at times up to 14.5 days, in a manner apparently parallel to the 200 R curve. It can be concluded that around 50-per-cent mortality, the slope of the curve is very steep for any given developmental stage.

99. In a more recent report (217) on mice of three different genetic strains and their crosses, the pooled data shows that 20 or 80 R at any age between 6.5 and 17.5 days p.c. does not cause any neo-natal mortality, while 160 R causes a peak mortality of up to 75 per cent at 10.5 days p.c., and 320 R results in a mortality of 100 per cent when received at 10.5 days p.c.. 23 per cent at 14.5 days p.c. and zero at 17.5 days p.c. These data are in very good agreement with those cited previously. Neo-natal mortality in beagle dog puppies exposed to 100 R of x rays during a period from just before to just afer implantation is highest for irradiations at 19 and 22 days p.c., corresponding to early organogenesis (fig. XIV).

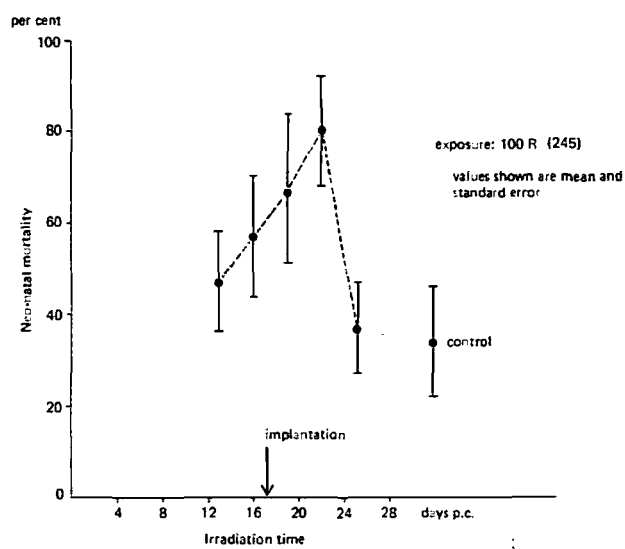

Figure XIV. Effect of irradiation at various p.c. times on neonatal mortality in the dog

100. In conclusion, therefore, at exposures below about 100 R there is no (or little) increase of neo-natal mortality, but the effect becomes manifest at higher exposures, with an increasing slope of the dose-effect relationship. As differentiation proceeds, the sensitivity of the embryo and foetus gradually decreases.

101. There is information available for two rodent species on the LD_{50} for irradiation *in utero* and on the variation during embryonic and foetal development shown in table 4. The variability among species and strains found in different experiments is very large, the identification of general trends being correspondingly difficult. It appears, however, that sensitivity is very high (with LD_{50} corresponding to exposures lower than

150 R) in the pre-implantation, implantation stages and early organogenesis stages. In the single case where timing was accurate, the fine structure of the radiosensitivity of the mouse embryo showed considerable variability, but a large share of this variation could be attributed to the technical conditions under which the observations were made rather than to intrinsic changes in the sensitivity of the embryo. LD_{50} data for the mortality *in utero* reported for the period between day 6 and 13 range from 165 to 700 rad. At the late stages of organogenesis, the LD_{50} begins to rise gradually to reach during foetal development values comparable to the post-natal LD_{50} levels.

6. Post-natal and long-term mortality

102. The mortality after birth of animals irradiated *in utero* was studied by Rugh and Wohlfromm (289), who irradiated CF1 mice at 6-18 days p.c. to establish the radiation dose that would kill, within 30 days after birth, 50 per cent of the mice born alive. The $LD_{50/30}$ values (table 4) were found to fluctuate with developmental age. The lowest values were at 8-10 days p.c., the time when the most active differentiation of the nervous system takes place. On days 6, 7 and 8 p.c., the LD_{50} *in utero* (286) was the same as the $LD_{50/30}$, which implies that exposures of about 400, 200 and 150 R at these ages, respectively, kill half of the offspring *in utero* and half of those born alive within 30 days. At later exposure times (see table 4) the $LD_{50/30}$ were consistently and substantially lower than the LD_{50} *in utero*, showing that, while the embryo cannot easily be killed before term, it can readily be damaged in a way which renders it unable to survive the first month after birth. Early post-natal deaths were more frequent among litters irradiated during early gestational ages.

103. The observations of Nash (217) are in general agreement with these data, in spite of minor technical differences. He reported that the survival to 60 days of mice still alive 12 hours after birth was maximum after irradiation at 6.5 days p.c. Irradiation at 10.5 days p.c. had the most severe consequences, while exposures at 14.5 or 17.5 days p.c. produced intermediate effects. For example, after 80 R at 10.5 days p.c., only 55 per cent of the mice alive soon after birth were still surviving at 60 days, while 62 and 78 per cent survived if the same exposure occurred at 14.5 or 17.5 days p.c., respectively. No consistent pattern of survival differences between sexes, doses or embryological stages was observed. Inbred mice appeared to survive less than hybrids, especially immediately after birth, and in the groups where the increase in post-natal mortality was most significant, inbred strains showed a larger response to the radiation insult than hybrid genotypes.

104. An unexplained and still not confirmed conditioning effect has been reported by Rugh and Wolff (293), whereby an exposure of 10 R of x radiation on day 15.5 p.c. enabled mouse foetuses to survive better when irradiated as adults with doses around the $LD_{50/30}$. This "beneficial" effect was also apparent at 14.5 and 16.5 days p.c., while higher exposures (25 to 300 R) led invariably to deleterious effects in adult life.

105. The data of Nash and Gowen (219) extended the observations to the whole life span of mice, showing that the reduction in longevity after 20 to 320 R at four gestational ages depended on genetic constitution, sex, gestational age at irradiation and exposure. The influence of these factors was evaluated in multifactorial experiments in which data on mature life spans of 647 animals were collected.

106. In the rat, the neo-natal death rate was significantly higher than control (6 per cent) when the litters were exposed to 110 R on day 13-15 p.c. (27 per cent) and on day 15-18 p.c. (13 per cent), to 150 R on day 14 p.c. (98 per cent), and to 220 R on day 12-16 p.c. (77 per cent) (118). Sikov, Resta and Lofstrom (322) carried out an analysis of the long-term mortality of rats surviving at weaning, with exposures of 20 or 100 R at 10 days p.c. and of 50 or 185 R at 15 days p.c. Sex differences were also found in this study; life-span shortening in females appeared to be greater than in males, in which the effects observed were of doubtful significance and in any case not very substantial.

107. It can be concluded that the lethal effects of irradiating animals *in utero* are not exhausted with pre-natal mortality but at appropriate doses may also become manifest in post-natal life. Thus, a dose of radiation insufficient to kill an animal *in utero* may still be lethal after birth. Post-natal $LD_{50/30}$ values calculated on live-born animals in the region of 150-300 rad have been reported for the rat and mouse irradiated between day 6 and 13 of intra-uterine life. Mortality after birth takes place essentially during the first month after birth. Long-term reductions in life span may also become evident for exposures in excess of 200 R in rodents, depending on a number of genetically controlled factors of the strain. A detailed discussion of tumour induction in animals irradiated *in utero* will be found in Annex I.

108. In the human species there are no data related with certainty to the lethal effects of irradiation during embryonic stages. Since there are great difficulties in tracing the pregnancy stage at irradiation in most of the reported experiments and since most of the experience refers to irradiation in the foetal stage, this subject will be reviewed in connection with the irradiation of the foetus (paras. 192-195).

B. DISTURBANCES OF GROWTH

1. Intra-uterine growth

109. Russell (294) reported foetal growth defects in mice irradiated between 0.5 to 13.5 days p.c. with exposures of 200, 300 and 400 R. The mean weight at birth of these animals was not significantly below control for irradiation times up to 7.5 days p.c. The effect was considerable with irradiations at later stages of development. The response curves as a function of irradiation time for the three exposures were found to be roughly parallel, with maximum effects between 10.5 and 11.5 days p.c. A complete and apparently linear dose-effect curve for heterozygous but genetically

uniform animals irradiated at 11.5 days p.c. was reported by Russell, Russell and Major (305) covering the interval 0-300 rad. The resulting average weight reduction was estimated to be 0.22 g per 100 rad within this dose range, in fair agreement with the previously reported data. Jacobsen (136), irradiating homozygous HC mice at 7.5 days p.c. (a relatively less sensitive stage, according to the data of Russell (294)), reported a reduction of 0.12 g per 100 R, for animals sacrificed at 19 days p.c.

110. In view of the experimental differences between the two sets of data it is difficult to draw a clear conclusion, but it seems possible to assume that weight reduction is a more sensitive indicator of radiation damage if irradiation occurs at 10.5 and 11.5 days p.c. rather than earlier or later in foetal life. Considerable strain variations are, however, to be expected (136, 266). This view is also supported by more recent work by Konermann (155), who studied experimentally the relative sensitivity of the mouse conceptus to irradiation during blastogenesis, organogenesis and foetal stages, with fractionated exposures of 10 to 80 R per day. Animals examined 18 days p.c. appeared to be most sensitive when irradiated during organogenesis. When irradiation continued during the foetal growth, a still higher effect was produced, with weight reductions up to 50 per cent at exposures of 80 R per day.

111. In a study of radiation effects on embryonic growth, Yoshizawa and Ueda (373) irradiated dd-Y mice *in utero* at various gestational ages (7-17 days p.c.) and at various exposure levels (0-300 R) and exposure rates (1-100 R/min) of a ^{137}Cs gamma source. The body weight of the foetuses and the growth of the caudal vertebrae were taken as indicators of the effects to be studied; they appeared to show similar dependencies on the experimental variables. The gestational ages 8-11 and 16 days p.c. were found to be sensitive stages for the inhibition of bone growth, and they appeared to be related to inhibition of the cartilage bud and to damage of the ossification processes, respectively. The delay in the degree of ossification and the decrease in body weight were insensitive to exposure rate in the interval indicated. However, both effects were clearly enhanced by increasing exposure. In this case (irradiation at 11 days and sacrifice at 18 days p.c.) the weight reduction was of the order of 0.23 g/100 R, in good agreement with the data above (para. 109).

112. In the rat, Wilson (362) examined growth retardation after exposures of 12.5-200 R at days 8, 9, 10, 11 p.c. The effect was assessed as weight loss at various times after irradiation, according to a fairly complete experimental schedule. The degree of retardation tended clearly to increase with increasing exposure (although not in direct proportion) at all embryonal ages tested. However, the exposure to obtain a given effect was larger in older embryos, showing that the embryo becomes increasingly resistant to growth retardation. In fact, the weight retardation effect per 100 rad may be estimated to be 14-30 per cent (depending on the observation day) of the control in the 8-day embryo, about 17 per cent in the 9-day embryo, 6-14 per cent in the 10-day embryo and about 2 per cent in embryos aged 11 days.

113. More recent data have added little to these general conclusions. Campi *et al.* (58) made similar observations after 100 rad of x rays given 10 days p.c. and showed that the longitudinal and transversal embryonic diameters, as well as the weight of the foetuses, were considerably reduced 7 days later. Skreb *et al.* (326) exposed embryos between 5 and 10 days p.c. to 100 R of 85-kVp x rays. In reasonable agreement with the data of Wilson (362), the weight of the embryos on day 15 was up to 30 per cent smaller than control, particularly if irradiation took place 8.5-9 days p.c., during the onset of mesoderm formation.

114. It is difficult however to draw more quantitative estimates from experiments where the sacrifice was carried out, not at a fixed time or at maximum weight loss, but at variable times post-irradiation. Weight reductions of 7 per cent after 135 R and 28 per cent after 270 R were reported by Skalko (324) on rats irradiated at 11 days p.c. and observed at term. Brent and Bolden (32) obtained a weight reduction of 11 to 16 per cent at term after 150 R at 6 days p.c., but were unable to show any effect at the same exposure given on the first day p.c. Growth retardation was also reported in mongolian gerbils given 200-400 R of x rays at the primitive streak stage (189). In the rabbit, irradiated at 3.5 days p.c. and observed 6 days later, 150 or 200 R significantly reduced the size of the embryo, in a manner roughly proportional to exposure (128).

115. The data reviewed show that in several species the period of major organogenesis is particularly sensitive to radiation-induced growth disturbances, possibly more than the foetal period but particularly more than the preceding blastogenesis phase. The size of this indicator varies with the time at which the dose is administered during organogenesis and with the interval between irradiation and observation. In all species there are insufficient data to evaluate the net effect of a dose at a fixed post-irradiation time or at the time giving maximum expression of the damage.

2. Post-natal growth

116. Radiation-induced growth disturbances may persist during post-natal life. Levy *et al.* (171) have reported significant reductions of the dimensions of the femoral, parietal and mandibular bones of the mouse, following an exposure of 300 R of x rays at 15.5 days p.c. This effect lasted at least up to 240 days of age, when the last samples were taken. Rugh, Duhamel *et al.* (271) made a complete skeletal study of animals exposed to 100 R *in utero* at different times of gestation (0-18 days p.c.) and which were alive at the age of 4 months. They showed that, both in male and female offspring, stunting in all bones examined was more pronounced if irradiation had taken place between 11 and 13 days p.c., the time when the embryo undergoes the earliest skeletal differentiation. Additionally, a significant reduction of body weight occurred in males irradiated on day 5 p.c. and on day 9-18 p.c., and in females irradiated on day 8-18 p.c., the most drastic reduction being the result of irradiation on day 11-14 p.c. This shows that the second half of gestation is the most significant period for radiation-induced

stunting. Stunting persists during the whole life, since similar results are obtained if the average weight between 3 and 35 months of age is taken as the indicator instead of single measurements at fixed times (272).

117. In other experiments by Nash and Gowen (218), three genetically different strains of mice were exposed to 20-320 R at different times between 6.5 to 17.5 days p.c., and then their post-natal growth was followed for a period up to 75 days of age. The observed body weight reductions were found to depend on dose, gestational age and post-natal age. Reduction was maximum for mice irradiated at 10.5 days p.c. and minimum for those irradiated at 6.5 days p.c., the other two embryological ages tested (14.5 and 17.5 days p.c.) giving an intermediate response. Weight reduction reached its maximal expression when the animals were about 40 days old and remained constant afterwards. There was a marked difference in response between strains, which could be attributed to the difference in the capacity for recovery from the radiation insult and also to variations in developmental age at the time of irradiation.

118. Results available for the rat lead essentially to the same conclusions. Alexandrovskaya (2) observed that 16-month-old rats which received a dose of 150-200 rad on day 12 p.c. had pronounced hypoplasia of the central nervous system. Murphree and Pace (212) reported that rats exposed to 110-220 R at various gestational ages from 13 to 20 days p.c. had average weaning weights lower than the controls. The weights of the body and of the testes in adult males which had been irradiated were also significantly lower than control, and the testicular weight depression was dependent on dose and age at irradiation. Sikov, Resta and Lofstrom (322) showed that an exposure of 20 or 100 R at 10 days p.c. and similarly an exposure of 50 or 185 R at 15 days p.c. reduced the weight at birth in all groups, except at the lowest dose. Growth depression persisting to older ages up to about 80 weeks was only evident in groups irradiated at 15 days p.c., and this effect was manifest also for single organs, particularly for the brain and the spleen, with differences between sexes. It seems likely that the reduction of body and organ weights, often associated with histopathological changes and depression of hormonal levels, cannot be entirely explained by stunting, being probably also the result of complex physiopathological deficiencies.

119. Significant reductions of the interzygomatic distance and of the skull length were observed in adult dogs exposed *in utero* to ^{60}Co irradiation during the organogenesis and foetal stages but not during the pre-implantation period (167). A linear dose-effect relationship seemed to apply between 20 and 330 R, and the fractional reduction per 100 R was estimated to be 4-5 per cent for the interzygomatic distance and 1.7-2.5 per cent for the skull length. Irradiation at the foetal stages was slightly more efficient (167). The volume of the eye in these animals was also smaller than in controls (168).

120. Growth disturbances observed in humans irradiated in the embryonic stages will be discussed in paragraphs 202-208, together with the description of growth deficiencies following foetal exposure. This form of presentation is consistent with the fact that growth changes (as opposed to malformations) are the most likely outcome of irradiation during the foetal stages.

C. MALFORMATIONS

1. General

121. Some qualifying considerations are necessary for the analysis of malformations produced by irradiation during the major organogenesis period. A major difficulty is the lack of standardized nomenclature of malformations, each author having followed his own criteria for classification. This difficulty is compounded by the fact that malformations of adjacent but embryologically unrelated structures are often found in the same animals, complicating substantially the systematic treatment of the data.

122. As most of the published work was performed for the purpose of embryological research, it is very hard to extract from these publications the information relevant to the study of radiation effects. Sufficiently complete analyses of dose-effect relationships for various malformations have been performed in only few cases; most observations have been made at a single or very few doses. In addition, if one considers the variability of species and strain, the very different criteria under which the malformations have been scored and the fact that experiments differed in irradiation conditions, it is not surprising that the various experimental series can hardly be correlated.

123. The Committee believes, nevertheless, that some general conclusions can be derived from consideration of such material. The main emphasis is obviously on reported data that could be used for assessing dose-effect relationships, and for that reason the following review should be regarded as selective and by no means complete.

2. External head abnormalities

124. External head abnormalities described in connection with embryonic irradiation comprise: *(a)* abnormal shapes of the head (dome-shaped or vaulted cranium; narrow, long head); *(b)* abnormalities of nostrils and the snout (tapered, beak-like); *(c)* abnormal shape of the maxilla, jaw and mouth; *(d)* cleft lip or harelip and cleft palate and face; and *(e)* abnormalities of the external ear. Cranial blisters are described below in subsection 4, malformations of the central nervous system (paras. 135-140), and microcephaly is treated in a special section (subsection 5, paras. 141-146) in view of its importance in human radiation biology.

125. In the mouse, the maximum sensitivity for inducing malformations with exposures of about 200 R occurs between 7.5 and 10.5 days p.c. (294) or between 7.5 and 13.5 days p.c. (72), although each malformation probably recognizes a specific "critical period" with smaller exposures (209). According to Jacobsen (136), exposures in the range 5-100 R at 7.5 days p.c. induce few malformations of the head, jaw and mouth. These

results are in accordance with those of Nash (217), showing that vaulted cranium is induced only at exposures of at least 160 R (at 10.5 days p.c.) and also with the observations of Dagg (68), where cleft palate occurred only at exposures of at least 100 R (at 11 or 10.5 days p.c.). Murakami *et al.* (209) found abnormally shaped heads, harelips and cleft palates following exposures of 200 R on day 9 p.c. The same authors (210) reported malformations of snout, maxilla, mandible, harelip and cleft palate following exposures of 150 to 300 R in the period 7-12 days p.c. It appears that in the mouse 50 R is the lowest exposure at which occasional abnormalities of this type are found (204).

126. Studies on the morphogenesis of the palate and on mechanisms of cleft palate induction after 300 R of x rays administered to two strains of mice at 11 days p.c. were reported by Callas (56) and by Callas and Walker (57). The progress in palate development was evaluated by morphological rating in relation to the chronological age and to the embryonic weight. These studies showed that the primary cause of the malformation could be traced to a delay of the movement of the palatine shelf during embryogenesis. The A/Jax mouse appeared to be more susceptible than the C57BL to the induction of this malformation.

127. Warkany and Schraffenberger (357) described malformations in the rat, following exposures up to 1120 R at 9-15 days p.c. These malformations included defects of the skull with partial protrusion of the brain, cleft palate and lip, and maxillary and jaw abnormalities. Their incidence depended markedly on exposure and time of irradiation, but the data are insufficient for an analysis of the dose-effect relationships. More recently, Rajtova and Horak (251) reported malformations of the chrondrocranium in animals exposed to 200 R at 12-15 days p.c. The maximum effects were seen with irradiation at 13 days p.c.; they included degenerative processes and defects of the nasal wall and septum, of the turbinate primordia and of the lamina cribrosa. The incidence of malformations observed with irradiation at 15 days p.c. was not greatly different than in controls.

128. Cleft palate and cleft lip were also found in hamsters (200 R on day 7.5 p.c. (111)), in monogolian gerbils (200-400 R on day 9 p.c. (189)) and in rabbits (400 R on days 9-11 p.c. (59, 61)). Severe cranio-facial malformations, harelip and cleft palate were observed in dogs exposed to 100-150 R immediately preceding or following implantation. They were frequently accompanied by major abnormalities of the brain and eyes (245). Cleft palate and micrognatia were also seen in monkeys following 250 R of x rays during major organogenesis (249).

3. Malformations of the eye

129. Russell (294) reported malformations of the eye in mice exposed to 200-400 R at 7.5-10.5 days p.c. They included various degrees of microphthalmia including anophthalmia, coloboma of different types, and narrowing of the pigmented ring of the iris. Eyelids open at birth is also a pathological condition in this species. Russell's data are insufficient for establishing relevant dose-effect relationships. Anophthalmia and microphthalmia were also seen by Murakami and Kameyama (204) in mice exposed on the day 8 p.c. to 100-150 R, but not if exposed to 25 or 50 R. Majima (181) was the first to report a dose-effect relationship for gross eye malformations, applicable to irradiation at 8.5 days p.c. (fig. XV). This relationship had a threshold of 25 R, in

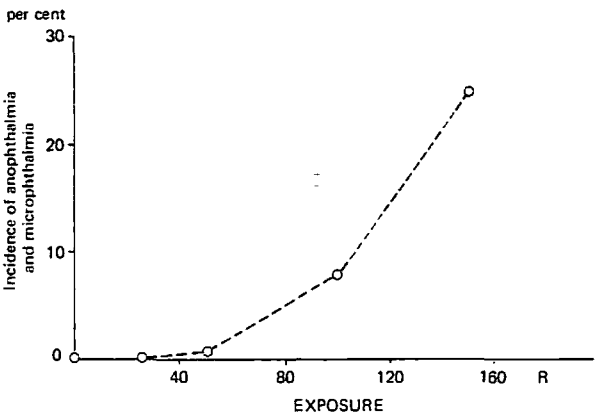

Figure XV. Dose-effect relationship for induction of anophthalmia and microphthalmia in the mouse (181)

the sense that no increase of abnormalities was seen at this dose. The defects were invariably associated with malformations of the central nervous system, and the author described the histopathogenic changes responsible for the malformations. In a second paper (182), Majima irradiated mice 8.5 days p.c. with a fixed dose of 200 R and studied the embryos by gross and microscopical observations at invervals of 1 day between 11 and 19 days p.c. Histology showed the presence of microscopic changes a few days after irradiation.

130. About 29 per cent of eye malformations in ddN mice were reported by Murakami *et al.* (209) following exposure to 200 R at 9.5 days of pregnancy. Murakami *et al.* (210), in their report dealing specifically with malformations of the extremities, include also data on the incidence of microphthalmia and anophthalmia in ddN mice exposed to 150, 200 and 300 R on day 7-11 p.c. From these data it is very difficult to identify the period of maximum sensitivity. Murakami (203) found differences between ddN and CFl mice in this critical period for the induction of eye abnormalities, using exposures of 200 and 300 R (fig. XVI).

131. Sakurai (307) confirmed interstrain differences and the presence of two sensitivity peaks in one of the two mouse lines examined. In addition, he studied microscopic morphogenetic changes at various intervals within 24 hours of irradiation. Experiments on eye malformations in mice were also reported by Badtke *et al.* (250) (130 R at various p.c. times between 7 and 11 days), showing a sensitivity peak between 7 and 8 days, and by Degenhardt and Franz (70) (140 R on day 6-11 p.c.), who obtained essentially the same type of information on the same mouse strain. Other data on eye abnormalities in the mouse are also to be found in papers by Jacobsen (136) and Nash (217), where exposures of 5-100 R did not have clear effects.

132. The most recent and complete set of data on the histopathology of radiation-induced eye malformations

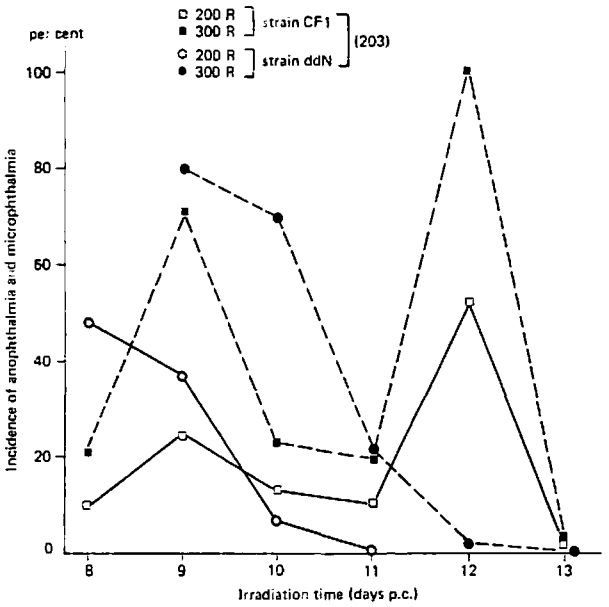

Figure XVI. Effect of irradiation at various p.c. times on the incidence of gross ocular malformations in the mouse

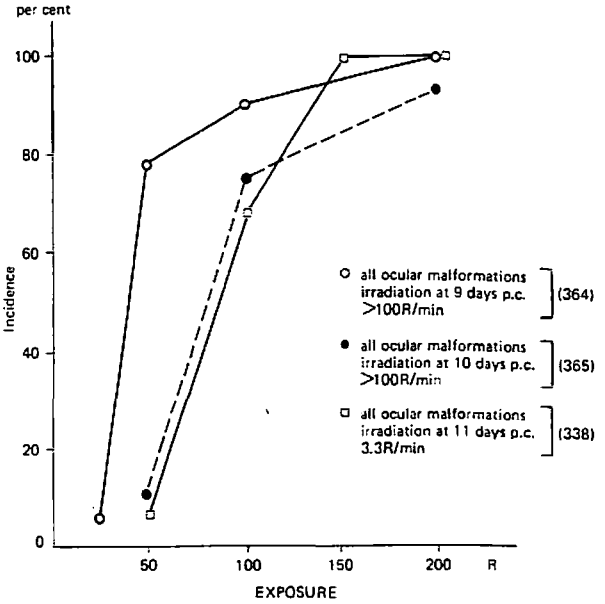

Figure XVII. Dose-effect relationships for the induction of gross ocular malformations in the rat

in the mouse is that of Christensen (65, 66). He performed extensive investigations on the C3H mouse between 7 and 14 days p.c. at exposures of 55 to 255 R. Animals were examined before birth and gross, stereomicroscopical and histological changes were recorded accurately. The amount of data provided is very large in respect to many effects, but, limiting the present comments to eye malformations, the maximum response was found at 8-11 days p.c. with 222 R. By far the greatest number of malformations were observed after this dose and only a few after 55 and 166 R. Some well defined effects (coloboma, microphthalmia and mild palpebral defects) were found to be stage-specific. Since the study was meant especially as a histopathological one, with a particular view to stage-specificity, the data on dose-effect relationships are not as informative as they might have been otherwise. However the data showed that severe microscopic changes were present in eyes that would be classified as normal on gross or stereomicroscopical examination. Other histological effects in various mammalian species were also reported by Rugh and Skaredoff (284), Lucas (174) and Hicks *et al.* (122), as well as in many of the previously cited papers on malformations of the eye.

133. In the rat, the eye has been reported as the most consistently affected of all organs. Anophthalmia, microphthalmia and other malformations are found following exposure at 9 or 10 days p.c. (362, 364, 365). Dose-effect relationships (in the range 25-200 R) have been deduced for irradiation at these times. Even the lowest exposure produced about 5 per cent ocular malformations if delivered at 9 days p.c. (fig. XVII) (364, 365). It appears that, with exposures up to 100 R, microphthalmia has the highest incidence, while for 200 R anophthalmia prevails. A 59-per-cent incidence of anophthalmia was reported by Skalko (324) in animals exposed to 270 R of ^{60}Co radiation at 11 days p.c. Strange and Murphree (338) have examined the exposure-rate dependence of eye malformations in this species (11 days p.c.), providing reasonably complete exposure-incidence curves in the range of 50-200 R at dose-rates of 1, 3.3, and 47 R/min; 3.3 R/min appeared to be the most effective exposure-rate (see also paragraph 318) and produced at 50 R a 7-per-cent incidence of animals with defective eyes (fig. XVII). These curves might be described as roughly curvilinear.

134. Microphthalmia, anophthalmia and other malformations of the eye were induced in hamsters. The incidence was 38 per cent with exposures of 100 R at 6.5 days p.c., 52 per cent with 200 R at 7.5 days p.c., and 65 per cent with 200 R at 8.5 days p.c. (111). Eye, brain and visceral malformations were seen in rabbits exposed to 130 or 250 R of x rays on the 10th day of pregnancy (353). Finally, ocular abnormalities have also been reported in dogs following exposures of 100-150 R before or after implantation (13-38 days p.c.) (245).

4. Malformations of the central nervous system

135. The gross malformations of the central nervous system (CNS) resulting from irradiation of embryos comprise exencephaly (or pseudencephaly), anencephaly, encephalocele, hydrocephaly (dysgenetic hydrocephaly) and spinal cord abnormalities (flexion, hernia, hydromyelia, myeloschisis). They are often accompanied by other malformations of the bones and structures of the head. The "cranial blisters" that some authors describe as skeletal abnormalities are in fact small brain hernias.

136. In mouse experiments with 150-200 R, the peak incidence of exencephaly is observed with irradiation at 8 to 9 days p.c. (fig. XVIII) (276, 277, 210, 72), while the sensitive period for hydrocephaly extends to 10 days p.c. (fig. XIX) (210, 72).

137. A detailed classification of the abnormalities of the CNS was published by Kameyama (142) and by Murakami and Kameyama (204). The mice were irradiated on day 8 p.c. and examined on day 13, and the x-ray exposures were in the range 25-150 R. Occasional

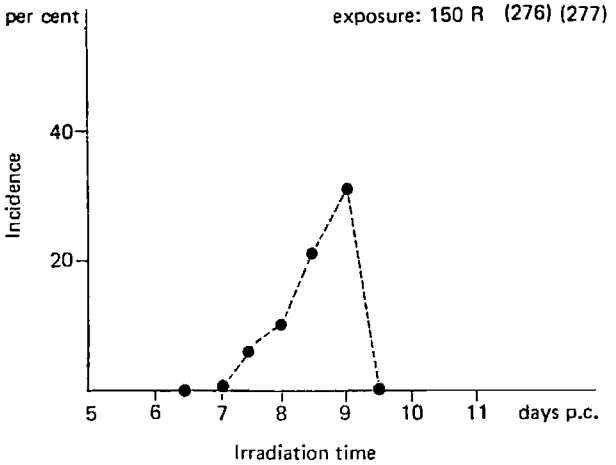

Figure XVIII. Effect of irradiation at various p.c. times on induction of exencephaly in the mouse

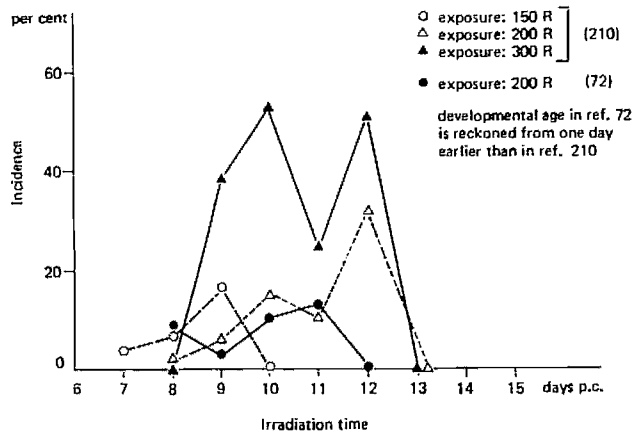

Figure XIX. Effect of irradiation at various p.c. times on induction of hydrocephaly in the mouse

malformations (exencephaly, hydrocephaly, flexion of the spinal cord) were observed at exposures as low as 25 R, the incidence increasing progressively at higher exposures. Exposure-effect data for exencephaly are reported also in two papers by Rugh and Grupp (276, 277) for the exposure range 25-200 R. Pooling together all abnormalities seen at each exposure level in the four groups of mice irradiated between 7.5 and 9 days p.c., it can be shown that the incidence is very low at exposures smaller than 100 R, while at exposures of 150 and 200 R the incidence is 17 per cent and 16 per cent, respectively. Murakami (203) and Murakami *et al.* (206) observed the incidence of exencephaly and hydrocephaly in mice of two strains exposed to 200 or 300 R at 8-13 days p.c. The observations were at 19 days p.c., and showed some difference between the strains. The same authors also described the histopathogenesis of these malformations in animals sacrificed serially with the purpose of correlating the malformations with the developmental events of the embryonic nervous system at the time of irradiation. Histopathological observations have also been reported by several authors (204, 276, 23, 72, 73, 237, 238, 239, 116, 126). Irradiating on day 7.5 p.c., Jacobsen (136) did not find cases of exencephaly with exposures of 20 and 100 R, although a few cases did appear in the control groups.

138. Wilson (362) summarized the observations on abnormalities of the CNS in rats reported by Wilson and Karr (365) and Wilson *et al.* (364, 363). The rat brain appears to be affected differently depending on time of irradiation, between 9 and 11 days p.c. On day 9 p.c., several brain malformations were produced, resulting from the fusion of the brain wall with the ectoderm. On day 10 p.c., the effects were hypoplasia and growth irregularities of various parts of the forebrain, while on day 11, eversion of the choroid plexus and other minor distortions were induced. From the few data relating dose and malformation incidence quantitatively, it would appear that exposures as low as 50 R on day 9 p.c. result in an observable incidence increase. With irradiation at older ages p.c., embryo CNS-abnormalities appear only with higher exposures. Skalko (324) reported an incidence of 81 per cent of hydrocephaly following an exposure of 270 R on day 11 p.c.

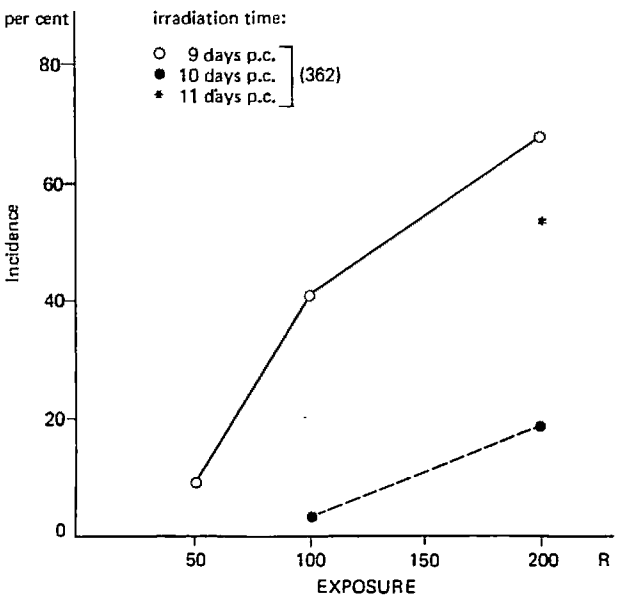

Figure XX. Dose-effect relationships for the induction of brain malformations in the rat

139. In reference 121 Hicks and D'Amato summarized their own previous work (118, 119, 122) and results from other sources. The summarized work related mainly to CNS malformations and correlates malformations with embryological stage rather than with radiation dose. Histopathological studies show that abnormalities of the microscopic architecture of the brain are seen in general at rather low doses. Riggs *et al.* (257) and Hicks and D'Amato (120) have reported results on various alterations of the nerve cell and of the cerebral cortex: cortex alterations can be induced by exposures as low as 10 to 40 R. It may be said, in conclusion, that although more observations have been carried out in rats than in mice, they are usually insufficient for dose-effect studies and their importance lies mainly in the establishment of correlations between time of irradiation and type of resulting malformation, owing to the differentiation of the relevant structures at the time of irradiation.

140. In hamsters, exencephaly was seen at exposures of 200 R on day 6.5 and 7.5 p.c. (111). In dogs, exposures of 100 to 150 R on day 13-38 p.c. caused CNS malformations, which were reported in a single class with ocular defects by Phemister *et al.* (245). Marmosets irradiated with 250 R of x rays during organogenesis developed cranioschisis (249).

5. Microcephaly

141. In the mouse, the peak of sensitivity for inducing microcephaly with 200 R is at day 10-11 p.c. (210, 206, 72); in the rat, on the other hand, it is at day 12-13 p.c. (206) (fig. XXI). Very few dose-response data are available for the mouse. Murakami *et al.* (210) report for

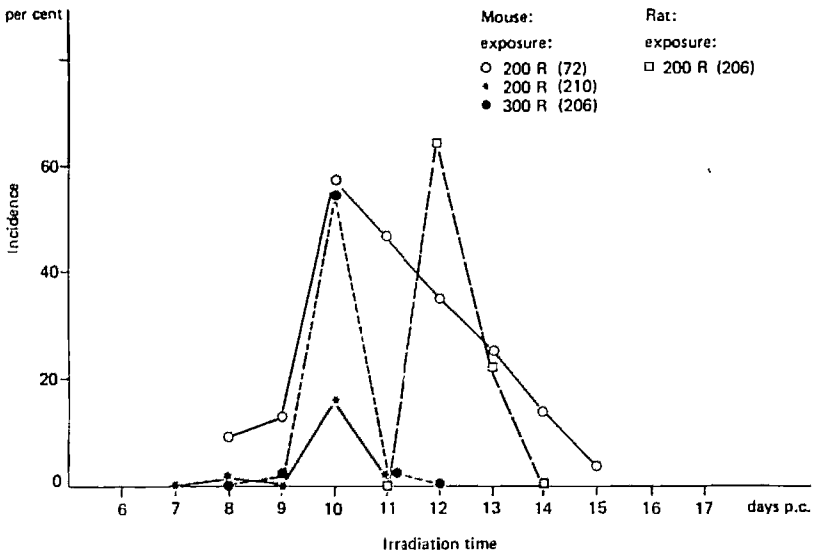

Figure XXI. Effect of irradiation at various p.c. times on the induction of microcephaly in the mouse and rat

irradiation at peak sensitivity no incidence of microcephaly with 150 R, about 15 per cent with 200 R and about 17 per cent with 300 R. In another publication (206), the incidence with 300 R is reported to be about 55 per cent, an incidence similar to Dekaban's estimate (72) of 55 per cent for exposures around 200 R. It is justified to assume that the technique of scoring the malformation may have influenced the estimates in these cases, since the head diameter is a continuous variable. It is doubtful (206) that the microcephalic condition in the mouse (which is accompanied by abnormalities in morphogenesis) could be compared to the "genuine" microcephaly seen in man. Ballardin and Metalli (13) have exposed (C57BL X C3H)F_1 mice to 50-200 R on day 9 and 16 p.c. The net weight of the brain was estimated post-natally at the age of 3 months. A statistically non-significant decrease of 1.5 per cent of the brain mass was shown following 50 R on day 9 p.c., while 100 R on day 16 p.c. resulted in a very significant decrease, amounting to 9.6 per cent in the male, and 7.5 per cent in the female, offspring.

142. The induction of malformations in the CNS of the human embryo (particularly microcephaly with associated mental retardation) has been the object of several reviews (95, 96, 97, 121, 213, 294, 370). These reviews considered the earlier work, which consisted mainly of isolated observations, mostly of a qualitative nature. More recently, Dekaban in his 1968 review (71) and the Committee in its 1969 report have analyzed in detail the whole subject of CNS abnormalities in man (345).

143. Dekaban (71), studying more than 200 literature cases of therapeutic pelvic irradiation of pregnant women, selected 26 cases as being sufficiently informative and estimated the probable doses received by the embryos. Having established that in no case was the exposure of the embryo lower than 250 R, Dekaban attempted to correlate the type of damage observed with the gestational age at irradiation (from about 2 to about 25 weeks). The most frequently observed abnormalities in this series were these: small size at birth and stunted post-natal growth; microcephaly, often associated with mental retardation; microphthalmia; pigmentary degeneration of the retina; genital and skeletal malformations; and cataract. Dekaban was able to conclude that incidence in man followed patterns similar to those established in experimental animals, and that the presence and type of abnormalities depended upon the gestational age at irradiation. Irradiation during the pre-implantation stages or at times not exceeding 4 weeks of gestation can lead to high lethality, but the children that survive are likely to develop normally. Between about 4 and 11 weeks many organs and systems appear to be sensitive to irradiation, as shown by the variety of malformations produced. The brain appears to be one of the organs most consistently affected, particularly with production of microcephaly. At 12-16 weeks, stunted growth and microcephaly is still induced, but gross abnormalities of other organs are not seen. Finally, microcephaly, mental retardation and stunted growth are induced, in a mild form, with irradiation at 16-19 weeks; irradiation in the period 20-25 weeks causes no obvious abnormalities but only minor defects of haemopoiesis and of the skin. It should be pointed out that large doses can be lethal to the embryo at any gestational age.

144. In the review carried out by the Committee in its 1969 report (345), a rough estimation is given of the

possible incidence of mental retardation associated with microcephaly. The value is about 10^{-3} rad^{-1}, derived from observations at high acute doses (in excess of 50 rad). The report stressed the uncertainties involved in extrapolating these findings to smaller doses, due to the absence of suitable human data and to insufficient knowledge of the mechanisms responsible for the production of malformations.

145. A recent report by Miller and Blot (196) considered the dose-effect relationships for microcephaly on the basis of the Hiroshima and Nagasaki experience and updated dose estimates. A progressive increase of the incidence with dose was observed in children exposed *in utero* before the 18th week of gestation and examined at 10 years of age (388 children in Hiroshima and 99 in Nagasaki). The Hiroshima data, which were more abundant, revealed a higher frequency and severity of the condition when exposure occurred within 3 to 17 weeks of gestation, but some effect was present with irradiation at older stages. While the lowest effective total kerma in Hiroshima was between 10 and 19 rad, in Nagasaki no effect was found up to a total kerma of 150 rad. It should also be pointed out that in Hiroshima the neutron kerma amounted to one fifth of the total kerma, and therefore the fraction of the absorbed dose due to neutrons would have been substantially lower than that due to gamma rays. In Nagasaki, the contribution of neutrons to the absorbed dose was much lower still. These facts suggest that the efficiency of neutrons for induction of microcephaly must be high.

146. Mental retardation, which is a consequence of substantial brain cell depletion at high doses, was similarly examined as a function of dose by Blot and Miller (24) in a fixed sample cohort of 1613 children exposed within 2 km of the hypocentre in the two cities. When they reached 19 years of age, they were tested for mental deficiency. The controls were children not exposed or exposed at distances of 3-5 km. Gestational ages between 6 and 15 weeks appeared to be most sensitive. Expressing the increase of mental retardation incidence as the ratio of the incidence observed in the sample to that observed in the two control proportions, the increase in Hiroshima in the total kerma range 200-299 rad was more than 100, while in Nagasaki it was only 12 in the same total kerma range and 53 for values of kerma higher than 300 rad. The difference between the two cities may have been due to the neutron component of the irradiation, which was almost absent in Nagasaki, or perhaps to other environmental differences between the two cities at the time of the explosions.

6. Malformations of the skeleton

147. In contrast with the paucity of quantitative data for many types of malformations, exhaustive descriptions of radiation-induced malformations of the skeleton of the mouse at several dose levels have been reported by Russell (296, 297) and Jacobsen (136). A less complete set of data on these types of malformations was reported by Novel (229).

148. The skeletal system is particularly suited for teratological experiments since bone embryonic primordia are sensitive to radiation and the defects are relatively easy to diagnose and quantify by staining procedures (136). Russell (296) has also pointed out that data on skeletal abnormalities could be used as an indicator of malformations of other important systems, such as the central nervous system.

149. It should be realized that the phenotypical variability of the skeletal system gives rise to quantitatively defined defects, even in normal unirradiated animals. This variability depends on a number of genetic and exogenous factors, to which radiation is added as a supplementary teratogenic agent. Malformations of the skeleton are usually classified according to *(a)* the anatomical region affection (skull, vertebral column, thorax etc.), *(b)* the topographic location (cervical, thoracic etc.), *(c)* the numbers of ossification centres and *(d)* their form (fusion, splitting, constrictions etc.). Complex systems of classification can be derived from the interplay of all these variables and exhaustive lists of possible defects are given in the papers cited above.

150. From the work of Russell (296) it appears that the developmental period of the mouse where skeletal abnormalities are induced extends from 6.5 to 13.5 days p.c. Each abnormality has its own period of maximum sensitivity. At the lowest effective dose, the period for each type of lesion lasts for only 1 or 2 days; for most malformations increasing the dose usually results in longer induction periods. Often biphasic or unusually long periods of maximum sensitivity are observed, probably indicating that developing organ primordia have a multitude of targets and that the same type of malformation may occasionally be produced by different pathogenetic mechanisms.

151. The results of Russell in 1956 (296) covered the exposure interval of 200 to 400 R and the whole of the period of major organogenesis in the mouse. From these results it was quite clear that the shape of the dose-response curves obtained at the period of peak sensitivity was different for each malformation.

152. Subsequent work (297) with BALB/C embryos irradiated on day 7.5 and on day 9.5 p.c., extended the exposure range downwards (25-100 R). At these exposures it was possible to differentiate better between those malformations which had a very high incidence at high doses and to search for the presence of thresholds. Concerning the day-7.5 series, the incidence of all malformations (of any degree) increased as a function of exposure, as shown in figure XXII. The author pointed out the difficulties in the interpretation of these curves due to the heterogeneity and the different degree of expression of the malformations. Even at 25 R, there was an increment in the frequency of abnormalities normally found, and furthermore, types of abnormalities normally not present in the controls were also observed. The significance of the incidence increment was assessed on the basis of two extreme and opposite assumptions: *(a)* that the malformations were completely uncorrelated with each other (i.e., by comparing the number of malformations obtained *versus* those expected in the

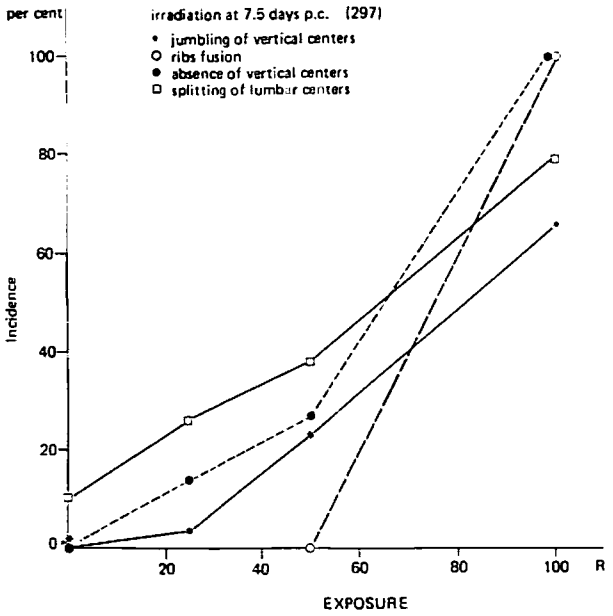

Figure XXII. Dose-effect relationships for incidence of skeletal malformations in the mouse

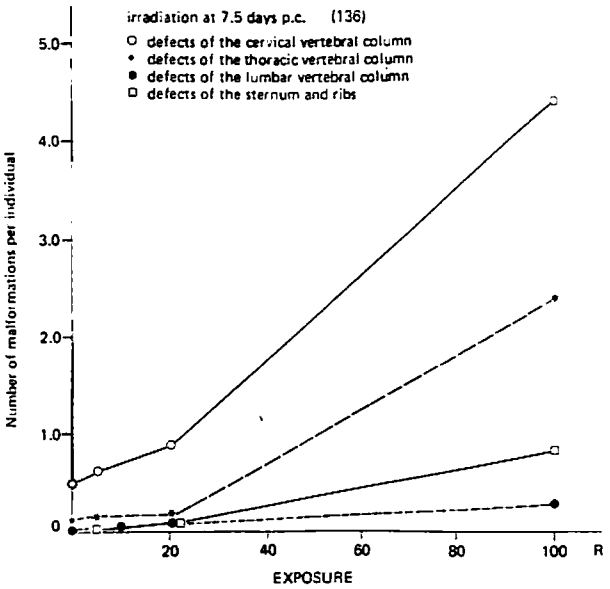

Figure XXIII. Dose-effect relationships for incidence of skeletal malformations in the mouse

control and in the 25 R group) and *(b)* that the malformations were completely correlated (i.e., by comparing the number of mice with one or more malformations in the two groups). The increment was shown to be significant under both assumptions, in spite of the small sample size, comprising 39 control and 30 irradiated animals. Similar considerations applied to four quantitative skeletal characters with irradiation at 8.5 days p.c.

153. Malformations of the vertebral column, with special regard to induction time, were studied by Murakami and Kameyama (205) on mice of the strains CF1 and ddN given a single 200-R exposure of x rays at 8-13 days of pregnancy. These authors reported a head-to-tail shift in the occurrence of malformations with advanced pregnancy stage (see also (208)) and the occurrence of two peaks of sensitivity in the vertebral abnormalities. The first peak was attributed to a disturbance of the early somitization, the second to a direct effect on the vertebral primordium itself. Interstrain differences in malformation frequency were noted, probably related to the rate of differentiation of the relevant structures. Other differences regarded the incidence of supernumerary or ectopic ribs, which were attributed to the genetic constitution.

154. The problem of the dose-effect relationship for skeletal malformations was the object of a thorough study by Jacobsen (136), who extended the range down to 5 R, thus covering the interval 5-100 R. After a detailed analysis of the abnormalities observed in different bones, where 5 and 20 R produced several defects, Jacobsen plotted, as a function of dose, the combined number of all malformations found in a given skeletal region (fig. XXIII). In all regions, an increase of exposure was associated with a rise of incidence. The lowest exposure tested, 5 R, produced an increase which was statistically significant at the 5-per-cent confidence level of the malformation incidence observed in all skeletal regions, when such increase was expressed by comparison with the appropriate controls. The experiment therefore did not establish the existence of a threshold, which might imply that exposures of less than 5 R could conceivably entail a risk of teratogenic damage (see also paragraphs 293 and 294).

155. Irradiation of the rabbit embryo (250 R on day 8-10 p.c.) has been reported to induce damage to the axial skeletal system (69). Dose-effect data for skeletal abnormalities in lambs were reported by McFee *et al.* (188). The experiments were carried out in the exposure range 100-400 R at day 23 p.c. The same paper includes a few data on cattle exposed on day 32 p.c. to 100-300 R, and also on the pig, with an average dose of 367 rad of neutrons received at different times (15-27 days p.c.).

156. Concerning information on humans, a roentgenographic survey of a small sample of 74 children exposed *in utero* during the Nagasaki explosion was performed in 1951 and 1952 by Sutow and West (339). These children had been exposed within 2 km of the hypocentre; the skeletal findings were compared with those of 91 children exposed within a distance of 4-5 km. There was no significant difference between the two groups. Furthermore, the occurrence of those skeletal anomalies which are found in animal experiments could not be documented in this human group.

7. Malformations of the extremities

157. The peak of sensitivity for the induction of malformations of the extremities by exposures in the interval 150-300 R, is found at 12 days p.c. in the mouse; the peak spreads over more days at higher exposures (fig. XXIV) (210). Sensitivity for digital malformations at 200 R is a maximum at 12 days of pregnancy (227), the morning after copulation being considered as day 1 of pregnancy. Considering the same morning as day 0, a careful series of experiments (343) has established the sensitivity peak to be at about 273 hours after mating, that is early on day 11

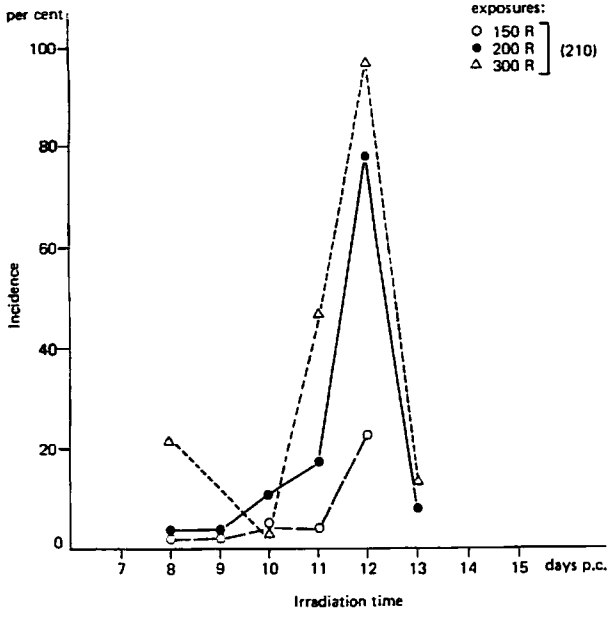

Figure XXIV. Incidence of malformations of the extremities in the mouse after irridiation at various times p.c.

(fig. XXV). The critical period for inducing abnormal development of the forelimb appears earlier and is longer than the corresponding period for the hind limb (294).

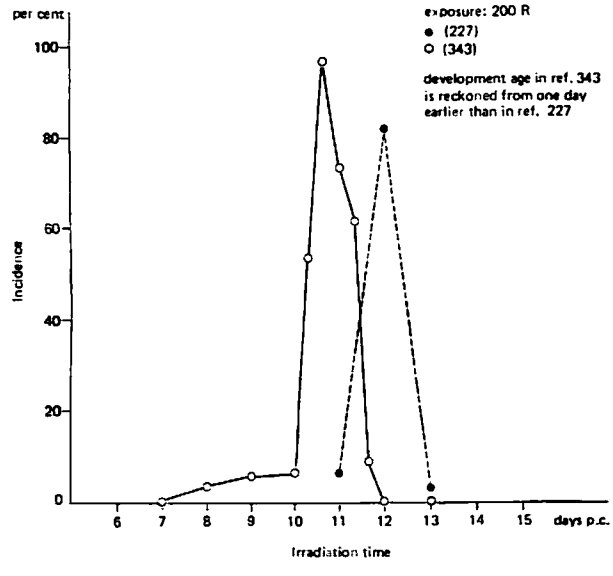

Figure XXV. Incidence of digital malformations in the mouse after irradiation at various times p.c.

158. Erickson and Murphree (82) described abnormal limb development in cattle, sheep and swine exposed *in utero* at various gestational ages to 200 R of ^{60}Co gamma rays. The period of maximum sensitivity was approximately day 32 p.c. for the cattle and day 23 p.c. for the sheep, in good correlation with the rudder stage of limb development. As in other species, the critical period for forelimb malformations occurred 0.5-1 day earlier than that for pelvic limb malformations.

159. Tail malformations are induced in the mouse by irradiation at a time between day 9 and 13 p.c. Following an exposure of 150 R, the peak sensitivity occurs on day 9 p.c. (210). When the exposure is increased to 200 R, the peak is on day 9-11 (210, 72), and with 300 R it extends to day 13 (210) (fig. XXVI).

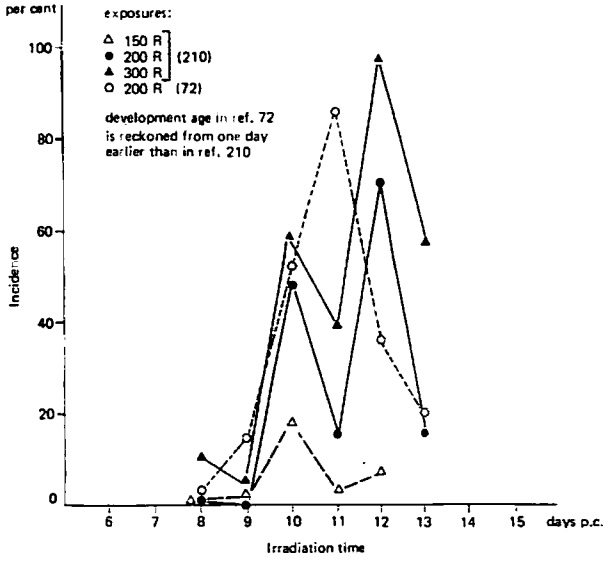

Figure XXVI. Incidence of tail abnormalities in the mouse after irradiation at various times p.c.

With larger exposures, therefore, the sensitivity peak becomes wider. Tail length is a parameter of interest because it can be associated with the number of vertebrae and may be scored by external inspection. Russell (294) reported results of experiments with exposures of 200-400 R at 4.5-13.5 days p.c., showing that the relative tail length is altered by irradiation on day 9-13 of pregnancy. Abnormal tail shape was in general correlated with tail-length effects. Jacobsen (136) found that, exposing on day 7.5 p.c. to levels in the range 5-100 R, the modal distribution of tail length shifted towards lower values with increasing exposure.

160. Warkany and Schraffenberger (357) described various types of skeletal abnormalities in the rat, among which malformations of the extremities were dominant. Depending on the radiation dose, these abnormalities were induced from 9-16 days p.c. On the whole, malformations of the long bones of the extremities occurred with irradiation at earlier stages, while toe and finger malformations were more common for later exposures. Similar observations were also reported by Wilson (362). Fused digits in forelimbs and hind limbs were observed in hamsters with an exposure to 200 R at 9.5 and 10.5 days p.c. (111) and in rabbits following 400 R on day 12-14 p.c. (59). Digital malformations appeared also in dogs following 150-200 R in the period 25-28 days p.c. (245).

161. Malformations of the tail, the extremities and various other abnormalities were examined as a function of exposure (150-300 R, 170-kV x rays) by Murakami *et al.* (210), irradiating mice at 8-13 days p.c. Dose-effect relationships of the threshold type were obtained for tail malformations; the highest yield was induced on day 12 p.c. With irradiation at this time, the induction increase in the range 150-200 R was about 1.3 10^{-2} R^{-1} (fig. XXVII), similar to that observed by Dagg (68).

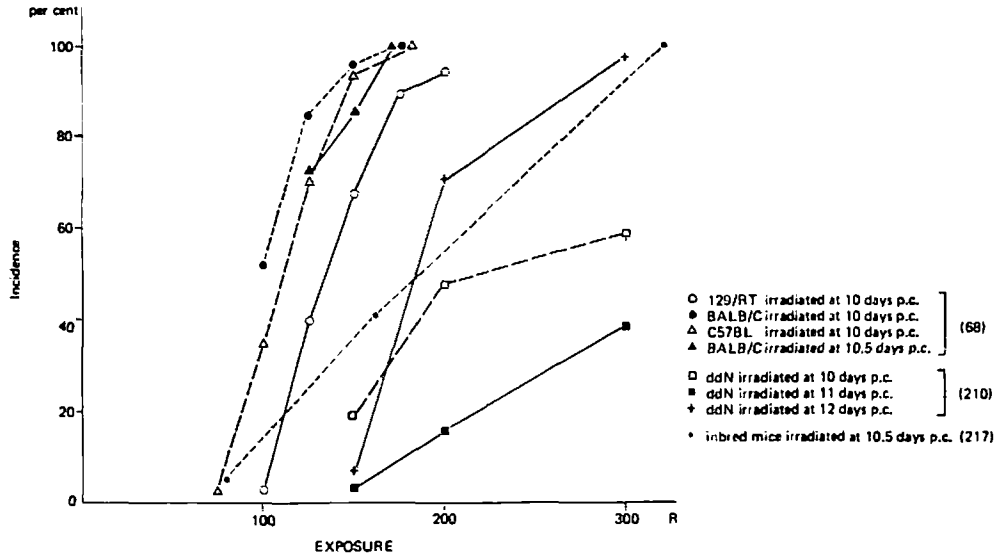

Figure XXVII. Dose-effect relationships for induction of digital malformations in the mouse

162. Malformations of the extremities were seen mainly in mice irradiated 11 and 12 days p.c., particularly following exposures of 200 or 300 R. A very detailed study of digital malformations in mice of the ddN and CF1 strains was performed by Nogami (227). Variables examined were the pregnancy time (8-13 days p.c. at a fixed exposure of 200 R), the exposure (150-300 R at a fixed time of 12 days p.c.) and the genotype. The incidence of individuals with malformations was proportional to exposure in the interval 150-300 R, at the rate of about $5\ 10^{-3}\ R^{-1}$ but below 150 R no data were obtained, which did not allow the assessment of a possible threshold (fig. XXVIII). Concerning the

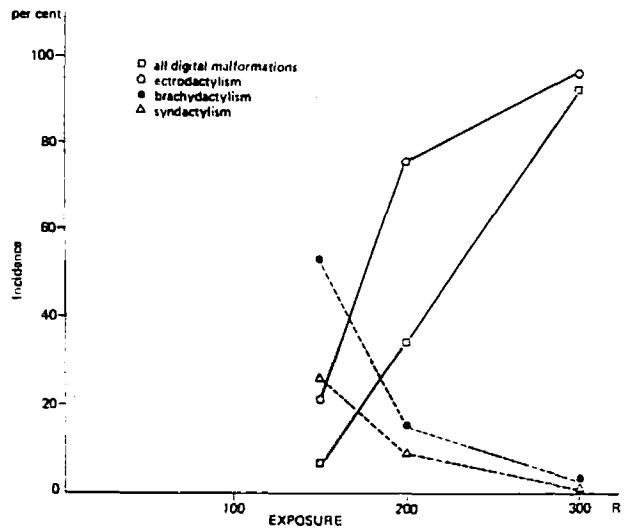

Figure XXVIII. Dose-effect relationships for various forms of digital malformations in the mouse (227)

The incidence of all digital malformations (□) was calculated over total living foetuses whereas the incidence of ectrodactylism (o), brachydactylism (•) and syndactylism (Δ) were calculated over foetuses with digital malformations only.

different types of malformations, ectrodactylism incidence clearly increased with dose following a threshold-type relationship, while brachy- and syn-dactylism displayed a decreasing frequency with dose (227).

163. Dagg (68) studied the induction of tail malformations and hyperphalangia of hind feet in three inbred strains and some reciprocal crosses. The defects were scored at 18 days p.c. on live foetuses that had been irradiated at 10, 10.5 or 11 days p.c. with exposures of 250-kV x rays in the range 75-200 R. Disregarding some differences between strains due to the variability in developmental age, the exposure-response curves for tail malformation were in general of the threshold type; the response increased linearly with exposures from about 75 to about 150 R (fig. XXVII). In this range the induction frequency can be calculated to be approximately $1.2\ 10^{-2}\ R^{-1}$, a value roughly applicable to the three strains used. The dose-effect relationship for malformations of the hind foot was more complicated. However, if the percentage of live litters with one or more hyperphalangous feet is plotted against exposure, the plot is consistent with a non-threshold linear relationship with a slope of about $5\ 10^{-3}\ R^{-1}$. Other plotting criteria could suggest curvilinear relationships. Mechanisms to explain the linear relationship have been suggested (68).

164. Nash (217) also observed a threshold-type dose-effect relationship for tail malformations in inbred mice following irradiation at 10.5 days p.c. with exposures in the range 80-320 R (fig. XXVII). Differences with respect to hybrid mice were also noted. No abnormalities of the feet were observed by external examination at exposures below 80 R, but at higher exposures overgrowth or reduction of the feet were clearly manifest. A different result was found by Jacobsen (136), who analyzed the degree of ossification of the paws, using alizarin-stained skeletons, and found effects at exposures as low as 5 R. He believed that the number of stainable centres of ossification in the extremities might be a suitable indicator, in sufficiently large samples, for studying the effect of small radiation doses. Limb malformations were reported to occur in marmosets given 250 R of x irradiation at 25 days of pregnancy, during the period of major organogenesis (249).

8. Other malformations

165. Malformations of the heart and great vessels of the rat were the subject of some early reports (295, 362). More recently, they were studied by Okamoto *et al.*

(233). The incidence of these malformations reached 85 per cent after a dose of 130 rad of 14.1-MeV neutrons, on day 8 p.c. Histopathological, cellular and kinetic changes of the relevant structures were described in other publications (199). Cardiac malformations were induced in dogs by exposures to 100-150 R at 21-22 days p.c. (245).

166. Malformations of the anus (small or imperforate) and of the urogenital system (hydronephrosis, convoluted or distorted ureter) were observed by Russell (294) in a small percentage of mice exposed to 200-400 R at 9.5 and 10.5 days p.c. In rats, Wilson (362) reported the occurrence of kidney agenesis after exposure to 100 or 200 R on day 9 p.c., and horseshoe kidney after irradiating on day 10 p.c. Both types of malformations were induced also on day 11 p.c. A 77-per-cent incidence followed an exposure of 200 R. Urogenital malformations (unilateral or bilateral kidney agenesis) with a peak sensitivity just before the appearance of the metanephric kidneys were reported in the dog (245).

167. Thoracic and ventral hernia in mice were described by several authors. Murakami *et al.* (209) obtained an incidence of about 5 per cent with 200 R on day 9 p.c. In a subsequent experiment (210) a maximum incidence of 44 per cent was obtained with 300 R on day 8 p.c. Jacobsen (136) described an incidence of about 2 per cent following an exposure of 100 R at 7.5 days p.c. In hamsters, Harvey and Chang (111) reported a 12-per-cent incidence of hernia and spina bifida following 200 R on day 7.5 p.c.

9. All malformations

168. In spite of the great interest for risk assessments of the overall induction of malformations, very few authors have given figures for the total percentage of malformed conceptuses in their experiments. Taking all malformations together, the peak sensitivity to induction occurs on day 9 p.c. in the rat embryo (325). In the dog the time immediately following implantation (corresponding to the primitive streak stage and early organogenesis) appears to be the most sensitive for the production of malformations (245). Concerning dose-effect relationships (fig. XXIX), Murakami and

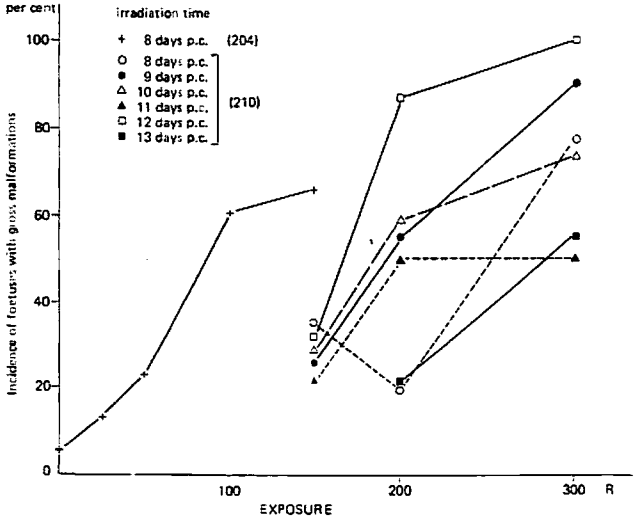

Figure XXIX. Dose-effect relationships for induction of gross malformations in the mouse

Kameyama (204) reported the incidence of grossly abnormal mouse embryos (living and dead on day 13 p.c.) following irradiation with various exposures (25-150 R) on day 8 of pregnancy. From this study the induction can be calculated to be about $5\ 10^{-3}\ R^{-1}$ without any apparent threshold. In a later report (210), Murakami gave the incidence of abnormal foetuses reaching 19 days p.c. for an exposure range of 150-300 R, with irradiation occurring in the period 8-13 days p.c. The induction in this range (discarding dead foetuses) appears to vary between $1.9\ 10^{-3}\ R^{-1}$ and $4.5\ 10^{-3}\ R^{-1}$, depending on age at irradiation.

169. Recent human studies relevant to all types of malformations deserve attention. Kinlen and Acheson (148) published a retrospective study of the irradiation history of 379 women hospitalized for spontaneous abortions and of 605 women who delivered malformed children. Their radiation history was compared with that of a control group. No significant difference was found. The sample size was clearly too small to determine the effects of doses at the diagnostic level. The authors concluded that, under the conditions of observation, there was no evidence that irradiation could play an important part in the etiology of abortions requiring hospitalization or in the induction of congenital malformations. Hagstrom *et al.* (103) made observations in about 700 women who received ^{59}Fe during pregnancy for metabolic studies, resulting in an estimated dose to the foetus of 5-15 rad and also in about 700 controls. Their findings were essentially negative for the induction of malformations in the offspring.

170. More recently, Diamond *et al.* (74) reported on a prospective study of about 20 000 white and black children who were exposed *in utero* over the period 1947-1959 in the course of abdominal irradiations of their mothers, mainly for pelvimetry, placentograms or simple radiography of the abdomen. The children were traced in 1961-1967 to determine their mortality and the cause of death according to the death certificates. The group was compared with a non-irradiated cohort of approximately 36 000 children matched by hospital and time of birth, sex, parity and race. A sample of about 152 000 person-years in the exposed group and 28 000 person-years in the control were thus collected and examined. The study was mainly concerned with leukaemogenesis, but data on malformations were also available and have been summarized by Lilienfeld (172). No statistically significant difference in the mortality from congenital malformations was seen between exposed and control children. Concerning the sensitivity of different gestation periods, there was no difference in the malformation frequency between two groups defined by the trimester at which they were irradiated. Within each trimester, the irradiated children had a slightly higher incidence of abnormalities than the controls, in both sexes and races. In white children, the mortality of the exposed group was almost twice that of controls (183 per 10^5 person-years against 98 per 10^5). In black children, on the contrary, the same mortality was observed in exposed and control groups (212 per 10^5 person-years and 229 per 10^5 person-years, respectively). The difference could not be attributed to congenital malformations.

171. In a prospective study (235), the morbidity and mortality of about 1000 white children exposed *in utero* (average foetal dose about 700 mrad) during routine diagnostic pelvimetry were followed for 15 years, compared to an adequate control group. The data (which had been reported previously by Griem *et al.* (99, 100)) were most carefully reanalysed and compared with previous studies, but were insufficient to associate radiation conclusively with any effect. It should be pointed out that only 3 children were exposed during the first 50 days of gestation and only 24 during the first trimester, while 87 per cent were irradiated during the second half of pregnancy. With this sample size, radiation effects could be detected only if they were induced in excess of 1 per cent, which is at least an order of magnitude higher than might be expected for the most frequently radiation-induced abnormality in man, namely microcephaly (see paragraph 144). In the opinion of the authors, the study is therefore of value in excluding the possibility that doses of the order of 1 rad or less could produce effects exceeding 10 times the incidence observed at high doses.

172. Oppenheim *et al.* (236) reported a comparison between studies in which the exposure to radiation was the result of medical indications (74) and studies involving non-selective exposure to radiation (100, 145, 235). Significant discrepancies were found, suggesting that the data reported in the first instance could be attributable to the bias introduced by the medical conditions requiring the exposure, rather than to the exposure itself. These new data therefore cast some doubt on the validity of the studies of diagnostic exposures and suggest that such exposures may actually be less harmful than previously assumed (236).

173. Neumeister (222) reported most recently on a series of 37 cases of embryonic exposure between week 1 and week 10 p.c. up to a maximum of 20 rad. These cases had been referred to a specialized unit of clinical radiobiology for expert opinions concerning a possible abortion. Of the 35 cases that were conducted to term, only 15 children were examined at 1-3 years of age. In all these cases the pregnancy had proceeded normally, the weight and body size and the subsequent development of the children were found to be normal and no difference was noted between the exposed individuals and their brothers or sisters. In one case where the exposure had been less than 1 R at 4-6 weeks p.c. a talipes calcaneus was observed, but a causal relationship with irradiation was excluded. A second case (exposure 3-5 R at 2 weeks) showed talipes calcaneus and a lumbar myelomeningocele; a relationship with the previous exposure was estimated to be improbable. In spite of the accuracy in the estimates of exposure time and of dose calculations, the size of this series is clearly too small to be of any general significance.

174. In connection with the possible effects of very low doses of radiation, some correlations have been attempted between the overall incidence of malformations in man and the level of natural radioactivity. In what they regarded as a feasibility study, Kratchman and Grahn (158) tabulated the incidence of deaths from congenital malformations for the years 1952-1956 in various areas of the United States of America and grouped these data by geologic province. They were able to show a higher mortality from malformations in the geologic provinces containing major uranium ore deposits, uraniferous waters or high helium concentrations. It should be pointed out that no measurements of radiation levels were made and also that only crude statistical indexes were used, without corrections for birth rate, maternal age, death rate or other factors that could influence the observed correlation. The data, however, were considered by the authors to be sufficiently provocative to justify further investigations.

175. In a highly speculative paper Wesley (361), took a different approach: he analysed the fraction of malformed births over the earth as a function of geomagnetic latitude, which is associated with different doses from cosmic rays. The relation between the world-wide incidence of congenital malformations obtained from vital statistics and the geomagnetic latitude appeared to be highly significant. The lines of equal incidence of malformations were said to match the corresponding lines of the magnetic field of the earth. According to the author, all congenital malformations could be attributed to "background" radiation (presumably its extraterrestrial component). It should, however, be pointed out that both the background radiation data and the epidemiological data on which much of this paper rests have been seriously questioned (46, 330).

D. OTHER EFFECTS

176. **Fertility and fecundity.** Male CF1 mice were exposed to 25 or 100 R in the period 0.5-18.5 days p.c. and tested for reproductive potential at ages ranging from 2 to 8 months. With the exception of a reduction of the reproductive quotient in animals exposed to 100 R at 10.5-12.5 days p.c., no significant effect on fertility was documented. In the opinion of the authors, the small reduction of the reproductive quotient could reflect a general disability of the animals, rather than a reduction of their true reproductive potential (288).

177. Concerning effects in the female, some rather incomplete data ae available for mice and rats. Female mice were exposed during the first and the second half of the organogenesis to 20-80 R per day for 5 consecutive days. Their reproductive capacity was then tested in a successive generation. Irradiation on day 11-15 p.c. was shown to have the greatest effect and the groups exposed to 60 and 80 R per day were unable to reproduce further. Animals exposed to 40 R per day produced litters with very high mortality, and the number of litters produced depended both on exposure and on gestational age at irradiation. The frequency of litters was particularly small among animals irradiated in the embryonic stage. The average litter size, on the contrary, was not greatly influenced by irradiation, the differences in the reproductive capacity being mainly reflected by litter frequency rather than by litter size (166). Rat females exposed *in utero* to 110 R on day 15 p.c., to 150 R on day 18 or 20 p.c., or to 220 R on day 17-20 p.c. were subsequently mated to normal males. These irradiations had no effect on the incidence of infertility and on the number of offspring produced.

The only effect consisted in a significant (20 per cent) reduction of the ovulation rate, which was dose-dependent (212).

178. Cataract formation has been reported as a result of exposing mice to about 100 R during the embryonic stages (270, 292). The induction of tumours following irradiation *in utero* is discussed in Annex I.

179. A significant decrease of the *in vivo* and *in vitro* incorporation of labelled aminoacids into proteins, 24 hours after irradiation, has been shown in embryo rats as a result of a dose of 180 rad on day 13 p.c. (313). Enzyme changes appearing post-natally in the brain and the liver of rats irradiated *in utero* (25 or 50 R on day 14 p.c.) have also been described (214, 215, 216). Concerning haemopoiesis, an arrest of cell division accompanied by alterations of the haemoglobin synthesis in the embryonic erythroid cells has been shown to occur in the mouse after a single x-ray dose of 120 rad received on day 10 p.c. (85).

180. Ultrastructural effects induced by 50 R in the liver cells of the rat embryo on day 13 p.c. and consisting essentially in changes of the aggregation of polysomes and in a delay in the appearance of the smooth endoplasmic reticulum provide some insight into the chain of molecular, biochemical and structural events taking place after pre-natal irradiation (62). Some information concerning the effects of radiation on the regenerative capacity of the muscle are also available. The disorders observed were more pronounced in animals irradiated during the second half of pregnancy, when histogenesis of the muscle occurs (163).

IV. THE FOETAL PERIOD

A. LETHAL EFFECTS

1. Mouse

181. The foetal period in the mouse begins approximately at 13 days p.c. It should be pointed out that many of the experiments on the induction of mortality during the major organogenesis period reviewed in paragraphs 84-108 covered some of the later stages as well. As the foetal development proceeds, the dose necessary to kill animals before or after birth increases gradually, particularly the pre-natal LD_{50}. The percentage of abnormal animals with a given dose, on the other hand, tends to decrease with foetal age.

182. Rugh and Wohlfromm (286) established that the pre-natal LD_{50} for irradiations at day 14-17 p.c. is higher than 700 rad (see table 4), with a clear tendency to increase with foetal age. Their experiments show that killing the foetus *in utero* requires very high doses, most of the lethality at lower doses being seen at birth or just after birth. Irradiation of the foetus results in fewer macroscopic anomalies than irradiation of the embryo, being instead consistently associated with stunting. These data are similar to the results of Dekaban (72), who exposed foetal mice to 200 R and scored the percentage of surviving and apparently normal animals. This indicator was shown to rise from 38 per cent for irradiation on day 13 p.c. to around 100 per cent for irradiations on days 17 and 18 p.c. The mean litter size, serverely affected by the exposures of the same magnitude during the embryonic period, gradually increased to normal for irradiations during the foetal stage. Experiments with fractionated (152, 155) or chronic irradiation (154) also show clearly that less lethality is induced during the foetal development than in earlier stages.

183. The study of post-natal lethality induced by irradiation in the foetal stage is a necessary complement to the experiments on *in utero* mortality. Rugh and Wohlfromm (289) extended their previously reported observations (286) to the first 30 days of life. They showed that a gradual increase of the post-natal $LD_{50/30}$ takes place with increasing post-conception age at irradiation from about 250 R on day 13 p.c. to about 600 R on day 18 p.c. The second day after birth showed the highest death rate. From these data it can be concluded that the late foetus is at least as radioresistant as the mature animal. Although limited to only 2 days in the foetal stage (14.5 and 17.5 days p.c.), the data of Nash (217) are also useful to compare the resulting pre- and post-natal viability with that observed with irradiation at earlier stages. They show a decline of sensitivity with increasing foetal age for induction of pre-natal and post-natal lethality, together with a slightly higher resistance of hybrid, as compared to inbred, genotypes. No differences of sex could be shown. Similarly, the data of Konermann *et al.* (155) on fractionated exposures at 40-80 R per day during the main developmental phases show that post-natal survival is only slightly affected. This observation is particularly striking when compared with the effect of the same exposures during organogenesis. Again, the first week after birth is the time when most deaths are observed.

184. Long-term survival was studied by Upton *et al.* (347), who reported that exposure to 300 R at 14.5 days p.c. produced much more life-span shortening in males than in females. Minimal reductions of longevity after exposure at later stages of gestation were reported. Nash and Gowen (219) also emphasized the effect of sex in the survival as adults of mice irradiated during the foetal stage.

185. Rugh and Wolff (293) claimed that an exposure of 10 R during the foetal stage increased the survival of mice receiving a mid-lethal dose at an age of 4 months. The age dependence of this beneficial effect is however uncertain, and higher exposures (25-300 R) to foetuses of any age are detrimental to survival after test doses. Christensen and Jackson (64) exposed mice 14.5 days p.c. to 150 R and subsequently determined their $LD_{50/30}$ at the age of 8 weeks. The data suggested that between 30 per cent and 53 per cent of the foetal exposure had been repaired by that time. The authors also concluded that the foetal stage was considerably more sensitive than the adult in terms of irreparable radiation damage, probably of the haemopoietic system. These results should be compared with the data of Sikov *et al.* (322) and others in the rat (see paragraphs 189 to 191).

2. Rat

186. In the rat the foetal period begins approximately 16 days after conception. The data in this species are far less complete and often limited to a few ages in the foetal period (see table 4). They are, however, self-consistent and in agreement with the results obtained in the mouse.

187. Murphree and Pace (212) irradiated with a few selected exposures (110, 150, 220 R) at ages from 13 to 20 days p.c. Their data show an increased resistance to post-natal lethality as a function of age. The majority of post-natal deaths were observed, as in mice, within the first week. Reincke *et al.* (253, 254) determined carefully the $LD_{50/30}$ of rats irradiated 5 days or 1 day before birth, confirming the increase of radioresistance of the foetus with age, and the absence of any sex effect. Sikov *et al.* (322) examined the effect of 50 or 185 R on day 15 p.c., showing that the incidence of still birth and neo-natal mortality was larger with the highest exposure, and that most live-born animals died within the first week. The post-natal mortality of the rat foetus was also studied by Ader and Deitchman (1), who used exposures of 200 R on day 16 p.c. It should be pointed out that in spite of similar values of $LD_{50/30}$ for the adults in both species, the $LD_{50/30}$ for the foetal rat is between 200 and 300 R and therefore consistently lower than that for the foetal mouse, which appears to reach 600 R during the late gestational ages.

188. In 1954, Russell (295) summarized the information on the mode of death of various animal species exposed during the foetal period. From the summary it may be concluded that the syndrome of haemopoietic failure is the most common cause of death at doses around the LD_{50}. More recent reports do not add further quantitative data on this subject.

189. Reincke *et al.* (254) studied long-term survival following foetal irradiation. They found that exposure to 220 R 5 days before birth resulted in 53 per cent survival after 1 month of life, and that the subsequent survival, up to about 4 months, was practically the same (48 per cent). The long-term survival of these animals was not significantly different from that of controls.

190. Sikov *et al.* (322) reported that the post-weaning mortality of female rats exposed to 185 R on day 15 p.c. was significantly higher than that of controls, while the median life span of males was not significantly affected, thus pointing again to a dependence of the long-term mortality on sex. An interesting observation in these experiments is that the $LD_{50/30}$ of an irradiation at 100 days of age decreases as a linear function of the dose of a pre-natal irradiation at all developmental ages. In the opinion of the authors, such a linear dependence would imply a general decrement of fitness as a result of pre-natal exposure.

191. According to Maisin *et al.* (180) the radiosensitivity of rats surviving an exposure of 70 R at 10 days p.c. is lower than that of non-irradiated control animals. Although a tentative interpretation was advanced, based on the larger elimination of the more sensitive animals by the first dose, no definite conclusion was drawn.

3. Human experience

192. Some studies have been made on the termination of pregnancy in women irradiated in the pelvic region because of various pathological conditions or for therapeutic abortion. These studies provide qualitative information on the mortality of irradiated human embryos or foetuses. The early observations of Murphy (213) are not very relevant for this purpose, but the data of Harriss (106) on therapeutic abortion are somewhat more significant. These data covered 138 cases of women irradiated at 6-18 weeks of pregnancy with exposures of 510 R of 200-kV x rays in the uterine fundus. The treatment caused interruption of pregnancy in 129 cases, within an average time of 4 weeks. The foetuses were grossly macerated and in one case a cyst of the brain was found. Non-specific degenerative changes in the placenta were also noted. Mayer *et al.* (187) reported that a single exposure of 360 R in the uterus is sufficient to cause abortion in the large majority of cases.

193. Autopsies of irradiated human foetuses are rare. Driscoll *et al.* (76) reported two cases where the mothers had been treated with radium for cancer of the cervix. The foetuses, measuring 15 and 21 cm, had been exposed to about 800 and 1600 R, respectively. One was examined 2 days and the other 10 days after the beginning of the irradiation. Damages to the nervous and the haemopoietic systems were observed, and the alterations of the mesenchymal cells extended to regions of the body where the estimated exposures had been of the order of 50 to 100 R. This pattern of damage is not unlike that described for other species.

194. The data on mortality of children irradiated *in utero* as a result of the Hiroshima and Nagasaki explosions are of epidemiological nature and are possibly more informative. Yamazaki *et al.* (371, 372) reported on the outcome of pregnancy of 98 women exposed in Nagasaki. Among 30 women with major signs of the radiation syndrome who were within 2 km of the hypocentre, 7 ($\sim$ 23 per cent) foetal deaths and 6 (20 per cent) neo-natal and infant deaths were observed. Of the 17 surviving children, 4 were mentally retarded. The overall morbidity and mortality was therefore about 60 per cent in this group. In another 68 mothers exposed within the same distance but with no signs of radiation syndrome, the overall mortality was 10 per cent, only slightly above the mortality of the control group (6 per cent). In the second and third trimester of gestation, the foetal, neo-natal and infant mortalities were significantly elevated among the offspring of mothers who suffered from the radiation sickness. The evaluation of these data is, however, very difficult, owing partly to the absence of proper dosimetry and partly to the possible effect of the blast and thermal radiation, as well as to the indirect effects of maternal haemorrhagia and infection.

195. Kato (145) studied the mortality at later stages of life, following for 24 years 1300 children exposed *in utero* in Hiroshima and Nagasaki. He showed a dose-related increase of mortality during the first year of life, an absence of any relationship between mortality and dose from 1 to 10 years, and again a dose-related

increase at later ages. These increases of mortality with dose were not attributable to concomitant variables, such as age of parents, birth order, socio-economic factors etc. Mortality after 10 years was not associated with any specific cause of death and, contrary to what might have been expected from the animal data, radiation mortality was only apparent among children exposed in the third trimester, possibly because of a higher rate of abortions and still births of embryos exposed earlier. Dosimetric uncertainties concerning exposure *in utero* do not allow more definite conclusions.

B. DISTURBANCES OF GROWTH

1. Mouse

196. Generalized and local growth disturbances are probably the most commonly described effects of irradiation during the foetal stages. The following review is rather arbitrarily limited to those reports paying special attention to growth defects.

197. Duplan and Izadian (78) studied pre-natally the body and liver weights of foetal mice exposed between day 14 and 18 p.c. to 200, 500 or 800 R and sacrificed 1-4 days after irradiation. The body weight was lowest for the higher exposures and for irradiation at early age p.c., the effect being more marked with long observation times. The liver weight, on the contrary, was most depressed when the interval between irradiation and sacrifice was short, suggesting that the effect was temporary.

198. In the experiments of Rugh, Duhamel *et al.* (271), mouse stunting was studied systematically with exposures of 100 R at various times from fecundation to 18 days p.c. The average weight of the animals at an age of 4 months was minimum for irradiations at 12 or 13 days p.c. (females and males, respectively). Although mature weight tended to increase with increasing foetal age at irradiation, it never reached control values in either sex. When followed to 35 months of age, the average weight of the animals was still depressed compared to controls. The dependence of this depression on gestational age at irradiation was very similar to the weight depression observed at 4 months of age (272). A "linear" decrease of body weight one day after birth with dose in the range 120-240 rad for irradiations on day 15 p.c. was reported by Hazzard and Budd (117). The body weight of the rats, averaging 6-8 g in the control new-borns, decreased to about 3-6 g with 240 rad. However, if the control weight is taken into consideration, the trend of the curve is clearly curvilinear.

199. With respect to fractionated irradiation, Konermann *et al.* (155) reported that the average post-natal weight of mice exposed to 40, 60 or 80 R per day during the foetal period was always below control in the 3 weeks after birth, with a maximum depression in the first week. The effect of the exposure rate appears to be minor. Post-natal growth measurements referring specifically to the skeleton are also available in the mouse, where stunting of several bones may be traced until sexual maturity (271).

2. Other animals

200. Sikov *et al.* (322) reported a small decrease in the birth weight of rats after exposure to 50 or 185 R on day 15 p.c. This difference persisted to an age of 80 to 100 weeks, both in male and female animals, and was more pronounced with the higher exposure. The weights of the brain, spleen, thymus and kidney were also depressed in the irradiated animals. Martin (186, 183, 184, 185) carried out a series of experiments on the response of the whole-body and organ growth in animals exposed at 18 days of gestation to 160 or 220 R of gamma radiation. Depression of the whole-body weight relative to controls was maximum at 21 days, but persisted up to 1 year of age, a time at which the weight was about 70 per cent of that of the controls. Although most organs were lighter in irradiated animals, those which were consistently different from controls (when referred to the body weight) were the brain, testes, pituitary and adrenals. The number of cells in the various organs, between 7 and 60 days, expressed as per cent of control, indicated that the kidney and liver followed in the main the body weight changes. Spleen and thymus, on the contrary, followed different patterns, reflecting presumably the sensitivity of the specific cell populations and their recovery kinetics. Other results of experiments on body weight of rats can be found in Ader and Deitchman (1). They used exposures of 200 R at 16 days p.c. and followed the body weight during 60 days of age.

201. Rugh, Duhamel *et al.* (273) followed the body weight during 23 months of life of two monkeys which had been exposed in the foetal stage to 200 and 300 R. The organ weight at the autopsy and some skeletal measurements were also reported. All the measured indicators failed to attain the normal values.

3. Human data

202. Only the general effects on human post-natal growth are reviewed in this section, the special case of microcephaly having been already considered in paragraphs 141-146. The data available regard the exposures of A-bomb survivors in Japan and, to a lesser degree, medical exposures.

203. About 1700 Japanese children exposed *in utero* to radiation from the atomic explosions were followed on an annual basis (366, 367, 368). More than 80 per cent of these children were subjected to anthropometric measurements and various other tests when they reached 17 years of age. They were subdivided into three major comparison groups: those exposed between 0 and 2 km from the hypocentre, those exposed between 2 and 5 km from it, and unirradiated controls. The group nearest to the hypocentre was further classified according to the estimated dose to the mothers (more than 25 rad and less than 25 rad (18)), and according to the presence of acute irradiation symptoms. In those exposed within 1.5 km, a reduction of mean head circumference (1 cm, or 2 per cent) was observed; additionally, the height and body weight, in both sexes and in both cities, were also reduced by 2.3 cm and 3 kg, respectively. In most cases the incidence of the effects was significant. Other indicators, such as the chest

circumference and the intercristic diameter, were also affected, although more irregularly. The analysis of induction by trimester of gestation revealed no consistent pattern.

204. In another study, 286 adolescents who had been exposed *in utero* at Nagasaki, were examined for growth and developmental defects (48). The indicators were the age at menarche, the degree of epiphyseal closure in the wrist and several other body measurements, such as head circumference, standing and sitting height, and weight and chest circumference. Numerous differences were found that were consistent with a postulated radiation effect. With regard to pregnancy stages at irradiation, no significant differences were observed in the males, but almost all measurements in the females exposed during the first trimester were significantly greater than in those exposed during the last trimesters. Head size was the single anthropometric indicator most significantly affected.

205. Another study, by Russell *et al.* (306), specifically concerns bone maturation. Here, 556 subjects exposed to the A-bomb explosions over Hiroshima and Nagasaki were examined to record the age at which epiphyseal closure of the wrist bones occurred. In both boys and girls, closure was found to take place 6-9 months later that in other Japanese children and in American children. Possible contributory factors were discussed. However, contrary to previous reports (48), no correlation was seen between the dose to the mother and the time of closure of the children exposed *in utero.*

206. Shohoji and Pasternak (312) used an elaborate Gompertz function to characterize and analyse the growth of about 900 children exposed *in utero* in Japan and to test for differences between sexes, cities, trimester of exposure and exposure groups. Differences observed between groups exposed at various post-conception times were found almost without exception to be non-significant. Differences between exposure groups were greater in males than in females, a fact pointed out earlier (368), but there was no consistent relationship between growth impairment and exposure group. These new findings provide some support for the previously reported retardation in stature observed in pre-natally exposed subjects (48, 368), but the authors believe that this support is inconclusive.

207. A comprehensive evaluation of all these studies indicates beyond doubt that reductions of body size and growth can be induced by radiation in humans. Moriyama *et al.* (200), Belsky *et al.* (20) and Blot (23) have identified the following effects on growth as characteristic of *in utero* exposure of children: *(a)* reduced height and reduced head and chest circumference, effects which are especially pronounced at high doses and persist to maturity; *(b)* microcephaly and mental retardation, which are more frequent in children exposed within the first trimester and for which the dose-effect relationships were discussed in paragraphs 141-146.

208. Regarding medical exposures, Nokkentved (228) reported on 152 Danish children who had been irradiated within the first 4 months p.c. in the course of diagnostic procedures, compared with 143 non-exposed siblings. Several types of x-ray procedures were involved, only a few being simple pelvimetries. In general, the irradiations were delivered in the course of only one examination, but in about 40 cases multiple examinations were performed, up to five in 2 cases. It was found that 15 of the irradiated children (9.9 per cent) and 13 of the controls (9.2 per cent) presented a variety of malformations, including heart malformations, spina bifida, inguinal hernia, microcephaly etc. Both the radiation dose estimated by the number of radiographs and the time at irradiation could not be clearly correlated with the incidence and type of malformations. However, the height of the children irradiated during the second month of gestation was clearly smaller than control, and this finding could not be explained by a number of biological, medical or social factors taken into consideration. Furthermore, the weight at birth of children irradiated during the second month appeared to be low, although the information was incomplete because this indicator was not determined in all children. This study confirms therefore the existence of a growth-retarding effect of irradiation during the second month of pregnancy. However, it does not contribute to improve the information on the incidence of malformations, because of the relatively small sample size.

C. MALFORMATIONS

1. General

209. It is widely accepted that following the termination of major organogenesis, the effects of irradiation become gradually more subtle and more difficult to document, at least macroscopically. The large number of reports on malformations induced during the embryonic stages (see chapter III, section C), compared with the few papers on teratogenesis during foetal development, is in itself a demonstration of that fact.

210. However, that statement, like any general assertion, needs to be qualified. In fact, the distinction usually drawn at the whole-body level between embryogenesis (implying differentiation of new structures) and foetal development (mainly involving the growth through cellular division of the newly differentiated structures) is hardly tenable at the level of single systems or organs. At any given time, new structures can still be formed while others are simply expanding; some organs may still be undergoing differentiative processes while others are enlarging. In addition, the period of maximum sensitivity to induce malformations of certain embryological structures, which at low doses is characteristically confined to the time of maximum differentiation, can be longer with sufficiently high doses (see paragraphs 28-29). Therefore, some malformations are in fact induced with irradiation at ages conventionally regarded as part of the foetal stage.

211. In general, the malformations appearing with increasing foetal age are more subtle and resulting functional defects gradually less pronounced. That influences the fate of the malformed offspring, since major abnormalities produced during organogenesis may be lethal during the intra- or the early extra-uterine life,

while less serious defects, produced at the foetal stages, may be compatible with life, although more or less seriously disabling.

2. Animal data

212. The considerations made in paragraphs 121-123 naturally apply to malformation induction during foetogenesis, but the extreme paucity of data does not allow any analysis of the time and dose dependence of the effects. Very few of the reports examined in chapter III, section C, cover also the induction of teratogenic effects in the foetal period.

213. Concerning **external head abnormalities**, Dekaban (72) reported that an exposure of 200 R in the mouse induced small or deformed heads in 14 per cent or 4 per cent of cases, if irradiation took place at 14 or 15 days p.c., respectively. No effect was seen for irradiation at later ages. Few observations have been reported on the induction of **ocular defects** in the foetal stage. Hicks *et al.* (122) carried out experiments with a few rats irradiated on days 16-20 p.c., showing a reduction of the ocular diameters and microscopical retinal changes (rosette formation).

214. Relatively more abundant are the data on malformations of the **central nervous system**. In the mouse, the induction of gross abnormalities by irradiation with 200 R after day 13 p.c. is less common than in previous stages but still present (72, 143). Microscopically, however, malformations can be ascertained far more accurately, and most of the brains prove to be abnormal with heterotopias, deformities and architectural alterations of various kinds, for irradiation at times at least up to 17 days p.c., although with progressively decreasing incidence (72, 73). The papers by Hicks *et al.* (121, 122) provide a good morphological description of the cerebral lesions in rats following an exposure of 200 R during the foetal stages.

215. These data, together with those of Satow and Miyabara (308), Kameyama and Hoshino (143), Hoshino *et al.* (126), Hayashi *et al.* (116), Mullenix and Norton (202), are of great interest for establishing the pathogenesis of the malformations or their relation to behavioural disturbances, but are of limited value for the purpose of establishing dose-effect relationships. There is, however, unanimity on the significant fact that the developing structures of the central nervous system remain highly sensitive to teratogenic damage until late in gestational life, when gross malformations of other organs may no longer be induced.

216. There are very few data for the induction of other types of malformations by irradiation of other mammals during the foetal stage. In conclusion, it appears that some gross malformations can be produced by irradiation during the foetal stages, particularly in the earliest phases and with doses of a few hundred rad. With increasing age, however, the foetus becomes progressively more resistant to their induction. Microscopic analysis of the anatomical structures, particularly the brain, shows the presence of lesions or architectural defects which would otherwise be undetectable by external examination of the embryos. The incidence of these deformities also decreases as the maturation of the foetus proceeds to completion.

3. Human data

217. In man, the malformation most consistently reported for irradiation during the foetal stages is microcephaly. Its production however, is not specific to the foetal period; on the contrary, the experience in animals shows that the time of maximum sensitivity occurs during embryogenesis. For that reason, both the animal and the human data relevant to this malformation were reviewed in paragraphs 141-146. It is however appropriate to point out that, particularly with regard to man, most of the information reviewed in those paragraphs applies to foetal irradiation as well.

218. A special case of malformation reported in the human after irradiation during the foetal period is segmental heterochromia of the iris. Lejeune *et al.* (169) preliminarily described their findings in a group of about 2800 children, including controls and children of mothers who during pregnancy had been irradiated for diagnostic reasons in the abdomen or the pelvis. Considering the whole population observed, 8 out of 567 irradiated children and 2 out of 2276 controls had heterochromia of the iris. When the comparison was limited to two smaller groups, 3 out of 421 irradiated and 1 out of 448 control children were found with this condition. It appeared that the critical period of the induction of heterochromia might be the 4th and 5th months of gestation.

219. Cheesman and Walby (63) retrospectively studied 7813 children, 4-7 years old, who entered school in Belfast in 1961. Of these, 67 (0.86 per cent) had heterochromia of some sectors of the iris. No significant difference in incidence was found between children who were reported by their mothers to have been irradiated for diagnostic purposes *in utero* (1.17 per cent) and the non-irradiated controls (0.81 per cent). Among irradiated boys the prevalence of heterochromia was slightly, though not significantly, higher than among the non-irradiated boys. That situation was not observed in girls. Eight affected boys had been irradiated *in utero*, and in 7 of these the irradiation had been performed during the 7th month of gestation.

220. Jacobsen and Mellemgaard (138) studied the offspring of 201 female patients irradiated in the gonadal region in 1924-1930 for radiological urinary examinations or for assessment of the position of the foetus. The offspring of these patients were subdivided into 250 born prior to irradiation of their mothers, 46 exposed *in utero* and 169 conceived after irradiation. No significant differences were found in the number of abortions suffered by the irradiated mothers, and in the morbidity, sex ratio and incidence of gross congenital malformations of the children. However, in 184 cases that were examined directly for ocular defects 4 out of 42 individuals irradiated *in utero* and 7 out of 142 children conceived after irradiation were found to carry severe ocular anomalies such as coloboma, atrophy of the iris, choroidal coloboma, strabismus etc. Although

no statistical significance in the incidence of such conditions could be demonstrated between the two groups and the doses delivered to the foetus were not known, 11 cases of eye malformations in a small sample of 184 subjects were thought to be an unusually high number, and the authors could not rule out the possibility that irradiation *in utero* (or before conception) might induce other and more serious malformations of the eye, in addition to heterochromia.

D. OTHER EFFECTS

1. Animal data

221. A number of papers deal with the damage of haemopoietic tissues during the foetal stages. Many of the earlier reports on foetal irradiation of various animals (11, 139, 295) refer to disturbances of haemopoiesis shortly after irradiation. Among the more recent contributions, Reincke (252) showed that rat embryos receiving 270 rad on the 18th day of pregnancy had a lower peripheral blood count which was at its minimum 8-12 days after the irradiation. This was followed by an over-recovery with a peak at 50 days, the haemopoietic regenerative capacity of the surviving animals being similar to that of normal adult animals. Rats irradiated 15 days p.c. with 120-240 rad showed a significant decrease of the white blood cell count (WBC) 1 day after birth. The haematocrit and the red blood cell count (RBC) were, on the other hand, unaffected (117).

222. In the case of mice exposed 15 days p.c. to 50 and 100 R, the WBC at day 17 p.c. was higher than controls, while the RBC was lower. This response is in contrast to the adult reaction. The platelet level was also depressed, but all the haematologic values returned to normal by the third week of age (285).

223. These data regarding the peripheral blood picture, as well as the data on the intrinsic radiosensitivity of the foetal haemopoietic precursors (323), show that the reaction of the foetal haemopoietic cells is compatible with the available information on sensitivity and cell kinetics of the blood-forming system of the rodent. These data are relevant to the post-natal survival of irradiated animals, discussed in paragraphs 181-195, and confirm the transient character of the haemopoietic changes induced by sublethal doses of radiation. The data of Christensen and Jackson (64) would imply, on the other hand, that the fraction of irreparable damage to the haemopoietic system of the foetal animal is higher than in the adult.

224. Kusama and Yoshizawa (165) studied the effects of ^{137}Cs gamma radiation (5-100 R) on the mitotic index of the ddY mouse foetal liver cells (14-16 days p.c.). Following an analysis of the dependence on time post-irradiation of the cellular changes at the various doses tested, they concluded that the threshold exposure in regard to the decrease of the mitotic index and to the frequency of prophase cells was between 5 and 10 R. Similar conclusions were reached by Hoshino *et al.* (126a) in an analysis of the mitotic delay as a function of radiation exposure in the matrix cells of the mouse telencephalon at 13 days p.c.

225. Studying the effects on male fertility, Rugh and Jackson (283) observed a 45-per-cent reduction of litter production in mice exposed to 200 R at 15.5 and 16.5 days p.c. Rugh and Wohlfromm (288) reported on the effects of lower exposures (25 or 100 R) at 0.5-18.8 days p.c. The male offspring were tested for their reproductive potential when their ages were 2-8 months. In contrast with irradiation during the embryonic stages, where some reduction of the reproductive potential was observed, the doses used during the foetal stages were insufficient to produce any reduction of fertility.

226. In females, Langendorff and Neuman (166) showed that exposure for 5 consecutive days to 20-80 R per day during blastogenesis, the first and second half of organogenesis, or the foetal period reduced the frequency, size and reproductive capacity of the litters. The greatest reduction appeared in animals irradiated between 11 and 15 days p.c.; with exposure rates higher than 60 R per day the offspring had no further descendants. The number of litters produced depended on the dose and the phase of gestation at irradiation, the differences of the reproductive capacity depending more critically on the frequency than on the size of the litters.

227. Ershoff (84a) described the effects of irradiation on the development and morphology of the reproductive system of male and female rats. Male animals exposed to gamma rays (300 R) at the rate of 17.92 R/min on day 18 p.c. or exposed to the same dose at the rate of 0.03 R/min over the period 13-20 days p.c. had a significant degree of gonadal damage. Females, in contrast had normal-size ovaries following the acute exposure but significantly smaller ovaries and an absence of follicles and corpora lutea following the long-term exposure.

228. Testicular atrophy in adult rats exposed to as little as 50 R on the 18th day of their foetal life was also reported by Brent (29) and cited as an unusual phenomen of an organ showing two widely separate peaks of sensitivity at 9 and 18 days of pre-natal development. Very recent data of Erickson and Martin (84) have revealed important discrepancies between the rat and the pig in regard to effects on the germ cells following continuous exposure throughout gestation.

229. Further information about the effects on the ovaries of the foetal mouse and rat as a function of gestational age (8-15 days p.c.) and radiation exposure (50-100 R) can be found in Mintz (197), Beaumont (15, 16), and Beaumont and Mandl (17). Other data on the fertility and reproductive capacity of rats exposed *in utero* have also been reported by Murphree and Pace (212) and Baev *et al.* (10).

230. Erickson and Martin (84) reported experiments on the pig irradiated continuously for 108 days (the gestation period in this animal lasts 112 days) at dose rates of 1.5, 3, 9 and 20 rad per 22-hour day with a ^{60}Co gamma source. Foetal dose rates were 0.5, 1, 3 and 7 rad per day. At all dose levels the health of the mothers, the number of live births and their post-natal viability appeared to be normal. At birth and again at 70 and 150 days of age the irradiated offspring were tested for body weight and organ development. Weight and

growth of the body were unaffected by dose rates of 3 rad per day or less. At this dose rate only the weight of the brain was decreased, and at 1 rad per day or less only the weight of the gonads was affected. Sterility was observed both in male and female animals down to 3 rad per day, and an appreciable reduction of the germ cell number was observed in both sexes even at 0.5 rad per day. Parallel experiments conducted on the rat under similar conditions of chronic irradiation (21 days of a 22-day gestation period) revealed an important inter-species difference in that the dose of 1 rad per day did not produce apparent effects on the germ cell population in either sex.

231. Cataract formation in the mouse irradiated during the foetal stages has been described by Rugh, Duhamel *et al.* (270) and Rugh, Wohlfromm *et al.* (292).

232. Two monkeys (*Macaca mulatta*), irradiated during foetal development (200 R on day 80 p.c. and 300 R on day 60 p.c.), were followed for 23 months of their lives. The studies covered the changes in the electroencephalographic, electrocardiographic and electroretinographic recordings. The brain appeared functionally impaired, concomitantly with signs of microcephaly. Depression of light reactions documented a reduced retinal function, while electrocardiographic changes were relatively minor (274).

233. Slightly but distinctly higher levels of urea nitrogen were detected in the blood of beagle dogs irradiated with 20 or 100 R *in utero* 55 days p.c. (341). In the interval 270-435 R of ^{60}Co radiation (delivered at the same time or soon after birth) high incidences of renal failure were reported, particularly in male animals (246).

2. Human data

234. Data have also been reported concerning the haematology of humans exposed *in utero* at Hiroshima (340). The sample size varied during the period of observation, 1951-1958, totalling up to 1020 exposed children and an adequate number of controls. The sample was divided by year of examination, gestation time at irradiation, sex, and distance from the hypocentre. Little indication was given of the actual doses received, apart from the remark that the exposure beyong 2 km was probably less than 20 R. No changes peculiar to the irradiated group were observed. A homogeneous subsample of 63 children, exposed during the first semester of gestation, was analysed. No correlation was found between leukocyte, erythrocyte and haemoglobin values and dose, since the changes associated with distance were comparable with the variation within each distance group. The progressively decreasing count of total leukocytes with age, which qualitatively is a common finding in man, appeared to be faster than normal, but this fact could not be attributed with certainty to any specific cause.

235. Haematological findings in adolescents exposed *in utero* at Nagasaki were also negative (47), in spite of a good assessment of the doses to the mother. It may therefore be concluded that, whatever haematologic changes might have taken place soon after exposure, there was complete haematological recovery by the age of 5 years. Furthermore, the profound changes of endocrine activity during adolescence did not bring to light any haematological deficiency in the exposed individuals.

236. It has been reported that parasitic infestation occurred at a significantly greater rate in children whose mothers were within 2 km of the hypocentre, a finding which, in the view of the authors, is probably to be associated more with dietary, living and socio-economic habits than with radiation (47).

237. Determination of butanol-extractable iodine in serum performed on 249 15-year-old children, some exposed *in utero* at Nagasaki and some unexposed, revealed no statistically significant differences between them with respect to dose and trimester of gestation at irradiation (49).

238. The urine analyses of children (9-16 years old) exposed *in utero* at Hiroshima or Nagasaki were compared with a suitable control group (90). An increased proteinuria was detected at various ages in Hiroshima boys and in all girls whose mothers were within 1.5 km of the hypocentre. Although in some of the groups the differences reached significant levels, the biological significance of these findings remain to be explained.

239. Two conflicting reports are available concerning the sex ratio of babies born from mothers exposed *in utero*. These reports should be examined with the purpose of analyzing the response of germ cells as a function of their stage of development at the time of exposure. It is known that in the human female the oogonial divisions stop about 5 months p.c., when all cells enter meiotic prophase. Meyer *et al.* (190, 191) reported on the sex ratio in children from a group of black women born in Baltimore in 1947-1949, about one third of whom had been exposed to x rays *in utero* in the course of diagnostic pelvimetry. No precise estimates of the radiation doses were given, but they may be assumed to be 1-5 rad in most instances (133). Each exposed person was matched with two controls by hospital of birth, parity and birth data. By 1966, 1993 members of this population had given birth to children and had experienced a number of foetal and neo-natal deaths and abortions. The rates of these events were indistinguishable in the exposed and control groups. A number of variables related to pregnancy, delivery and clinical history of the babies were also identical, showing that matching had really resulted in comparable groups of exposed and unexposed mothers. Under the conditions of exposure examined, it clearly appears that the reproductive capacity of the individuals had not been affected, at least up to 17-19 years of age. However, when the exposed group was subdivided as a function of gestation time at irradiation, it was possible to show that mothers exposed early (0-29 weeks) in their own foetal life had an unusually high and statistically significant excess of male babies. This suggests, in the view of the authors, an excess of pre-natal loss of female conceptuses, which might occur as a result of non-disjunction in the irradiated oocytes, because XXY males would be 10-30 times more viable than XO females.

240. The conclusions reached by Meyer *et al.* (190, 191) are indeed difficult to reconcile with the data of Jablon and Kato (133) based on the experience of Japanese A-bomb survivors. No effect on the sex ratio of the offspring was found, irrespective of the dose group or the trimester of gestation at irradiation. The data were completely negative, despite the larger radiation doses and sample sizes involved in the Japanese series. The question of possible alterations in the sex ratio of children born to parents which had been exposed *in utero* must therefore remain open for the time being.

241. Another epidemiological study was published recently (192) concerning 1458 black women exposed *in utero* to diagnostic doses (1-5 rad) of x rays and the same number of carefully matched controls. The reproductive patterns of the two groups were investigated as a test for possible injuries to the ovaries and oocytes irradiated during foetal life. To this end, the number of live births and foetal deaths in the offspring of the two groups were ascertained and compared. A 10-15 per cent increase in the fertility of exposed women was found. It was statistically significant ($P = 0.011$) and remained so even after adjustment between exposed and controls for socio-economic and medical factors. There was some evidence that this higher fertility might be decreasing with time and that a parallel rise in the rates of spontaneous abortions and foetal deaths might occur in the exposed group. If this trend is confirmed, it is possible that the total reproductive capacity of the exposed individuals may eventually be less than that of the control sample. A prevalence of other minor health problems was also found in the follow-up of the exposed women.

242. In a publication by Blot *et al.* (25), various reproductive indices were determined up to 1973 for a cohort of 2457 persons exposed *in utero* to the A-bombs in 1945 and for another 63 persons in a different sample who had a small head-circumference. It was found that the marriage rate was significantly lower in persons heavily exposed *in utero* (more than 100 rad maternal dose) than in unexposed or more lightly exposed individuals. This difference was attributed in part to the lesser marriage ability of the mentally retarded, who were significantly more numerous among the heavily exposed, and in part to other unknown variables, including possible social discrimination against survivors of the bombing. However, among those married, the frequency of childless marriages, the number of births and the interval between marriage and first birth showed no consistent relation with exposure.

V. INTERNAL IRRADIATION

A. GENERAL

243. The first reported observations on the effect of injected radioisotopes in the foetal mammal are those of Bagg (11). He injected radon solutions in amounts of tens of millicuries into pregnant rats at different gestation times and described post-implantation death and various types of malformations in the offspring. More recently, some data on teratogenic effects of internal irradiation have been published, but information on any one nuclide is still very scanty. It does not seem possible to draw general conclusions, and the main value of the existing data is the indication of possible levels of toxicity for the various radioisotopes. The available data will be reviewed according to the nuclide tested, but only for those nuclides for which there seems to be significant information. It was felt that the present state of knowledge in this field would not justify any attempt to express the data in terms of the radiation dose actually received by the conceptus or its organs and tissues. Exposure or dose data are therefore given according to the way they were reported in the original publication.

244. Two documents have been submitted to the Committee summarizing the effects on foetus and progeny of mothers exposed to radionuclides before conception (177) and reviewing the various effects in animals treated with radioactive substances in the course of intra-uterine development (178); both of them dealt with work carried out in the USSR. An indexed bibliography dealing specifically with the transfer through the placenta and into the foetus of radioactive substances injected to mothers is also of interest for reference to published data on this subject (335). The emphasis of the presentation to follow, in accordance with the objects specified in the introduction, will however be centred on the teratological effects themselves induced by different doses of the administered nuclides, rather than on the mechanisms and rate of transfer of such nuclides from the mother to the foetus. For these the reader is referred to the specialized literature included in the previously mentioned publications.

B. TRITIUM

245. Concerning the passage of tritium administered under the form of tritiated water from the mother through the placenta and into the foetus, Moskalev *et al.* (201) reported that placental accumulation depended only very slightly on the gestational age at the time of treatment; it was found to be 0.38 per cent at 15 days and 0.45 per cent at 19-21 days of pregnancy. In the foetus, 0.38-0.40 per cent of tritium was found on day 13-15 p.c. and 2.0 per cent on day 19-21. Istomina *et al.* (132) studied the transfer of tritium from the mother to the offspring by milk. Lyaginskaya (176) investigated the relationships between the pregnancy stage at the time of treatment with HTO in the rat and the ensuing effects in post-natal development. For a dose of 0.3 μCi/g, little relationship was found among these variables, although treatment at implantation did cause a somewhat increased pre-natal death of the embryos and administration during the foetal stages resulted in greater post-natal death. However, at this dose no teratological effects were manifest. LD_{50} values for foetal mortality in rats after single HTO treatments at various doses were 0.1 μCi/g (corresponding to an estimated dose to the foetus of 100 rad) at 4 days p.c.; 10 μCi/g (400 rad) at 9 days p.c.; and 100 μCi/g (1000 rad) at 17 days p.c. (178).

246. Cahill and Yuile (53, 54) evaluated the resulting foetal tissue doses in rats, the body water of which was

maintained throughout pregnancy at a constant tritium level in the range 1-100 μCi/ml. This was achieved by adjusting the ingestion of tritiated water. Dose rates in embryos and foetuses were calculated to range from 0.3 to 30 rad per day. Most mothers were sacrificed before birth for observation of the conceptuses, but in some cases the observations were carried out on born offspring and followed to their adulthood. Several statistically significant effects were found at various HTO levels, in no apparent relationship with dose. These included microcephaly, sterility, stunting, reduction of the litter size and increase in the resorption frequency. Stunting appeared at 20 μCi/ml and its degree increased at higher concentrations in direct relation to dose. Organ weight decreased in proportion to dose. The incorporation of tritium into foetal organs was directly proportional to the maternal HTO activity during gestation and amounted to 20-30 per cent of this activity. After 180 days of life, stunting only persisted in males with concentrations in the range 50-100 μCi/ml.

247. A paper by Dobson (75) dealt specifically with the RBE of tritium relative to ^{60}Co gamma radiation in long-term exposures. To this end, tritiated water in various doses was administered in drinking water to pregnant mice throughout gestation and lactation for a total of 33 days, the specific activity of the body water being checked by the radio-assay of urine samples. Other groups of mice were exposed to ^{60}Co gamma radiation at various dose rates for the same time lapse. The number of oocytes in the progeny of these animals was counted at the end of treatment, and it was found that oocyte survival decreased exponentially with tritium concentration in body water with an LD_{50} level of about 2 μCi/ml body water, corresponding to an effective dose to the foetus and the new-born offspring of about 6.5 rad. The survival curve of oocytes with respect to ^{60}Co gamma rays was convex upward, indicating a decreased killing effectiveness of the gamma-ray treatment at low doses. By comparing individual gamma-ray and tritium experiments it was shown that tritium was more effective, and limiting RBE values were found to vary between 2.5 and 4.2 with a likely maximum value of about 3 at doses approaching zero. Short-term and protracted exposures were also compared by the same end-point, and higher RBEs for protracted irradiations were obtained.

248. Recent attempts were made by Cahill *et al.* (55) to assess by a number of different end-points (morphological, biochemical and functional) the effects on rats of a simultaneous long-term administration of lead and tritiated water. The experiments allowed the important general conclusions that combination of the treatments resulted in less-than-additive effects and that a significant reduction of brain weight by tritium exposure was apparent at dose rates of the order of 300 mrad per day continuously from conception to 180 days of age. Haemopoietic disturbances (anisocytosis, leukopenia, thrombopenia) in the progeny of rats given tritiated water at doses of 0.008-0.3 μCi/g were described by Zhukova (reported in (178)). Animals from mothers treated at 0.3 μCi/g on day 4 p.c. were the most severely affected. Finally, Lyaginskaya (178) reported a decrease in the life-span of three subsequent generations of rats irradiated *in utero* with tritiated water on day 4, 11 and 17 p.c., particularly upon treatment on day 4 p.c.

249. Concerning administration of tritium in the form of tritiated thymidine, it has been possible to study a number of effects on both the mother and the foetus induced by a continuous perfusion of tritiated thymidine (^{3}HTdR) to pregnant rats from day 9-22 p.c. (88, 101). Activities of 1.6 μCi/g per day were in general well tolerated; but higher levels, from 3.2 to 6.4 μCi/g per day, produced a marked bone-marrow syndrome in the mother. Although the litter size at birth did not appreciably change at these levels, the percentage of still-born offspring increased with the activity injected, while the number of offspring surviving more than 12 hours after birth decreased in proportion to that activity. With 8 μCi/g per day, no rat was born alive. Retardation of growth and macroscopic and microscopic malformations of the head, brain, eyes, ears, mouth and extremities were observed at these high levels. With 6.4 μCi/g per day, no gross external abnormalities were seen, but the general development and the haemopoietic system of the animals were severely impaired in proportion to the administered activity. The post-natal growth and weight of surviving animals also showed activity-related pathological changes.

250. In another paper (311), the incorporation of tritium from ^{3}HTdR in developing rats was studied by biochemical techniques. The total incorporated activity and the DNA specific activity showed a direct relation to the activity of the tritium injected in the mother. The distribution of radioactivity between the DNA and the low-molecular-weight fraction was independent of the administered activity, and the time variation of the DNA specific activities was characteristic for each organ. Because of all these facts, the system of continuous perfusion was recognized as a suitable procedure for studying ^{3}HTdR toxicity in the embryo.

251. Mouse embryos were also grown *in vitro* from the 2-cell stage to the blastocyst stage in the presence of ^{3}HTdR (329). Concentrations of tritium above 0.1 μCi/ml were definitely lethal, and concentrations between 0.01 and 0.1 μCi/ml caused a highly significant reduction of the number of cells in the blastocyst. The latter effect could be largely accounted for by selective cell death occurring at the 16-cell stage. As the cells in the inner mass were most susceptible to killing, it was possible to obtain blastocysts composed entirely of trophoblast.

C. PHOSPHORUS-32

252. Burstone (50) described the effects of ^{32}P on the development of embryonic tooth primordia in mice, showing that injections of 5-17 μCi/g in pregnant animals 2-6 days before birth gave rise to developmental disturbances of teeth, observable within about one month after birth. He also reported that activities above 10 μCi/g produced general post-natal growth retardation and that this effect was more evident when ^{32}P was given early in pregnancy.

253. Sikov and co-workers carried out a series of systematic quantitative studies on the consequences of ^{32}P irradiation throughout gestation. Sikov and Noonan (320) gave several IV injections of the nuclide to female

rats on day 6, 8, 9 and 10 p.c. They then established the values of the LD_{50}, for lethality of the foetuses before day 14 p.c. These LD_{50} values increased with the age of the embryos at treatment, from 0.46 mCi on day 6 p.c. to 1.29 mCi on day 10 p.c. The uptake of the isotope by the foetus was assessed, and from this the doses to the embryos were calculated for each day of gestation. At the LD_{50} levels mentioned above, the doses varied from about 6000 rad on day 6 p.c. to about 10 200 rad on day 10. The uptake appeared to be proportional to the activity injected, indicating that there was no major interference with the phosphorus metabolism. A reduction of embryonic weight was found at the time of observation, the reduction being greater when embryos were irradiated earlier.

254. Growth retardation (321) and skeletal defects (316, 317) were also studied in rats, following the administration of 0.6-2.0 mCi of ^{32}P on days 14 and 17 p.c. The study of specific defects and the measurements of various bones were carried out using serial sacrifice from injection to birth. A dose-related decrease of the foetal size and of the bone sizes was observed and this decrease was found to be greater in animals tested at the younger developmental age. The same pattern applied to skeletal malformations, which were also more frequent and severe in the group injected on day 14 p.c. Differences with respect to previous experience with x irradiation were noted (357). With the aid of a dosimetric study (314), such differences could in part be attributed to the pattern of accumulation of the radiation doses at the two ages tested. Other possible explanations related to the effects of the dose rate or of the LET of the radiations compared (315).

D. STRONTIUM-89 AND STRONTIUM-90

255. Most of the early papers on the effects of ^{89}Sr and ^{90}Sr dealt with the transfer of the nuclides through the placental barrier (244, 360, 124, 221). Finkel (86) concluded that, in the mouse, negligible amounts of ^{89}Sr were transferred through the placenta during the first 15 days of gestation. She described an increase in the percentage of still births, some growth retardation, bone fragility and anaemia in mice treated *in utero*. In the rat, the retention of ^{90}Sr in the placenta was estimated to be 0.02 per cent of the amount injected and was found to be rather independent of the gestational age at treatment. However, the passage of the nuclide to the foetus was such, that for early gestational ages its content equalled that in the placenta (0.01-0.02 per cent) but at 16-19 days was about 20 times higher (201). Hopkins and Baxter (125) reported that the fraction of the ^{90}Sr injected into pregnant female rats at 17 days p.c. which was retained at birth by the offspring decreased with increasing maternal age at injection, although the ratio of offspring body burden to maternal content was independent of maternal age under the specific conditions tested. There was no marked difference in the percentage of the dose of ^{90}Sr retained by new-born offspring in the dose range 24-382 μCi.

256. Single injections of ^{90}Sr to pregnant rats at various dose levels were used to establish the values of LD_{50} in the offspring. They were found to be 0.4 μCi/g (corresponding to a calculated foetal dose of 3.5 rad) at 4 days p.c. and 0.8 μCi/g (10 rad) at 15-19 days p.c. (data reported in (178a)). A dose of 10-15 μCi/kg of ^{90}Sr injected IV in pregnant dogs at 1-9 days before birth produced no obvious malformations (87). Burykina *et al.* (51) concluded that in their experiments the chronic introduction of ^{90}Sr (0.02 μCi/kg per day in the course of 3-3.5 years) produced skeletal doses of about 50 rad/year in the parents. Under these conditions, disturbances in the development of the progeny were observed, together with a decrease of their viability. A reduction in the number of oocytes was described by Nilsson and Henricson (224) in mice after IV injection of the pregnant females with 20 μCi of ^{90}Sr. The effect was more pronounced with injections at day 16 than at day 11 p.c. Finally, Kincade *et al.* (147) described changes in the haemopoietic and immunopoietic cell populations of the foetal liver, marrow and spleen after ^{90}Sr treatment.

E. IODINE-131

257. After single parenteral injections of ^{131}I (4 μCi/g) at 1-16 days p.c. in the rat, pre-implantation embryos were found more susceptible than those at later stages; for treatment at day 1 p.c. a three-fold increase in foetal intra-uterine mortality compared with controls was obtained (164). Oral administration of 1.0 μCi of the same nuclide on day 13 produced an accumulation of 0.035 per cent in the placenta and 0.01 per cent of the administered activity in the foetus. By day 20 or 21, the amount in the placenta was increased only slightly while the foetal retention was 28-40 times that at day 13. This increase was related to the increase in the mass of the foetal thyroid and to an improvement of its ability to concentrate the isotope (179).

258. Chronic treatment at the level of 65 μCi per rat daily throughout pregnancy led also to a significant increase of the death rate (about 41 per cent), of which 10 per cent could be accounted for by pre-implantation, and 31 per cent by post-implantation, mortality. Delay in the development of the progeny, microcephaly and liver damage (chromosomal aberrations) were also apparent (164). Iljin *et al.* (data in 178a) also reported on repeated treatment of rats with ^{131}I at 1-7, 8-14 and 14-21 days p.c. for a total of about 30 μCi per rat given at progressively lower doses. According to the various treatment schedules, an increase in mortality at birth of about 15-25 per cent was seen. A delay in thyroid development was also apparent. Finally, histological changes in adult mouse thyroids following treatment of the mothers with ^{131}I at 18 days p.c. were described by Walinder and Sjödén (352) but no reference was made to teratogenic effects induced by the treatment.

F. OTHER NUCLIDES

259. Female rats were exposed to monomeric or polymeric ^{239}Pu on day 15 or 19 p.c., and the distribution of the nuclide in various portions of the foetoplacental unit was studied by counting and by autoradiography (319). At the above gestational ages, 50 μCi produced no pre-natal mortality. On the other

hand, a substantial difference in the mortality at 14 days following an injection on day 9 p.c. was observed; 2-12 μCi induced about 60 per cent mortality and 25 or 50 μCi produced death of all embryos. None of the surviving foetuses showed gross morphological malformations. In view of the high activities administered, the value of these experiments is purely theoretical and without applicability to risk estimation.

260. In order to establish the $LD_{50/30}$ of ^{241}Am for the rat foetus at various stages of development, the pregnant females received IV injections of the nuclide at 10, 13, 16 and 19 days p.c. The concentrations of the solutions were increased stepwise from 1.2 to 7.6 per cent to cover the required range of doses, while the volume injected was kept approximately constant. Since the placenta behaved like an inconstant barrier (the ratio of the maternal to foetal concentrations of ^{241}Am varied from 6:1 to 2:1 (201)), the LD_{50} values were expressed as the doses to the mother that produced 50-per-cent mortality of the foetuses at different ages, followed by the calculated cumulative rad doses to the foetuses: 10 days p.c., 0.03 μCi/g (100 rad): 14 days p.c., 0.01 μCi/g (800 rad): 19 days p.c., 40.2 μCi/g (1000 rad) (375).

G. CONCLUSIONS

261. It seems impossible at present to draw any precise, general conclusions about the action of radionuclides in the development of the conceptus because of the paucity of data on dose-effect relationships for the nuclides tested. None of the effects observed up to now appears to be specific to internal irradiation, and these effects may be viewed as the end-points of a continuing action exerted during the various stages of embryonal and foetal life. Their precise interpretation and evaluation must be based on a precise knowledge of the dose accumulated by the mother and the foetus at any particular stage and in any particular sensitive structure under all possible conditions of administration. The information we have at present is far from being good enough for that.

262. In spite of some attempts to compound the known data on the placental transfer of the various nuclides into a general model of transport and accumulation (242, 332, 333), the information is still too fragmentary, not only with respect to the dosimetry, but particularly in regard to the effects. Careful consideration of the data reviewed allows only a schematic enumeration of the main variables that have been shown to interact in the production of the end-effects. They are *(a)* the nature of the radionuclide in respect to its physical characteristics and to the different organotropic behaviour; *(b)* the chemical form in which the nuclide is administered, in so far as it may influence its pattern of accumulation and deposition; *(c)* the route of administration and the dosage schedule, particularly because the rate of passage and accumulation from the mother into the conceptus may be critical in relation to the rate at which the ontogenic events take place in a rapidly-growing and differentiating organism; *(d)* the developmental age at irradiation, since periods of maximum sensitivity are to be expected in the case of internal as well as for external irradiation, even though they may be difficult to resolve owing to the continuous action of the deposited nuclides; *(e)* the animal species, not only in regard to the peculiarities of the differentiation pattern, but also in respect to all physiological differences in the absorption and deposition that could alter the incidence of the biological end-points; *(f)* the age of the pregnant animals at treatment, for which information is virtually absent; *(g)* the possible role of the maternal irradiation. Further extensive experimentation in all these fields, at least for the most hazardous nuclides, is clearly called for.

VI. MECHANISMS OF RADIATION TERATOGENESIS

263. The present chapter has two purposes:

(a) It tries to identify some common features and trends among the data and effects described. This information may explain the origins of malformations and the likely pathways involved in their manifestation;

(b) It discusses the scanty information available on the role of some radiobiological variables (LET, dose fractionation etc.) and of some of the modifiers of the teratogenic response (oxygen effect, chemical protection etc.).

264. Since the mechanisms of the lethal action *in utero* have already been discussed (paras. 66-70, 94-97, 186-191, 221-224), the discussion will be limited essentially to the induction of growth disturbances and malformations. A few remarks about the applicability to the human case of data obtained experimentally in animals are also included.

A. INFLUENCE OF THE MATERNAL ORGANISM

265. One issue concerning mechanisms which has attracted much attention, particularly in the older literature, is the influence that the irradiated maternal organism might have on the appearance of foetal abnormalities. The reasons for such a continued interest can hardly be explained, since it stems mainly from experiments of doubtful significance and it is known that malformations can also be induced by irradiation in oviparous species. The close relation of the conceptus to the mother in mammals is not by itself a sufficient reason to postulate any abscopal mechanisms. In a critical evaluation of the data, Russell (295) observed in 1954 that two facts stand against such a hypothesis: *(a)* the existence of sharply defined periods of sensitivity in the embryo, which cannot be easily reconciled with the relatively long-lasting effects of radiation in the mother, and *(b)* the extremely short time between irradiation and the appearance of embryonic lesions, which would require the improbable existence of very rapid mechanisms.

266. Among the more recent contributions, Chang and Hunt (60) have reported experiments in which pre-implantation rabbit embryos irradiated *in utero* were transplanted into non-irradiated recipients or into animals exposed to 400 R at different times after an

induction of ovulation by hormonal treatment. Under these conditions, embryonic mortality was increased by the irradiation of both the ovum and the mother, but the relative contribution of the two factors was found to depend on time elapsed since ovulation. Brent and Bolden (32) raised an objection to these experiments on account of the comparatively high doses used, which might actually have resulted in an increased foetal mortality (though not necessarily in an increased yield of malformations). They also criticized the lack of synchronization between development of the embryo and of the decidua, which is critical for proper embryo implantation. Experiments similar in many aspects to those of Chang and Hunt (60) were reported at the same time by Issatchenko (131) who transplanted 2-day-old rabbit embryos from irradiated animals (250 R) to normal females and *vice versa*. Under these conditions an increased mortality of the embryos was observed above that obtained by irradiation of the embryo alone, thus confirming the presence of an indirect effect of the irradiated maternal organism.

267. Duplan and Monnot (79) irradiated pregnant mice (200 and 400 R of x rays) with shielding of the foetuses and observed a dose-related increase of pre- and post-natal mortality in the offspring. Also, protection of the mother's abdomen resulted in a higher percentage survival of the non-irradiated offspring when compared with the shielding of the head and neck. Valentini and Hahn (349) studied the survival of rat embryos in the right uterine horn irradiated with 200-400 R at day 1.5 or 4.5 p.c. and found a significant increase when the left lower body quadrant was concomitantly shielded. These results would indicate that irradiation of the mother might be a contributing factor in pre-implantation embryonic mortality.

268. A series of papers by Brent and co-workers have contributed greatly to clarifying this issue. These authors were able to show that exposures of 200 R in rat embryos at 9 days p.c. were definitely lethal (38). When the embryo was shielded while the mother was exposed to x rays at 400 R of whole-body irradiation or to over 1000 R of partial-body irradiation, no embryonic malformations were seen in embryos at term. Foetal mortality, on the contrary, was higher than in control animals, presumably as a result of radiation sickness in the mother. When the placenta was exposed to 400 R (28), while both the mother and the conceptus were shielded, there were no lethal effects, growth disturbances or induction of malformations.

269. In another paper dealing with pre-implantation embryos (32), Brent and Bolden used shielding techniques to differentiate the results of ovary, oviduct, uterus and zygote irradiation (150 R). Treatment on day 1 p.c. showed that uterine and ovarian irradiation had no effect on foetal mortality, which instead was caused by irradiation of the oviduct containing the fecundated ova. Malformation incidence was very low, in accordance with the observations reported in paragraphs 75-79. Although this experiment does not rule out possible effects of oviduct irradiation, it strongly suggests that the major and primary action is caused by direct irradiation of the ova. Brent and Bolden (34) showed also that embryonic rats in the first day of development irradiated with doses of 150 R were resorbed in 60-70 per cent of the cases when irradiated directly, while irradiation of the mother and shielding of the embryos did not appreciably increase the resorption level above control. The same experiment with a dose of 400 R resulted in a 25-per-cent resorption of the unirradiated ova, showing a moderate indirect effect at the higher doses.

270. It may be concluded that irradiation of the mother is likely to be of very minor importance for the induction of malformations, particularly at low doses. On the other hand, it is conceivable that mortality of the embryo and foetus may be indirectly affected by the irradiation of the mother, especially at doses of a few hundred rads.

B. NATURE OF THE PRIMARY DAMAGE

271. In the mid 1950s, Russell and her collaborators (295, 302, 303) presented a complete analysis of the nature of the primary damage which develops into teratological effects. In the more recent literature, there have been few systematic treatments of the subject, although some special subjects have been dealt with more frequently (318, 255).

272. The materials reviewed in the preceding sections of this report show that the developing embryo is composed of a variety of dividing, differentiating, interacting and migrating populations of cells, arranged in complex and ever-changing patterns. Unlike the adult, the embryo is characterized by the absence of cell populations in steady state, and it is this circumstance that may be related to the variable radiation response as a function of dose and time. Molecular embryology is beginning to elucidate some of the intracellular mechanisms of gene regulation and some of the possible intercellular interactions taking place in orderly sequence in the various embryonic cell lines. However, the occurrence of certain "macroscopical" events in developing embryos cannot yet be related with certainty to specific molecular changes (19, 12, 26).

273. Nevertheless, two qualitative features of embryogenesis are important in relation to the effect of radiation. The first is the sequential character of development, the occurrence of certain events appearing to trigger the initiation of other events taking place at later times. The second is the constancy of the timing of the events, which occur within rather narrow intervals of time from conception. The first of these features explains the peculiar character of the radiation-induced malformations, which often appear to be the consequence of an arrest of development at some rudimentary stage; the second explains the specificity of irradiation at certain well defined times in the production of given types of malformations.

274. Conceptually, the mechanism of radiation-induced malformation may be examined at different levels of biological organization: *(a)* the subcellular level, where the problems of concern are the distribution of primary events within the cell and the resulting changes in subcellular structures; *(b)* the cell as a separate unit

reacting to the lesions of its components; *(c)* the cell population level, including the damage and repopulation of the compartments originating from common precursors and also the relations with other cell populations; and finally *(d)* the developmental pathways that lead from the injury of single cellular precursors to the final malformative change.

275. The information available at all levels is extremely limited. For some of the issues discussed in the following paragraphs there is no experimental data at all, and therefore the problems can only be formulated in very general terms.

276. At the subcellular level, it seems quite likely that the primary events taking place in embryonic cells are qualitatively equal to those occurring in other cell types. The differences between embryonic tissues with respect to water content, oxygen tension, concentration and properties of radicals seem insufficient to justify important differences of the primary effects (309). Substantial knowledge has developed in recent years about the effects of radiation on DNA and the action of reparative enzymes in mammalian cells (5). This information is regarded as of great radiobiological importance because of the essential role of DNA in cell division and differentiation. However, there are no direct data in embryonic or foetal cells.

277. Direct quantitative data on embryonic or foetal cells and tissues are at the present time few and scattered. Those available concern changes in the synthesis of DNA (198, 183, 184, 185, 324, 311, 199, 53, 54), RNA (198, 183, 184, 185) and proteins (198, 183, 184, 185, 313, 85); the disturbances in the ontogenesis of particular enzymes or enzyme systems (351, 216, 215, 214, 233, 163, 94); the ultrastructural changes of cytoplasmic organelles (233, 258, 259, 62); the analysis of kinetic changes of specific cell lines or tissues (83, 186, 185, 84, 165, 40, 41, 42, 199, 126, 107, 234). The species differences and the non-systematic character of the observations in regard to irradiation time, dose delivered, heterogeneity of end-points etc. preclude the formation of any coherent picture of the fundamental pathways through which gross teratological effects become expressed.

278. It seems logical to postulate nevertheless that the observation in irradiated mammalian cells *in vitro* and *in vivo* apply as well to cells irradiated *in utero* (309). It is also reasonable to assume, as a first approximation, that damage to the nuclear structures of the cells should be preferentially considered. In this context, two possible mechanisms of damage of the genetic structures have been proposed as the initiating processes: gene mutation and chromosomal aberration.

279. The role of gene mutations (365, 363, 364) is probably insignificant, in view of the very low frequency of these events at doses shown to be teratogenic, and also because of the low degree of expression of these mutations in diploid cells (295). In analogy with observations made on irradiated somatic cells of the adult (5), it seems quite reasonable to assume therefore that the major component of cellular damage is attributable to chromosomal abberations (295). Chromosomal aberrations are likely to impair cell reproduction owing to the chromosomal imbalance of the daughter cells or possibly to mechanical disturbances of the mitotic process.

280. It is generally agreed that cell inactivation can be the common denominator of all types of malformations. Microscopical evidence of cellular damage is, in many instances, the first change observed in irradiated embryonic cells of the nervous system (258, 120, 121, 161, 237, 238, 239, 308, 21, 207, 144), the eye (162, 284), the skeleton (295, 210), the urogenital system (243, 121) and many other tissues.

281. This uniform pattern of cell reaction is consistent with the great similarity of the malformative response obtained in any given primordium or stage (295). It should, however, be reconciled with the observed selectivity of the damage, which appears to develop preferentially in certain structures at certain times.

282. Mechanisms of differential sensitivity to radiation may be invoked to explain selectivity. Furthermore, in accordance with what is observed in adult tissues, it is possible to postulate a different intrinsic cell sensitivity to inactivation in different phases of the mitotic cycle, and also a differential sensitivity of tissues having different kinetic structures. Repair phenomena at the intracellular level and repopulation of the tissue compartments may also contribute to the specific sensitivity of the embryonic primordia during certain phases of their development when cell division and differentiation are most active. The normal sequence of these cellular periods is strictly dependent on some unknown regulatory mechanisms, and indirect damage to these mechanisms may also operate in the induction of abnormalities.

283. The loss of reproductive integrity of a cell is reflected in the immediate descendants of the affected precursor cell. It is also conceivable that damage of a given structure may result in secondary effects on other structures or processes which are functionally dependent on the originally damaged precursor and which may, in turn, be additionally affected by the radiation exposure. It should not therefore be expected that the large variety of processes involved can be directly inferred from a simple analysis of the malformative end-point (303).

C. DOSE-EFFECT RELATIONSHIPS

284. In the absence of direct information about fundamental mechanisms it appears nonetheless possible to formulate simplified mathematical models and to test their compatibility with observed data on dose-effect relationships. Such an exercise has been carried out by Russell (303); the model is illustrated in the following paragraphs.

285. If it is assumed that all reproductive cells in a given embryological structure have, as a first approximation, the same probability p of being inactivated by a given radiation treatment, and if it is further assumed that p is a function of dose, the number of inactivated cells in the

structure will be distributed according to a binomial distribution of the type

$$P(x) = \binom{n}{x} p^x (1-p)^{n-x}$$

where $P(x)$ is the probability of encountering x inactivated cells, and n is the number of reproductive cells in the structure. It may also be postulated that there is a threshold x_T of the number of inactivated cells below which no teratological damage will be apparent. This threshold could be different for each structure and presumably related to its repair capacity. If the damage inflicted on the structure exceeds the value of the threshold, a malformation would be induced and its severity would be in proportion to the number of cells damaged above the threshold. The probability of inducing a malformation would then be

$$P = \sum_{x=x_T}^{n} \binom{n}{x} p^x (1-p)^{n-x}$$

286. Under these hypotheses, Russell (303) has shown that, irrespective of the value of n specifically assumed for each structure, a dose increase will produce an increase in both the number and the severity of the malformations. Furthermore, even with fixed values of p and n, owing to the variability introduced by cell division of the cells retaining their capacity for proliferation and of their descendants, some variability in the malformative end-point will be expected. This variability will operate even under conditions of good homogeneity of the genetic background of the animals and of the experimental conditions under which a given dose-effect relationship might be determined. Other causes of variability, discussed at length in previous sections of this Annex, will obviously add considerably to these inherent causes of variation.

287. It follows therefore that the derivation of the actual values of the parameters mentioned above through the simple mathematical analysis of measured dose-effect relationships would give highly uncertain results of purely speculative value. It would not be justifiable to interpret such data in terms of simple underlying mechanisms, even in the most simple case of an apparently linear response.

D. THE PROBLEM OF THE THRESHOLD

288. The frequently encountered sigmoid nature of dose-effect relationships for damage to the embryo and foetus (see chapter III, section C), the action of repair systems at the subcellular and tissue levels (paras. 271-283) and the theoretical notions to be gained by models of the type described in paragraphs 284-287 strongly suggest the existence of non-linear components in the dose-effect relationships or possibly the existence of true thresholds.

289. Two approaches have been followed in regard to such problems. One is the determination of the lowest doses at which various abnormalities have actually been observed (lowest teratogenic doses). The other consists of experimental tests aimed at establishing the existence of thresholds.

1. Lowest teratogenic doses

290. The literature contains many tabulations of the minimum doses at which different types of malformations have been observed in various experimental animals (27, 92, 370). Table 5 presents an updated

TABLE 5. SYNOPSIS OF THE LOWEST TERATOGENIC DOSES OBSERVED IN MICE AND RATS

Species	*Gestational age (days p.c.)*	*Exposure (R)*	*Effects observed*	*Reference*
Mouse	0.5	5	Increase in resorption frequency	278
	0.5-1.5	15-20	Exencephaly	276
	0.5-1.5	5	Polydactilia	277
	7.5	5	Increase in resorption frequency	231
	7.5	5	Skeletal malformations	
	7.5	5	Decrease in litter weight (winter sample)	136
	7.5	5	Hydramnios	
	7.5	5	Reduced tail length	
	7.5-8.5	25	Malformations of the axial skeleton	297
	8	25	Hydrocephalus, flexion of the spinal cord, architectural changes of ependymal cells	204
	8.5	50	Eye defects	181
Rat	0-8	5-25	Growth disturbances	27
	8	12.5	Growth disturbances	362
	8-9	36-40	Ocular and cerebral malformations	139
	9	25	Growth disturbances	365
	9	50	Increase in resorption frequency	364
	9	12.5	Ocular and cerebral malformations	93
	9	100	Heart and aortic, face, and urinary tract malformations	362
	9	50	Brain and spinal cord malformations	362
	9	25	Microphthalmia, anophthalmia	362
	16-22	10-40	Permanent alterations of nerve cells and cortical architecture of the brain	120

summary for the mouse and rat, in which species sufficiently low doses have been tested. Doses of the order of 5 rad, administered during the period of major organogenesis, have definitely been shown to induce malformations, particularly in the skeleton of the mouse, together with some lethal effects and growth disturbances. There appears to be no systematic investigations with rats at the same dose level, but it seems likely that for doses of a few rads, careful experiments might reveal teratogenic effects, particularly growth disturbances and ocular defects. The table also shows that in the nervous system, where cell division and differentiation proceed to very late foetal age, doses of a few tens of rads can produce microscopic lesions of the nerve cells and malformations of the cerebral architecture. The observation accounts for the fact that microcephaly and mental retardation can be induced throughout foetal life with comparatively high frequency (see paragraphs 141-146).

291. The fact that teratogenic effects have not been shown in humans with doses of the same order of magnitude in the course of pelvimetry or other diagnostic procedures (see paragraphs 202-208 and 217) could possibly be attributed to the developmental heterogeneity of the irradiated samples and to the late age at irradiation, which in the majority of cases was after the organogenesis period. It can be concluded, however, that in those animal species where low doses of irradiation have been thoroughly tested at the time of the sensitivity peak, there is evidence of some effect at doses as low as 5 rad.

2. Experimental tests

292. Much of the work concerning the experimental demonstration of threshold is insufficient to permit drawing definite conclusions. The usual reasons are the small number of animals used, the absence of wide-range dose-response data, the relatively high doses employed and, in some cases, technical imperfections. Threshold problems have been particularly considered by Jacobsen (136). His experiments concerned skeletal abnormalities induced in 7.5-day-old mouse embryos by exposures of 0, 5, 20 and 100 R. The data are limited to one type of malformation and to a single embryonic age (in order to improve the precision of the estimates), but the limitations are largely compensated by the number and accuracy of the observations. However, it is impossible to predict to what extent his conclusions would apply to other malformations and embryonic ages.

293. Jacobsen concluded that dose-effect relationships for single malformations are of little practical relevance for an overall evaluation of the teratogenic effects, mainly because of the low frequency of occurrence of such events. He therefore grouped the scored malformations according to skeletal region. The effects were found to be linear or almost linear with dose, within the confidence limits, for the control, 5-R and 100-R groups, while the 20-R group was in most cases slightly below the expected value. This pattern was found to apply to most of the skeletal regions examined and also to other traits not involving the skeleton. It was found in summer as well as in winter experimental samples.

294. In spite of the slight departure from linearity, however, the author concluded that there was no suggestion of threshold, since both the 5-R and 20-R points were significantly above the values of control. Clearly these experiments do not exclude the possibility that thresholds might exist at exposures below 5 R, but experiments at lower doses would require a much greater number of animals and result in having, in principle, the same problem, but within a lower dose range.

295. It may be concluded that the most refined experiments so far exclude the existence of threshold for exposures as low as 5 R at least under the specific conditions tested. The low-dose effects (at 25 R or below) which have been recognized in animal experiments (136, 204, 231, 297) may be regarded as an increased incidence of some types of malformations or effects occurring spontaneously in the species tested. It may be very difficult to establish threshold doses for these effects, since the incidence of spontaneous malformations and minor anomalies is controlled by the genetic constitution of the strain or of the individual, which has an intrinsic variability.

E. FACTORS MODIFYING THE TERATOGENIC RESPONSE

296. In addition to the factors examined systematically in the other sections of the Annex with regard to each type of malformation, there are other factors that can modify the teratogenic response to a given radiation dose. These include physical factors such as LET and dose rate and the modifying effect of oxygen and chemical protectors.

1. Radiation quality and LET

297. The type and energy of radiation, as reflected by the ionization density and the LET, are among the most important radiobiological parameters affecting the degree of response (256). There are, however, very few experiments on LET effects on the induction of malformations in mammalian embryos. Furthermore, these experiments are not systematic and, in particular, the data do not include the effect of a range of LET values for various abnormalities at different embryological ages.

298. Some very early reports (11, 52, 106) are hardly amenable to quantitative analysis. Sikov and Lofstrom (315) reported on the RBE of ^{60}Co gamma rays and 250-kV x rays in rats irradiated at various gestational ages (9-10.5 days p.c.). The exposures (110-450 R) were delivered either acutely every 12 hours or intermittently throughout most of the half-day interval between exposures. Embryos were examined at 14 days p.c.: mortality and malformations of the mandible, eye, maxilla, extremities and tail were considered. It was found, in general, that gamma radiation produced less effect than x radiation, giving rise in most instances to RBE values in the range of 0.80-0.95. However, for malformations of the eye, maxilla and mandible induced at 9.5 days p.c., substantially lower RBE were obtained. The slopes of the dose-effect curves for mortality were

the same for both radiation schedules used, regardless of embryonic age and protraction. Concerning malformations, similar dose-effect curves were produced by the two radiations but sometimes protraction resulted in curves of smaller slope; a reduced magnitude of some effects and an increased value of the RBE were induced by protraction. The effects were interpreted as depending on the differences of recovery rates of embryonic structures, especially when the change of RBE by fractionation was particularly evident.

299. Friedberg *et al.* (91) irradiated mouse embryos in the pronuclear-zygote stages with 300-kV x rays (67 rad/min) or with fission neutrons (2 rad/min) and examined them for embryonic survival of the uterine content of the mother 16 days later. Non-threshold exponential dose-survival relationships were found to apply to both x rays and neutrons in the range of 0-100 rad and 0-19.5 rad, respectively. A comparison of the slopes resulted in an RBE of 4.5. With increasing dose, the pre-natal mortality increased, and the embryos died at earlier development stages.

300. These data are clearly insufficient to allow generalization, although they appear to be compatible with our knowledge of RBE for other somatic effects in mammalian systems. More systematic investigation for other radiations and LET spectra are required to cover the subject adequately.

2. Dose rate and fractionation

301. In contrast to the paucity of data on the effects of radiation quality, there are comparatively numerous studies on the effects of dose rate and fractionation. The reason for this interest is the possibility that protraction might not reduce the effect in a system like the embryo. In view of the complex pattern of cell types, each with a different time-related pathway of division, differentiation and interaction, a protracted dose could in principle produce more adverse effects in the embryo than an acute dose of the same magnitude. However, it should be pointed out that it is extremely difficult to control these experiments, mainly because of the rapid changes in sensitivity taking place as a function of time in the various structures and of the changing pattern of malformations specific to each developmental period.

302. The report by Auerbach (7) did in fact show some increased hazard in mammals of fractionated, as compared to single-dose, irradiation. Hybrid mouse embryos at 9.5 days p.c. were exposed to either 300 R or to three 100-R fractions delivered at 30-min intervals and were examined by uterine dissection 3-6 days after irradiation. The criteria of damage used were the incidence and degree of lumbosacral spina bifida and coloboma of the eye. While the total incidence of malformations was not affected by fractionation, their severity increased: this effect was seen in both abnormalities, in spite of their different developmental pathogeneses.

303. The observations of Rugh and Grupp (279) covered the period from 0 to 8.5 days p.c., and included almost 3600 embryos exposed to 50 R in two equal fractions separated by different times. Exencephaly was the malformation particularly studied. When the dose fractions were separated by less than 4 hours, there was no difference compared with the effect of a single combined total exposure. Longer fractionation intervals seemed to reduce the incidence of anomalies but not the incidence of early intra-uterine death.

304. Russell, Badgett and Saylors (298) carried out rather more elaborate experiments, studying different effects (mortality, weight loss, long-term survival, fertility and morphology). They tested the effects of *(a)* 171 R (0.096 R/min) accumulated during the first 2 weeks of pre-natal development; *(b)* 200 R given acutely (83 R/min) at one of seven stages of pregnancy (0.5, 1.5, 4.5, 7.5, 9.5, 11.5, 13.5 days p.c.); *(c)* 191 R administered in 15 daily acute fractions of 12.8 R within the same time. As expected (see chapters II and III), acute irradiation produces a great variety of incidence and severity of effects, strikingly dependent for their type and degree on the stage at irradiation. Chronic irradiation, on the other hand, induced no special effect, except for shortening of the fertility period in females. Daily acute fractions had no more adverse effects than continuous exposure.

305. On the likely hypothesis that cell killing might be the main cellular effect responsible for the initiation of malformations (see paragraphs 280-283), these results were interpreted to mean that cell killing in embryos is lower with chronic than with acute irradiation. The fact that single doses of radiation given at the sensitive periods were effective in causing abnormalities, while lower doses within the same sensitive periods were not, is compatible with the model reviewed in paragraphs 284-287, assuming that the total dose administered during these periods was insufficient to inactivate more than the threshold number of cells required for the production of abnormalities. The difference to Auerbach's findings (7) could be explained by the assumption that cyclical periods of higher sensitivity could have been responsible for the potentiation of the effects by fractionation.

306. More recently Yoshizawa and Ueda (373) submitted six different groups of ddY mice at 11 days p.c. to 200 R given at the rate 1-100 R/min. The body weight and the delay in ossification of the caudal vertebrae scored at 18 days of pregnancy were assumed as indicators of whole-body and systemic damage. Both these parameters were found to be in good relationship to increasing exposure, but they were insensitive to the exposure rate within the range indicated.

307. The work of Kriegel and Langendorff (159) does not allow a direct comparison of the effects of acute and fractionated doses. It gives, however, information on the incidence of malformations and of lethal effects induced by fractionated, daily x-ray exposures administered during the total pregnancy period of the mouse. Levels of 2.5-10 R per day had an effect on embryological development. At 20 R per day a small increase in resorption rate and in malformation incidence was observed together with a decreased weight of the conceptus. Fractionation régimes of 80 R per day caused the interruption of pregnancy. Another series with 80,

120, and 160 R per day for limited pregnancy periods of days 11-16, 11-13 and 14-16 p.c. was reported by Kriegel and Reinhardt (161). At 18 days of gestation striking effects on growth and malformations of the tail and the extremities were obtained.

308. Konermann (152, 153, 154, 155) published a series of papers dealing specifically with the effects of fractionated and chronic irradiation. In the first report (152), the differential stage sensitivity was particularly examined at exposure regimens of 5-100 R per day. It was shown that the developmental stage, rather than the dose, affected the type and severity of the morphological damage. Studying the effects on foetal weight and the teratogenic effects as a function of dose and time, the paper concluded that limited processes of restitution may correct in part the primary radiation-induced lesions. The second paper (153) dealt with skeletal malformations and their relations to external morphological abnormalities.

309. The third contribution (154) is of particular importance for comparing the effects of fractionated and continuous irradiation during blastogenesis, organogenesis and foetogenesis, and also during the whole period of gestation. Resorptions, intrauterine death, malformations and foetal weight were the end-points studied. The degree of effect for a given fractionated dose was compared with the effect of the same dose under continuous irradiation. The minimum dose, the 50-per-cent dose and the maximum effective dose for lethal and teratogenic actions were compared, and it was concluded that continuous exposure required 1.5 times higher doses than fractionated exposure for the same degree of effect. This factor was considered to be small compared to the ratios between the dose rates of the two exposure types ($2\ 10^3$ to $2\ 10^4$), thus confirming that the stage sensitivity of the embryo is by far the most important factor determining the final outcome of irradiation.

310. The last paper (155) examined the recovery mechanisms in the embryo by the use of the exposure-fractionation technique. Groups of mice irradiated with daily fractions (10-80 R per day) on day 1-5 p.c. or 6-13 p.c. were compared with other groups receiving a second series of doses on day 14-18 p.c. The foetuses were examined on day 18 p.c. The percentage of normal, abnormal and dead animals and their weight showed that sensitivity during the foetal period was not enhanced in the dose range studied by previous irradiation during blastogenesis. On the other hand, most parameters studied, and particularly weight loss, showed an effect of potentiation, by pre-irradiation during organogenesis.

311. Observations on mice irradiated continuously throughout gestation were also reported by Warren and Gates (358). A recent paper by Friedberg *et al.* (91) dealt with the survival of mice irradiated in the pronuclear-zygote stage with single or fractionated doses of x rays (60 rad or 30 rad + 30 rad) and fission neutrons (14 rad or 7 rad + 7 rad). The interval between the two doses was 4 hours. No significant differences were observed between the single-dose and the split-dose groups. In view of the changes in sensitivity during the fractionation interval (see also reference 299), the effect of the split doses could be interpreted assuming that the first fraction blocks the embryo from proceeding towards a less sensitive stage.

312. There are also experiments on the effects of dose rate and fractionation in other animal species. In rats, Sikov and Lofstrom (315), using the experimental schedule described in paragraphs 297-300, produced evidence of a reduction of the teratogenic action by dose protraction. Brown *et al.* (45) bred female rats under gamma radiation levels of 2-10 R per day. They found no essential difference in the litter size and in the number of offspring born in six successive litters of the mothers living in the continuous radiation field. However, at 20 R per day, the fifth litter was drastically reduced in size and the sixth litter had no offspring born. Malformations were not seen, but there was evidence of some weight reduction. Animals born from the third litter were tested for fertility and found to be normal up to 5 R per day but sterile at 10 or 20 R per day.

313. In a series of papers on morphological damage of brain structures induced by fractionated irradiation, Brizzee *et al.* (42, 134) reported the results of exposures of 13.5 and 14-day embryos singly to 150 R or to various fractionation patterns within the same half-day period. The damage to brain structures shown at 19.5 days p.c. was higher after single exposures and decreased progressively when two 75-R fractions were administered at intervals of 1, 3, 6, 9 or 12 hours. Subdivision of the dose into 2, 3, 5 or 9 equal fractions over the same time also progressively decreased the effect, which was less in these animals than in those of the previously mentioned variable-interval group. It was concluded that, for a fixed dose over a given time, the size of individual fractions is more important than the number of fractions in determining the final effect.

314. In another experiment (41) a group of embryo rats was irradiated on day 13 p.c. with single whole-body exposures of 12.5-200 R. A second group received 100 R on day 13 p.c. and, after 9 hours, a second exposure varying of 12.5-125 R. The damage to the olfactory lobes and the cerebral hemispheres, as seen on day 19 p.c., was small for the exposures between 12.5 and 87.5 R in the single irradiation groups and for exposures between 12.5 and 50 R in the split-irradiation groups. At higher exposures, the damage manifestly increased in both groups.

315. The logarithm of the mean depth of the cortical zone was plotted *versus* the radiation exposure. The plot showed a shoulder up to 62.5 R, followed by an exponential decrease to 200 R. Some shoulder (up to 50 R) was also evident in the split-dose series, which could indicate the presence of some degree of cell recovery with time between the two doses. Treatment of the animals with hypothermia to 20°C during the fractionation interval (40, 43) reversed to some extent the decreased effect of the split dose, indicating a possible inhibition of the repair processes.

316. In the experiments of Martin (184), an exposure to 160 R on day 18 p.c., at rates of 1, 3 or 47 R/min produced some effect on the pre-natal and post-natal

body weight. The amount per cell of protein and RNA in the brain were not affected consistently by the irradiation. The cerebral cortex of the irradiated animals, however, weighed less than that of controls and had a lower content of DNR, RNA and proteins, and this effect was apparently not influenced by the exposure rate. The other portions of the brain showed partial recovery of the total DNA, compared to the control value. Exposure rate had some effect, since recovery was higher in the 1-R/min group and progressively lower at higher exposure rates. After 2 months of life, the brain of the controls and of the 1-R/min group contained more DNA than those of the groups irradiated at higher exposure rates.

317. Reviewing the information on the influence of exposure rate, Brent (30) concluded that exposure rates below 5 R per day did not produce observable deleterious effects in the surviving offspring. He also reported results of experiments in which rat embryos were exposed to 150 R on day 9.5 p.c. at different rates from 0.5 to 100 R/min. These results indicated that protraction reduced the resorption and the growth retarding effects. Higher exposure rate groups had a higher incidence of malformations and were more severely malformed. Malformations like anencephaly, microcephaly, microstomia, evisceration, renal agenesis and absent pinna did not appear in animals irradiated at low rates. However, any malformation with an incidence higher than 45 per cent in the high exposure-rate groups was also seen following protracted irradiation.

318. After obtaining an exposure-effect curve (50-200 R gamma radiation) for ocular malformations in rats at 11 days p.c. to establish a suitable level for exposure-rate studies, Strange and Murphree (338) irradiated these embryos with 100 R given at 1, 2, 3.3, 5, 10, 25 and 47 R/min. Grading the ocular damage observed at 30 days of age, they showed an increase of eye abnormalities up to 3.3 R/min, a gradual but not significant further rise up to 10 R/min and a significant drop at 25 and 47 R/min below the levels observed at 3.3 and 10 R/min. The increase in susceptibility of this system with increasing rate of exposure falls within the usual pattern found in dose-rate experiments and is compatible with the commonly accepted notion that any end-effect results from competing phenomena of damage and repair, both of which are time-dependent. However, the fall at the high exposure rates is a surprising finding. The authors suggest that there may be a limited and short period of sensitivity in the life of the target cells and that the probability of hitting this sensitive stage with an effective dose might decrease at very high exposure rates. Whatever the explanation may be, these data represent further evidence that the complexities in the division and differentiation mechanisms of a developing embryo, by comparison with a more conventional cell population at equilibrium, may justify unusual findings with respect to specific end-points.

319. Continuous low-intensity gamma irradiation was given to pregnant rats at 50 R per 20-hour day, starting on the first day of pregnancy (67). Embryos, foetuses and uteri were examined at 10-20 days p.c. for growth and the presence of abnormalities. At this exposure level the total number of implants was not affected but an increase of mortality was seen at day 12 p.c., the great majority of lethal effects occurring before day 15 p.c. The pre-natal growth of the embryos was greatly delayed and many types of abnormalities, including microcephaly, anophthalmia and skeletal malformations, were also found.

320. Malformative defects of the limb possibly associated with a specific dose rate have been described in irradiated cattle, sheep and swine by Erickson and Murphree (82) and McFee *et al.* (188). Murphree and Graves (211) studied the effect of exposure and exposure rate on lambs irradiated on day 23 p.c. with ^{60}Co gamma rays. Pregnant ewes were exposed to 282 R at a rate of either 1 or 47 R/min. About 15 per cent of the ewes exposed to 1 R/min and 38 per cent of those exposed to 47 R/min died about 23 days after irradiation. The foetuses recovered from these dead animals were all smaller than normal. In the 1-R/min group, 4 ewes produced 4 deformed lambs; in the 47-R/min group, 1 ewe had twins, one of which was deformed. Of the 5 deformed lambs, 3 had ulnar aplasia and 2 aplasia of the ulnae and femora. A second series with a total exposure of 188 R was performed. Out of 28 lambs born in the 1-R/min group, 10 had deformities of the extremities, eyes and head. In contrast, only 1 out of the 29 lambs born in the 47-R/min had leg deformities.

321. In conclusion, the majority of the data available for most species indicate a decrease of the cellular and malformative effects by lowering the dose rate or by fractionating the dose. However, examples of deviations from this trend have been well documented in a few instances and are not inconsistent with the knowledge about mechanisms of the teratogenic effects. It is therefore impossible to assume that dose rate and fractionation factor have the same influence on all teratological effects.

3. The effect of oxygen

322. There has been some research on the influence of oxygen pressure on the induction by radiation of teratogenic effects in mammalian embryos. Russell *et al.* (305) (also reported in Russell (295)) showed that hypoxia resulted in substantial protection in mouse embryos exposed to 100-400 R on day 11.5 p.c. Hypoxia was induced by breathing a mixture of 5 per cent oxygen and 95 per cent helium. A number of end-points were scored at birth, such as the mean birth weight, mortality, tail length and shape and foot malformations. Irrespective of the shape of the dose-effect curves for the indicators examined, the magnitude of the protection afforded by the low oxygen pressure was approximately the same for all indicators. Oxygen seemed to act as a simple dose-modifying agent, with an oxygen-enhancement ratio of 2-3.

323. Rugh and Grupp (280) treated pregnant females (8.5 days p.c.) with a mixture of 6 per cent oxygen and 94 per cent nitrogen for 8-13 min, and then exposed these animals while still unconscious to 200 R. Non-irradiated animals kept at low oxygen pressure

served as controls. The foetuses were observed by uterine dissection on day 18.5 p.c. Anoxia alone had no effect on the embryos. Low oxygen pressure in combination with radiation resulted in 71 per cent normal embryos, while the same dose at normal oxygen pressure would yield only 41 per cent normal embryos. Resorbed embryos and exencephaly in foetuses, after irradiation in hypoxia, was recorded as 16 and 13 per cent against 34 and 21 per cent in the corresponding controls. Therefore anoxia produced some degree of protection against both lethal and teratogenic damage. Since there are insufficient data to draw a dose-effect curve, the numerical factor to be attached to this protective action cannot be evaluated with precision.

324. Uterine vascular clamping (35) is an alternative procedure for producing anoxia of the embryo. When this technique was applied to one uterine horn of the rat for 45 min on day 8 or 9 p.c., it had minimal detrimental effect on foetal growth and survival. This technique has been shown to protect against radiation-induced lethality and weight loss (36). Another method of producing hypoxia indirectly, by inducing hypoglycemia with insulin, was found to be totally ineffective in the mouse (280).

325. It may be concluded that the oxygen effect in the embryo is similar to that observed in the irradiation of other cellular systems of the adult animal.

4. Radioprotective and radiosensitizing drugs

326. There are numerous reports on the effect of radioprotective drugs upon the induction of embryonic and foetal damage by radiation. The protective effect of cysteinamine (269) and cysteamine (369) had been shown in irradiated foetal mice with respect to survival, growth rate, weight and induction of malformation. Rugh and Grupp (280) examined the effect of these substances on CF1 embryos exposed to 200 R on day 8.5 p.c. When 3 mg of cysteinamine were administered IP 30 min prior to exposure, the incidence of normal foetuses increased from the expected 41 per cent to 73 per cent, resorption decreased from 34 per cent to 8 per cent and exencephaly incidence decreased from 21 per cent to 16 per cent. In the case of cysteamine (3 mg IP withing 30 min of exposure) the shifts were: normal animals, from 41 per cent to 80 per cent; resorptions, from 34 per cent to 12 per cent; and exencephaly, from 21 per cent to 8 per cent. These two drugs therefore appeared to act beneficially, increasing survival and reducing the incidence of malformations in the irradiated embryo. However, these experiments with a single dose of radiation do not allow the derivation of good estimates of the protection factor. AET did not counteract the radiation effects.

327. Numerous other treatments (hypotonic and hypertonic solutions, dextrose, alcohol, chlorpromazine, and homogenates of spleen, marrow and liver) tested for possible action in the same experiments (280) were also found ineffective. Konermann (156) reported complete dose-exposure curves, in the range 150-450 R delivered in single irradiations at 3, 6, 9, 12 and 15 days p.c., with and without cysteinamine (a single amount of 200 mg/kg given 8 min prior to irradiation). The end-points, checked by uterine dissection on day 19 p.c., were morphologically normal and abnormal animals, malformed and dead foetuses, frequency of embryonic deaths, foetal and placental weight, and skeletal malformations. Marked differences were observed in the relative protective effect of the drug for various radiation doses and various stages irradiated. Protection was shown to exist both in the pre-implantation and in the organogenesis period, and the value of the protection factor was different for different malformations.

328. In the rat, Starkie (331) reported a partial inhibition by cysteamine of the radiation effects on the testis. Animals were irradiated at 17 and 21 days p.c. with doses of 50-150 rad and the testes examined histologically at the age of 25 days. Kalinina (140) tested the effects of a number of possible radioprotective substances, such as phenatine, magnesium sulphate, chlorpromazine and mercaptamine, injected in appropriate doses 15-20 min before irradiation (200-300 R on day 11 p.c.). Embryo and placental weight, mortality and malformations were scored on day 22 p.c. The mortality rate, and to some extent the incidence of malformations, were lower in the injected groups.

329. Baev *et al.* (9) tested the protective effect of cysteinamine and cysteamine in the case of fractional exposure to radiation throughout gestation (40 R per day for 20 days). The irradiated offspring were followed to adulthood, and the changes in litter size, post-natal death and body weight were noted. While protection was afforded by both drugs in regard to litter size and weight, the post-natal death rate was unchanged. Twenty females and 24 male offspring surviving after drug treatment and tested when sexually mature (10) showed greatly reduced reproductive performance, sterility and increased frequency of dominant lethal mutations. A protective effect of cysteinamine, most pronounced after completion of organogenesis, was also described by Kirushenkov (151). Treatments of pregnant females with proteolytic enzymes (348) or with progesterone (353) were also reported to act beneficially in protecting the foetus from radiation-induced malformations. In contrast to that result, small doses of iodacetamide (194) and miracil D (193) were shown to act synergistically in potentiating the teratogenic action of radiation.

330. It may be concluded that many of the known radioprotective drugs which are active in modifying the radiation response of adult systems are also effective against the damage caused by irradiation *in utero*. In the latter case there is evidence that the protection factor may vary according to the stage irradiated and to the particular type of damage analysed (lethality, growth disturbance and type of malformation).

F. SIGNIFICANCE OF THE EXPERIMENTAL DATA TO MAN

331. The majority of authors who have contributed experimental information on teratogenic effects of radiation have considered, directly or implicitly, the

applicability of their findings to the human species. A number of papers have also specifically dealt with this subject (see for example 295, 297, 301, 304, 261, 265, 268, 27, 136, and 345). The following paragraphs discuss the opinions expressed by the authors and summarize the views of the Committee regarding present knowledge and the need for future research in radiation teratogenesis.

332. It is clear from all the preceding sections that for teratogenesis, more than for any other early or late somatic effects of radiation, data on humans are extremely limited. Apart from growth disturbances, microcephaly, mental retardation and a few other defects of less importance, there are very few systematic data applicable to man, particularly at the low doses of interest. However, the scanty data available for other abnormalities are probably sufficient to permit the assumption that the effects observed in animal experiments also occur in man. The animal experience therefore appears to be of unique and special importance for the assessment, even if only qualitative, of malformative effects in man.

333. Animal research has established two important qualitative facts: *(a)* there is a uniform pattern in the sequence and timing of the early developmental stages in the mammalian species tested (see chapters I-III); and *(b)* there is a general similarity among the various species with regard to the type of malformations induced and the teratogenic mechanisms (see chapters III-VI). However, these facts are in themselves insufficient to justify any direct quantitative extrapolation of effects between species for a number of reasons: *(a)* the great specificity of the malformations induced at comparable stages in different species and even among different strains of the same species (see chapter II); *(b)* the species difference in the duration of the foetal period (see table 3), which causes marked discrepancies in the final state of the malformations and causes serious obstacles in comparative studies between animals and man as, for example, with the central nervous system (141); *(c)* the extremely variable form of the dose-effect relationships in different species (see chapter III).

334. For all the above reasons there is general consensus (304, 136, 267, 268, 344 and 345) that data applicable to man can only be derived from human epidemiological studies. These studies are, however, not available at present, at least on the scale required and at the low doses of interest. The Committee believes that this point should be particularly emphasized so as to discourage numerical extrapolations not sufficiently justified by present knowledge.

VII. SUMMARY AND CONCLUSIONS

A. GENERAL

335. Scientific contributions concerning the somatic effects on experimental animals irradiated *in utero* have been reviewed with the aim of extracting information relevant to the assessment of similar effects in man. Data on embryological effects in the human have also been reconsidered and updated. In addition to lethal effects, effects on growth and development, and miscellaneous pathological consequences of the exposure, malformations have been particularly examined as typical sequelae of irradiation *in utero*. The amount of data directly or indirectly related to this subject is indeed rather large, but most of it has been produced with the ultimate object of analysing developmental mechanisms. Thus, the quantitative information to be gained on the main radiobiological variables (dose, dose rate, fractionation, LET etc.) is definitely insufficient, particularly in regard to the human embryo. The Committee emphasizes, however, that appropriate evaluation of whatever data is available may help to set the scanty knowledge on man into a better perspective. It may also strengthen the qualitative extrapolation of effects between species, pending the quantitative assessment of radiological hazards which must of necessity be carried out in man.

B. METHODOLOGY AND TECHNIQUES

336. Among the variables or conditions affecting the induction of embryological effects in mammals, the genetic constitution, the breeding characteristics of the species and the reproductive history of the mother have been shown to influence the degree of the lethal and teratogenic responses of the conceptus; other variables have a relatively minor but not trivial importance. There are well defined periods of maximum sensitivity during gestation for the induction of different types of malformations; these periods are related to the stage of major differentiation of the relevant embryonic structures. It is possible to reconstruct developmental tables in animals and man to compare the approximate critical times for the occurrence of certain recognizable ontogenic events and to facilitate rough intercomparisons of pregnancy stage and of embryonic differentiation. In animals, a number of variables affecting the scoring of lethal, developmental and malformative effects have been recognized, and their importance for correct radiobiological assessments has been discussed. Regarding the human experience, insufficient knowledge of the conception time, lack of precise dose estimates, paucity of irradiated groups and difficulties in the selection of control groups prevent any precise estimate of hazard. Following an analysis of the main periods of pre-natal development in various mammals, a systematic review of embryological effects is provided.

C. THE PRE-IMPLANTATION PERIOD

337. Killing of the embryo prior to implantation stands out during this period as the most conspicuous effect of irradiation, which may be expressed in polytocous animals as death of single embryos or death of the entire litter. Post-implantation and post-natal death are regarded as relatively less important hazards of the exposure during the pre-implantation stages. In addition to considerable differences in sensitivity between animal species, there have been described substantial changes in the susceptibility to this type of damage within each species, particularly during the early segmentation of the fertilized egg. In the mouse, the species where the most

data have been obtained, a number of reports point out, in good agreement, that the absolute increment of embryonic loss soon after fertilization could be of the order of 10^{-2} R^{-1}. Chromosomal damage to the irradiated blastomeres followed by degeneration of the primitive embryo cells appears to be the major mechanism responsible for embryonic death. During this stage, the reduction of body growth is not an effect clearly and universally recognized. The malformations documented, particularly in the nervous system of the rodent, may also be regarded as less frequent events, in comparison with their higher frequency during the following stage of organogenesis.

D. THE PERIOD OF MAJOR ORGANOGENESIS

338. Lethal effects during this period may be studied through several indicators, such as the complete failure of pregnancy, the decrease of the average litter size, the mortality *in utero* of the irradiated embryo and the neo-natal and long-term survival of the live-born animals. Concerning pre-natal mortality, the sensitivity of the embryo is highest soon after implantation and during early organogenesis, with a subsequent decrease at later times. The shape of the exposure-lethality function appears to change substantially with the developmental stage, and the majority of data point to curvilinear functions. There is some information on the effective doses, particularly in rodent species, in regard to pre- and neo-natal death. They have shown LD_{50} values lower than 150 R at the pre-implantation and early organogenesis stages, after which these values invariably increase to attain during the foetal stages levels comparable to the post-natal LD_{50}. Long-term reduction of life span may also be documented in rodents for exposures of a few hundred roentgens; these effects strongly depend on a number of genetic factors. Information in man is virtually absent.

339. Data obtained from several animal species indicate that the period of major organogenesis is very sensitive to growth disturbances, probably more than the following foetal period but definitely more than the preceding pre-implantation phase. When growth defects are scored prior to birth, the magnitude of the growth deficit appears to vary with the interval between irradiation and observation. Only in very few cases are there sufficient data to evaluate the net effect of the dose after a fixed post-irradiation time or at the time of maximum effect. Growth disturbances induced by irradiation of the embryo but persisting in adult life and expressed at the whole-body or organ level have also been described in the experimental animal.

340. In spite of the great wealth of information on malformations induced during organogenesis in various animals, it appears extremely difficult to summarize these data into any coherent quantitative conclusion for the following reasons: the species and strain variability; the scarcity of complete dose-effect series; the different criteria of scoring the induced aberrations; and the different embryological and physical conditions under which irradiation has been performed. A few general statements may however be justified:

(a) With due regard to developmental and anatomical differences between species, similar classes and types of malformations occur upon irradiation at comparable developmental ages. This finding is sufficiently general to suggest that man might not represent an exception in this respect, even though no quantitative comparisons between experimental animals and human species would be warranted at present;

(b) Within each species there is a well defined time at which each malformation may be induced. Increasing the dose usually results in a spread of the sensitivity peak and in an increase of the malformation incidence. In some cases, biphasic periods of sensitivity are observed, related presumably to different mechanisms of induction resulting in similar malformative end-points;

(c) The time specificity of each malformation usually coincides with the major phase of differentiation and organization of the relevant structure. Cell killing followed by an arrest of organ development at some rudimentary stage may be identified as the mechanism initially responsible for the malformative event;

(d) Data are too few and their variability too high to allow any firm conclusion about the relative radiation susceptibility of different embryological structures within each species and, even less, between various mammals, but malformative responses have in a few cases been described down to exposures of 5 R;

(e) In the vast majority of cases the malformation incidence has a curvilinear trend with dose, implying relatively less effect per unit dose at low than at high doses. However, linear or quasi-linear dose-effect relationships are not uncommon, particularly when embryologically or topographically related malformations are grouped together in such a way to express the malforming effects as the ratio of malformed to normal animals, irrespective of which type or number of malformations might affect the malformed conceptuses. Such cases have been documented only in animals; it is conceivable that in the case of animals absolute increases in the incidence of malformed foetuses of the order of 5 10^{-3} R^{-1} of low-LET radiation delivered at high dose rates might occur. It should however be emphasized that such estimates are very tentative and their projection to other species and particularly to man is unwarranted;

(f) In man the best documented type of malformation is microcephaly, which in its most extreme cases is accompanied by mental retardation. Following high acute doses its incidence has been tentatively estimated at around 10^{-3} rad^{-1}, with the lowest effective doses ranging between 10 and 150 rads under different conditions of exposure;

(g) Other epidemiological surveys in man following doses in the region of 1-20 rad have given either negative or non-significant answers; they could only be of some value in excluding the possibility that at these doses the human embryo could be 10 times more sensitive than the incidence of malformations at higher doses would imply.

341. Among other miscellaneous effects of irradiation during embryogenesis, changes in fertility and fecundity, cataract, and relatively minor defects have also been studied in animals.

E. THE FOETAL PERIOD

342. Lethal effects have been described in the rodent for irradiation during this period. Although limited to selected ages, these data show consistently a reduction of sensitivity with advancement of foetal age. There is also some information in man obtained in cases of radiation-induced therapeutic abortion and, with some dosimetric uncertainties, following the A-bomb explosions in Japan. This information refers to both pre- and post-natal radiation lethality and to long-term effects on survival.

343. Generalized and local growth disturbances are commonly described effects of irradiation of the foetus, and they are seen in many cases to persist throughout the extra-uterine life. In man numerous studies agree in pointing out a growth-retarding effect of irradiation manifested by a reduction of various body parameters, in addition to microcephaly and mental retardation.

344. It is commonly accepted that as foetogenesis proceeds the malformative effects of radiation become more difficult to document macroscopically since, for the same radiation dose, the size of the anatomical structures involved becomes progressively smaller and the resulting functional defects less important. It should however be expected that these subtle malformations, rather than the major defects induced at organogenesis, would be the ones more likely to survive and to result in the main social burden. Data in animals relate particularly to effects on the eye, the nervous system and the gonads. In man, besides microcephaly, heterochromia of the iris has also been described.

345. Other pathological effects on the foetus regard the haemopoietic system at the bone-marrow and peripheral level; haemopoietic failure at this stage is closely related to the whole-body lethal effect. Laboratory investigations carried out on samples of children and adolescents irradiated *in utero* have shown a good capacity for recovery of whatever haematological damage might have been induced soon after exposure. The question of a possible alteration of the sex ratio of children born to parents exposed *in utero* is still controversial.

F. INTERNAL IRRADIATION

346. The interpretation and evaluation of the developmental effects of irradiation *in utero* by incorporated radionuclides must be based on a precise knowledge of doses received at specified dose rates by the mother and the conceptus at any given developmental stage and in any sensitive structure under various conditions of treatment. The information available falls far short of this objective. The effects observed are similar to those described for external irradiation; they are, however, less specific owing to the fact that exposure to the nuclides usually extends throughout embryonic and foetal stages. Among the main variables known to interact in the production of these effects, the following have been identified: the physical nature of the nuclide and the chemical form in which it is administered, the route and schedule of administration, the dose, the developmental age at irradiation, the animal species, and the possible role of the irradiated maternal organism.

G. MECHANISMS OF RADIATION TERATOGENESIS

347. Most of the data support the contention that indirect effects of the mother's irradiation do not play a major role in the induction of malformations, particularly at the low doses of interest for radiation protection. On the other hand, it is conceivable that high doses given to the mother might also influence the mortality of the embryo and foetus.

348. Malformations are typical sequelae of damage inflicted by radiation on a developing organism. They are produced through a disturbance or disruption of the orderly sequence of ontogenic events that result in a developed foetus. At the subcellular level it appears quite unlikely, even in the absence of much direct information, that the primary biophysical events taking place in embryonic tissues may grossly differ from those occurring in adult tissues. At the cellular level chromosomal aberrations are thought to be responsible for the loss of reproductive capacity of the irradiated embryonic tissues. This notion is in agreement with what is observed in adult tissues and has been substantiated for many embryological structures as well. Selectivity of the damage with respect to different tissues which are seen to respond at different times is postulated to depend on changes in the intrinsic radiosensitivity of cells, on the variable kinetic parameters of the different embryonal tissues and on the capacity for repair and repopulation of each tissue. Radiation damage to regulatory mechanisms could also be regarded as a component of the teratological damage, but up to the present all these processes have only been considered theoretically and have never been experimentally documented. Simple mathematical models for the development of malformative damage have also been proposed and they are not incompatible with the observed dose-effect relationships. The analysis of such relationships in order to gain a better knowledge of mechanisms would however be unwarranted in the absence of further experimental evidence.

349. Regarding the possible existence of thresholds in dose-effect relationships there is consistent evidence showing that doses as low as 5 rad may still be effective in inducing selected malformations. Direct experimental tests of the absence of thresholds in this dose region would tend to exclude their existence at even lower doses. Theoretically, the possibility does exist that thresholds might occur at even lower doses, but experiments of sufficient precision to reveal them would be technically difficult or even impossible for statistical reasons.

350. Data on the effect of radiation quality and energy in respect to teratogenic damage are extremely rare and definitely insufficient for a more than speculative knowledge of the relevant RBE factors. Within these limitations it appears, however, that present information is not incompatible with the notion that higher RBE

factors might apply to the more densely ionizing radiations and to the case of dose protraction. More refined information on RBE factors relating to different malformations is absent.

351. Data in many species would indicate some decrease of the malformative effects induced at low dose rates or with dose fractionation. However, the nature of the embryonic material is such that under special conditions a potentiation, rather than a reduction, of effect might be possible; a few examples of such effects have indeed been found. In any case, it seems impossible to assume that the same reduction factors for low dose rate or fractionation might apply to all effects induced by radiation in embryonic tissues.

352. Anoxia and treatment with radiosensitizing and radioprotective drugs have been shown consistently to act as modifiers of the damage to the embryo in the same sense and by about the same factors as for adult tissues. The protection afforded is variable and depends on the age of the embryo and the type of damage observed.

H. RESEARCH NEEDS

353. The qualitative value of animal experimentation for the assessment of human effects in no way limits its usefulness, particularly in view of the lack of precise information for many types of teratogenic effects in man. The Committee has identified several fields where further information would be highly desirable. The fields, which relate to both human observations and animal experimentation, are as follows:

(a) Studies of stochastic[2] *versus* non-stochastic effects occurring in the embryo and foetus at various stages of development would appear to be of great value for their implications on risk assessments in man. These studies would imply the ascertainment of some cellular parameters which have been postulated in some models (see paragraphs 284-287) but have never been determined experimentally;

(b) Too little is known about whether, and to what degree, the mechanisms and kinetics of inactivation, recovery and repair of adult somatic cells and tissues apply also to embryonic and foetal systems (see chapter VI, section B). A better understanding of the primary effects might also be of help in developing more refined models of teratogenic damage, reflecting the effects of the main radiobiological variables (dose, dose rate, LET, fractionation etc.). For example, the concepts of microdosimetry (146) have so far not been extended to damage *in utero*, and such an approach in this field (see chapter VI, section C) might lead to a re-evaluation of old data or to the design of new and more precise experiments;

(c) The study of pathogenetic mechanisms and development patterns of malformations are thought by some (267) to be of little value at present, while actions in the fields of etiology and prevention are advocated as the future major steps. This opinion could be supported in regard to accumulating further descriptive work on malformations. However, the Committee believes that extensive data on specific malformations as a function of dose (and particularly at low doses) and in several animal species would be highly desirable and would considerably increase our confidence in interpreting the estimates in man (136);

(d) In planning and performing such experiments, the co-operation of radiobiologists and embryologists is essential to ensure that such large and costly undertakings would eventually be of value for human assessments. In addition to the technical points underlined in chapter I, the selection of relevant end-points for experimentation should reflect the fact that relatively minor morphological and functional defects in man may be more important than extensive malformations which would in most cases be incompatible with extra-uterine life;

(e) One area where data are extremely scarce is the influence of radiation quality on malformation induction (see chapter VI, section D.1). More systematic experiments, especially at low neutron doses, should be performed with various LET spectra and at different stages of embryonic development to accumulate more precise data on the RBE values for different types of malformations, which at present are only largely estimated on the bases of inferential evidence (256);

(f) Effects with dose fractionation and low dose rate also deserve better attention, in view of the possibility that special régimes of fractionation or particular dose rates may be more harmful than single acute doses (see chapter VI, section D.2);

(g) Internal irradiation by various nuclides has only been episodically explored. It will be necessary to extend present experience to the potentially most hazardous and important nuclides with studies of uptake, distribution, clearance, dosimetry and effects on both the mother and the foetus;

(h) There should be more surveys to evaluate the type and frequency of x-ray examinations of the lower abdomen of pregnant women and the resulting doses to embryos (see Annex I). Such data have already been obtained in some cases (44, 359, 361), but they should be extended to different socio-economic and medical situations in order to obtain representative estimates of the risks involved;

(i) Finally, no occasion should be lost for accumulating data on irradiated human populations; only on the basis of such data are refined risk estimates possible. It is essential, therefore, to continue the study of the irradiated populations already surveyed. Epidemiological surveys on other population groups yet to be identified will also be required to improve the present incomplete knowledge, at least to the point of excluding the possibility that exposures might be more hazardous to man than to experimental animals.

[2] In the present context the terms "stochastic" and "non-stochastic" are used as defined for the purpose in question by the International Commission on Radiological Protection: "stochastic effects are those for which the probability of an effect occurring, rather than its severity, is regarded as a function of dose, without threshold. 'Non-stochastic' effects are those for which the severity of the effect varies with the dose, and for which a threshold may therefore occur" (129a).

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