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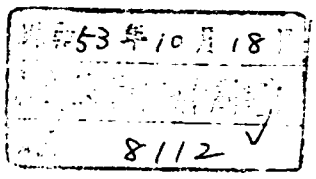
United Nations Scientific Committee
on the Effects of Atomic Radiation

1977 report to the General Assembly, with annexes



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ANNEX G

Radiation carcinogenesis in man

CONTENTS

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(H) and P(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

$56\ (51\text{-}61)10^{-6}\ \text{rad}^{-1}$ in Hiroshima,
$35\ (29\text{-}41)10^{-6}\ \text{rad}^{-1}$ in Nagasaki, and
$46\ (42\text{-}50)10^{-6}\ \text{rad}^{-1}$ 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 $1.22\ (0.25\text{-}2.8)10^{-6}\ \text{rad}^{-1}\ \text{y}^{-1}$. 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 $17\ (3\text{-}36)10^{-6}\ \text{rad}^{-1}$ at this dose level.

79. The 7 cases of leukaemia (2.33 expected) were diagnosed at 11.0 (± 2.1 SE) years after exposure and death occurred at 11.6 (± 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 $P = 0.05$).

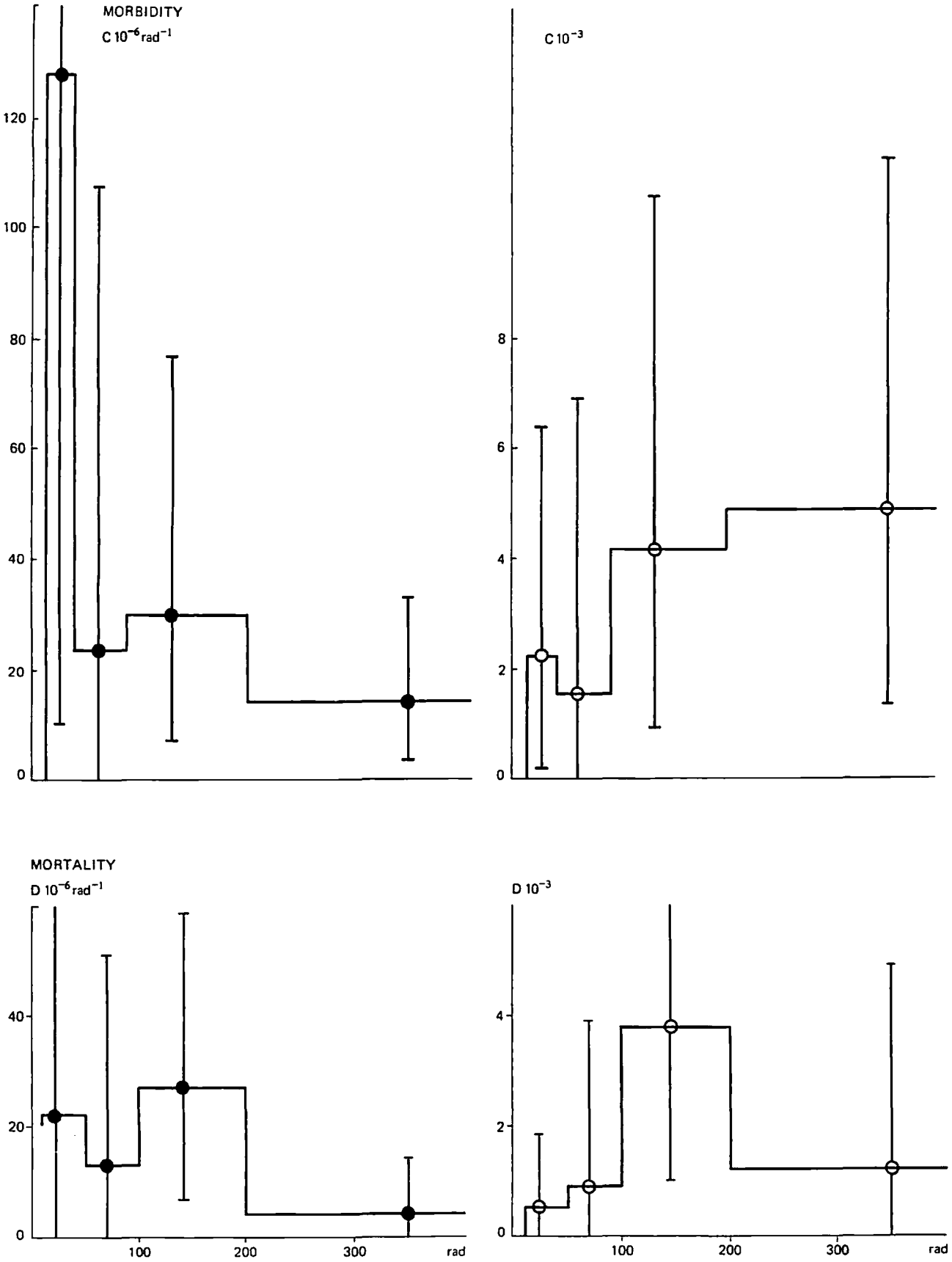

Figure I. Variation of breast cancer induction rate with T65 kerma (Hiroshima and Nagasaki, females, all ages, periods as in Table 12)

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.

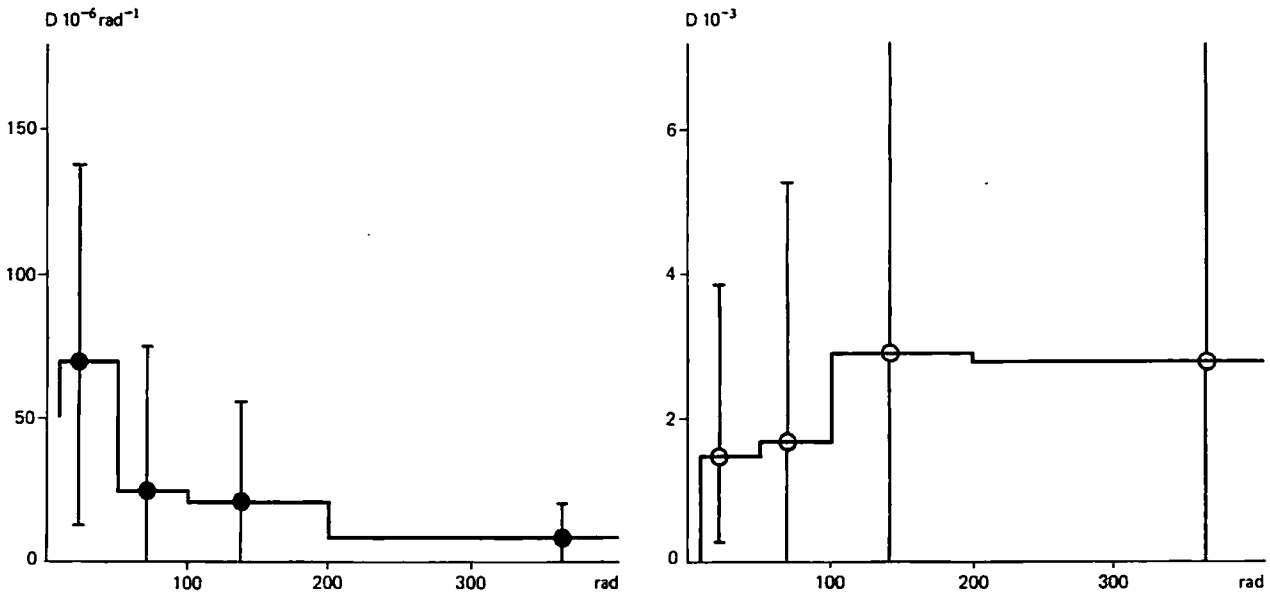

Figure II. Variation of lung cancer induction rate in Hiroshima with T65 kerma

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.

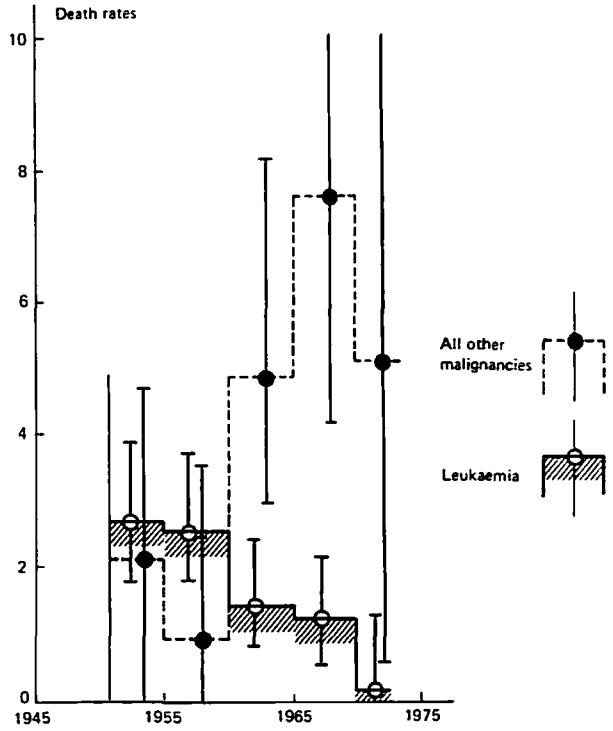

Figure III. Variation of death rates from leukaemia and from all other malignancies with time since exposure

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

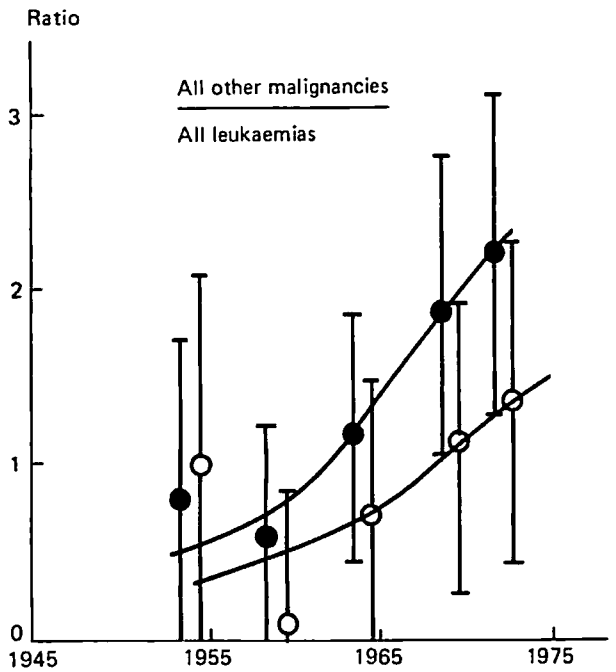

Figure IV. Ratio of numbers of deaths from all other malignancies other than leukaemia to those from leukaemia

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 $(25\text{-}50)\ 10^{-6}$ 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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