SOURCES AND EFFECTS OF IONIZING RADIATION

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NOTE

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ANNEX I

Epidemiological evaluation of radiation-induced cancer

CONTENTS

INTRODUCTION

1. Epidemiological studies of the cancer risks associated with both external and internal exposure to ionizing radiation were the subject of an extensive review in the UNSCEAR 1994 Report [U2]. Covered in that review were studies of cancer mortality and incidence up to 1987 among the survivors of the atomic bombings at Hiroshima and Nagasaki, who received a single dose of radiation; patients exposed to radiation for diagnostic or therapeutic purposes, usually as multiple doses; and radiation workers and individuals exposed chronically to environmental radiation. Estimates of risks observed in the major epidemiological studies of external low linear energy transfer (low-LET) exposures were presented in a common format. Data from the Life Span Study of survivors of the atomic bombings, in particular, were used to estimate the lifetime risk of total cancer mortality following external exposure to low-LET radiation [U2]. Lifetime risks for specific cancer sites were also estimated, based on a Japanese population.

2. Information from follow-up through the end of 1990 of mortality among the survivors of the atomic bombings has recently been published [P9]. The extended period of follow-up was not very informative for survivors over 40 years old at the time of the bombings, since many of these people had already died. On the other hand, the data for survivors exposed at younger ages, particularly in childhood, are highly valuable, because these people have only recently reached the ages at which baseline rates for most solid tumours begin to increase sharply. Methods used in the UNSCEAR 1994 Report [U2] to project risks beyond the period of follow-up assume that the relative risks for solid tumours either remain constant throughout life (following a minimum latency period) or decrease at long times following exposure. It was shown that lifetime risk estimates based on the latter approach were 20%–40% lower than estimates based on the former [U2]. This difference was larger for those exposed at young ages. Further follow-up of this group is needed to reduce the uncertainties in lifetime risk projections.

3. Although the Life Span Study of survivors of the atomic bombings is the single most informative study on the effects of low-LET exposure of humans, a considerable amount of data is available from many other epidemiological studies. For example, studies of people with partial-body exposures, such as those from medical examinations or treatments, provide valuable information on risks for specific cancers. Despite the extensive knowledge of radiation risks gained through epidemiological investigations, much still remains to be learned. For example, the effects of chronic low-level exposures and internal exposures are not well described. Further data are being obtained through updates of individual studies and parallel analyses for sites such as breast and thyroid. Information is also becoming available from *inter alia* further studies of occupational exposures, including workers at the Mayak nuclear facility in the Russian Federation and from past radiological events in the former Soviet Union, such as at Chernobyl and around the Techa River.

4. In addition to individuals exposed to low-LET radiation, various groups with exposure to high-LET radiation have been studied. Some of these exposures have arisen in occupational settings (e.g. radon in mines, radium in dial painting, or plutonium in some nuclear facilities), some from medical interventions (e.g. injections with ^{224}Ra or thorotrast), and some environmentally (e.g. radon in homes). Combined analyses of existing data, as well as several studies of residential radon that are in progress, should provide additional information on the risks of high-LET radiation. A review of these data in a format similar to that for low-LET radiation may be helpful in comparing risks.

5. The mortality follow-up of the survivors of the atomic bombings yields little data on cancers that are usually non-fatal. However, comprehensive cancer incidence data are now available for the survivors of the atomic bombings in Japan [T1], and comparisons between the two types of endpoint have been reported [R1]. Data on cancer incidence from this and other studies will assume greater importance as the treatment of cancers improves.

6. While there is a need for estimates of the total risks of cancer mortality and incidence arising from radiation exposure, there are also situations in which risk estimates for specific cancer sites are of particular value. These include (a) evaluating the effects of partial-body irradiation arising either from external exposure or from internal exposure to radionuclides and (b) estimating the probability that a prior radiation exposure led to the development of cancer in an individual, i.e. the probability of causation [I12, N1]. Epidemiological studies carried out in countries with differing baseline rates for certain cancer sites may also assist in determining how to transfer radiation-induced risks from one population to another. This is an important topic in view of the differences in baseline rates for cancers such as breast, lung, and stomach between Japan and many other countries. Depending on the form of the model used to transfer radiation risks derived from data on the Japanese atomic bomb survivors to other populations, quite different estimates of radiation-induced cancer risks can arise for such sites [L12]. It was concluded in the UNSCEAR 1994 Report [U2] that the epidemiological data available at that time provided no clear indication of how to transfer risks. Ongoing and future studies of genetic (host) susceptibility and interactions with other carcinogens have the potential to both increase knowledge and provide new information on radiation risks.

7. The UNSCEAR 1994 Report [U2] contained a comparison of risk estimates for specific cancer types derived from various epidemiological studies. The aim of this Annex is to provide a more detailed comparison of site-specific cancer risks. It incorporates more recent data, including the updated mortality follow-up for the survivors of the atomic bombings and additional analyses of cancer incidence data for this group. The methodology and findings for this and other studies are described and compared. The potential for bias or confounding, the impact of errors in dosimetry, and other sources of uncertainty are discussed. Among the general considerations addressed are the advantages or limitations of the various types of epidemiological studies, statistical power, the influence of factors that modify radiation-induced risks, and the approach to be taken in examining risks. This approach is applied to data for specific cancer sites, namely oesophagus, stomach, colon, liver, lung, bone and connective tissue, skin, female breast cancer, prostate, bladder cancer, brain and central nervous system tumours, thyroid cancer, non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, and leukaemia. Risk estimates for all cancers combined are then derived, although it should be recognized that cancer is a heterogeneous group of diseases.

I. FEATURES OF EPIDEMIOLOGICAL STUDIES

8. Epidemiology is the study of the distribution and determinants of disease in humans [M10]. One of the key facets of epidemiology is that it is observational rather than experimental in nature. In contrast to randomized clinical trials, there is the possibility that bias or confounding associated with the design and conduct of an epidemiological study may give rise to spurious results. Another difficulty, which may also arise in randomized trials, is the possibility that low statistical power can hinder the ability to detect, or to quantify with precision, an elevated risk. Bias, confounding, and statistical power are discussed in more detail below. It should be emphasized that not all epidemiological studies are equally informative or of equal quality. Some have such low statistical power that they provide very little information on risks; others are so susceptible to potential or actual biases that the findings have little or no validity. It, therefore, is important to consider such methodological issues when interpreting the evidence from different studies.

9. Epidemiological investigations of radiation effects are usually constructed around either a cohort study or a case-control study. In a cohort study, a defined population (preferably with a wide range of exposures) is followed forward in time to examine the occurrence of effects. Such a study may be performed either prospectively (i.e. by following a current cohort into the future) or retrospectively (i.e. by constructing a cohort of persons alive at some time in the past and following it forward, possibly to the current time). In a case-control study, people with and without a specified disease (the cases and controls, respectively) are compared to examine differences in exposures. Some case-control studies are nested within a cohort study, in that the cases and controls are selected from the cohort. The nested case-control study design is often used when it is difficult to obtain estimates of radiation dose or other exposures for all members of a cohort, but possible to collect them for a smaller number of individuals. For example, in an international study of patients treated for cervical cancer, radiation doses were estimated for patients with various types of second cancer, as well as for matched control patients [B1]. An alternative approach is to collect detailed information for cancer cases plus a random sample of the original cohort. The case-cohort study design [P1], which was utilized in an early analysis of cervical cancer patients [H1], is useful when studying the occurrence of several different types of cancer.

10. Cohort-based studies, particularly those performed prospectively, tend to be less susceptible to biases than case-

control studies, which depend on the retrospective collection of data [B18]. Case-control studies can be informative about risks, but particular attention needs to be paid to the potential for biases associated with the fact that the studies are retrospective. Because randomized controlled trials employ an experimental method, they are less susceptible to bias and have fewer methodological limitations than either cohort or case-control studies. However, only a few randomized trials of the effects of radiotherapy in treating cancer have provided information on radiation risks (e.g. [F3]). At the other extreme, results from correlation studies (studies based on data aggregated over, for example, geographical regions) are often unreliable. As will be described later, such studies, which are sometimes referred to as "ecological studies", have high potential for bias, owing to the lack of data on individual exposures and confounders. Therefore cohort-based and case-control studies that contain data at the individual level form the main bases for estimating radiation risks in humans.

11. To be able to draw substantive inferences from epidemiological studies, it is important to ensure that the potential for bias or confounding is as low as possible and that the statistical precision of the results is reasonably high. In low-dose studies, methodological issues become particularly important, because even a small degree of bias or confounding can distort study results substantially. In spite of the difficulties that can arise in designing and performing epidemiological studies, epidemiology does have the advantage over molecular, cellular and laboratory animal studies of providing direct information on health risks in human populations.

A. BIAS AND CONFOUNDING

12. Bias can be defined as any process at any stage of inference that tends to produce results or conclusions that differ systematically from the truth [S10]. Although it is possible to address issues such as lack of statistical power or random errors in dose estimates through statistical approaches, described later, bias in an epidemiological study can render its findings meaningless. Bias can arise in a number of ways. One potential source of bias is the failure to obtain follow-up data for all but a very small proportion of the people in a cohort study. Those lost to follow-up are often more likely to have migrated or died than other members of the cohort. If they cannot be identified, they will continue to contribute person-years (PY) to the study beyond the period during which any cancer that had developed (incident or fatal, depending on the type of study) would have been recorded. Thus they will appear, incorrectly, to be immortal. Even if those lost to follow-up can be identified, specifying the date on which they should be withdrawn from the study is not always straightforward. For example, in commenting on a study of second cancers after treatment for Hodgkin's disease in childhood [B16], Donaldson and Hancock [D25] pointed out that in this and other hospital-based studies, patients who develop a second cancer would be more likely to return to the hospital or clinic than patients free of the disease. If the end of follow-up is taken as the date last seen at the hospital, then many of the disease-free patients may be withdrawn from the study at an early time even though, had they later developed the disease, the follow-up would have been longer. Thus, hospital-based studies are susceptible to the possibility of differential follow-up, which may lead to an overestimation of disease rates.

13. It is also important that the completeness of the follow-up data be uniform and not vary according to the level of exposure. This is a particular concern for diseases that are not immediately apparent, such as thyroid tumours without apparent symptoms. Increased levels of screening in a radiation-exposed population may show a raised disease incidence relative to an unscreened group. Ideally, comparisons would be made between groups with a similar level of screening, as, for example, in a study of irradiation for lymphoid hyperplasia [P8] in which both the exposed and comparison groups were screened. If, however, the level of screening was correlated with dose, examination of any dose-response relationship would be biased.

14. The issue of differential disease ascertainment can also be important in some occupational studies. If occupational groups have better medical care than the general population, the cause of death for certain diseases (e.g. multiple myeloma and brain cancer) may be determined with greater accuracy in these groups. This could lead to spurious findings if comparison is made with the general population. For example, an apparent excess of brain tumours among a group of workers with potential chemical exposure may have been due to more detailed screening for the disease [G21]. However, this type of problem may be alleviated if disease rates within occupational groups can be compared. As an example in the context of radiation, Ivanov et al. [I13] reported a statistically significant elevated risk of leukaemia incidence among Chernobyl recovery operation workers when compared with risks for the general population. However, the workers received frequent medical examinations, and so the accuracy and completeness of the leukaemia diagnoses are likely to differ from those for the general population [B27]. Indications that differences in the ascertainment of leukaemia may have affected these findings came from a case-control study nested within the cohort of recovery operation workers [I14]. In contrast to the difference in leukaemia rates between these workers and the general population, no correlation between leukaemia risk and either radiation dose or other aspects of their work around Chernobyl was found within the cohort. It is likely that bias arose in the cohort analysis, in part because of the over-ascertainment and misdiagnosis of some leukaemias among the recovery operation workers and under-reporting of leukaemia diagnoses in the general population used for comparison [B27].

15. The problem of differential disease ascertainment is not restricted to occupational studies. An example is given in Section IV.B.2 of how the recording of cancer on death certificates for the Japanese atomic bomb survivors may have been affected by the knowledge that the person was a survivor [P9]. Even though this type of bias might be small in absolute terms, it could have a particular impact when the risks of

cancer mortality at low doses are being estimated [P9]. The data on cancer incidence for the survivors of the atomic bombings, by contrast, are less susceptible to this type of bias because of the more objective means of ascertaining cancer.

16. Another issue of importance when comparing occupational groups with the general population is the healthy worker effect, whereby individuals selected for employment tend to have better health than the population as a whole [F4]. The healthy worker effect may be intensified because the workers who continue to be employed are healthy individuals and they receive better medical care. As an example of this effect, Carpenter et al. [C19] reported that mortality rates for all cancers combined were significantly lower than national rates among both radiation workers and non-radiation workers in three nuclear industry workforces in the United Kingdom. To overcome the healthy worker problem in studying occupational radiation cohorts, it is preferable to compare radiation workers receiving different levels of dose or dose rates rather than to compare radiation workers with the general population.

17. In case-control studies, it is important that the cases and controls should be chosen from the same well defined population and that the ascertainment of both sets should be complete. In particular, when it is necessary to approach potential study subjects or their next-of-kin for interviews, the refusal rate should be low for both cases and controls if selection bias is to be minimized. It should be noted that in cohort and case-control studies where exposures, both to radiation and other agents, are ascertained retrospectively, it is sometimes necessary to rely on the study subjects themselves or surrogates for such information. This might lead to bias, if the ability to assess exposures accurately depends on whether the disease in question arose or not. For example, in a proportional mortality study of naval shipyard workers in the United States, an increased risk of cancer and leukaemia relative to other causes of death was reported among nuclear workers [N6]. This was based on radiation exposure histories ascertained by newspaper reporters from the next-of-kin of deceased workers. However, the findings were not borne out in a subsequent cohort study in which radiation exposures were determined using employment records [R12]. The epidemiological biases associated with the initial study were discussed in detail by Greenberg et al. [G11]. In particular, the relatives of workers who died from cancer were more likely to have been located and interviewed than the relatives of other deceased workers. This, in combination with the lower all-cause mortality among nuclear workers relative to the comparison group, contributed to the spurious findings. More generally, the use of historical records, where available, is to be preferred to avoid differential ascertainment of exposures.

18. A particular problem when considering a large number of hypotheses in a study is that of multiple comparisons. A statistically significant finding is often referred to as one that would arise only once in 20 times by chance alone, i.e. 5% of the time. Therefore, if 20 non-overlapping cancer categories are examined in an epidemiological study, one of them would be expected to show a statistically significant result at the 5% level even if the underlying risk was not elevated. This finding could represent either an excess or a deficit if a two-tailed test (i.e. a statistical test that looks in both directions) has been applied. Consequently, it is important to examine the consistency of findings for specific cancer sites across studies, as well as the consistency with other evidence, e.g. from experimental data. Problems of multiple comparisons can arise in studying not only multiple endpoints but also in testing a large number of hypotheses. For example, Jablon et al. [J1] studied cancer around a large number of nuclear facilities throughout the United States. They found that the facility-specific relative risks for childhood leukaemia formed a symmetric distribution, with roughly as many values below 1 as above it. Thus, unless there is prior reason to focus on specific facilities, those results that achieve the nominal levels of statistical significance need to be viewed in the light of the distribution for facilities overall. An extra problem that requires scrutiny is the possibility of selective reporting of results, i.e. the greater tendency for positive findings to be reported than negative findings. It is possible that some reports of highly specific positive findings, based on either small studies or sub-analyses of larger studies, reflect such a publication bias. For example, Carter et al. [C20] published the results of a study that did not show an association between Down's syndrome and maternal radiation only after a positive report appeared in the literature.

19. It is also necessary to address the potential for confounding, which can lead to bias. A confounding factor is correlated with both the disease under study and the exposure of primary interest. While many factors other than ionizing radiation affect cancer rates, in most epidemiological studies of radiation-exposed groups there is no reason to think such factors will be strongly correlated with radiation dose, although weak associations might arise by chance. For example, in studies of the survivors of the atomic bombings and many medically irradiated groups, it is unlikely that there would be a strong association between, say, levels of smoking and the dose received. One possible confounder in occupational studies is time since start of radiation work. This tends to be correlated with cumulative radiation dose and with time-related factors associated with the selection of people into radiation work. However, since the time variation in risks associated with such selection factors tends to be greatest soon after starting work [F4], analyses that omit the first few years of follow-up (when radiation effects would be unlikely to be manifested in any case) may permit resolution of this point. In studies of medical exposures, confounding may arise if the clinical indications that lead to the exposures are related to a subsequent diagnosis of cancer; this is sometimes referred to as "confounding by indication". For example, in a study of patients administered ^{131}I for diagnostic purposes, a slightly elevated risk of thyroid cancer was found [H4]. However, this risk was not related to dose and was concentrated among patients referred because of a suspected thyroid tumour, indicating that the elevated risk was probably due to the underlying condition. Similarly, in a another study, an increased risk of leukaemia and non-Hodgkin's lymphoma that arose shortly after diagnostic x-ray exposures appeared to be due to pre-symptomatic conditions of the diseases that led to the exposures [B24].

20. It is desirable to check for confounding by factors that have a sizeable influence on cancer rates if the level of radiation risk is predicted to be low or if the range of doses is narrow. For example, in case-control studies of indoor radon and lung cancer, it is very important to take account of individual smoking habits. On the other hand, if the level of radiation risk is predicted to be high, instances where data are available on potential confounders may permit not only adjustment for such factors but also examination of how such factors may modify the radiation-induced risk. For example, data on smoking habits among radon-exposed miners can allow examination of the joint influence of radon and smoking on lung cancer risks. Risk modification is discussed later in this Annex and is also covered in Annex H, *"Combined effects of radiation and other agents"*.

21. In contrast to cohort, case-cohort, and case-control studies, which utilize data on specific individuals, correlation studies are based on data averaged over groups. A particular form of this study is the geographical correlation study, in which disease rates in geographical areas are compared with average levels of exposures, e.g. to natural or environmental radiation. An example of such a study, which concerns lung cancer and indoor radon in areas of the United States [C18], is discussed in Section III.E. Since studies of this type do not involve data on individual exposures or confounders, they are susceptible to biases that do not arise in studies for which such data are available [G2]. These biases can be large, although their magnitude is dependent on the particular situation. In addition, migration can be a large problem in geographical correlation studies, because people exposed in one region can die or develop the disease of interest in another region. This suggests that estimates of radiation risks should be based on cohort, case-control, or case-cohort studies. However, correlation studies sometimes can be useful for generating hypotheses or as a means of surveillance for large effects, such as in the study of childhood leukaemia and lymphomas in Europe following the Chernobyl accident [P12], although the potential biases specific to this form of investigation should be borne in mind.

B. STATISTICAL POWER

22. A very important facet of any epidemiological study is its statistical power, i.e. the probability that it will detect a given level of elevated risk with a specific degree of confidence. The power of a cohort study will depend on the size of the cohort, the length of follow-up, the baseline rates for the disease under investigation, and the distribution of doses within the cohort, as well as the predicted level of elevated risk. Similarly, statistical power in a case-control study depends on the number of cases, the number of controls per case, the frequency and level of exposure, and the predicted exposure effect. Statistical power is generally evaluated before a study is conducted. Afterwards it is more correct to refer to statistical precision, which is reflected in the width of the confidence intervals for risk estimates.

23. The following example illustrates how the above factors can influence statistical power. Suppose cancer rates are ascertained in a cohort consisting of two groups, one of which was unexposed (the control group) and the other of which consists of persons who received a single common dose, D (the exposed group). The groups are assumed to have the same distributions for age, gender, and period of follow-up. (For simplicity, the following calculations do not take explicit account of these factors.) Statistical power can be evaluated by simulating the number of cancers in the two groups under a model such that the ratio of the cancer rate in the exposed group to that in the control group (i.e. the relative risk) is $1 + aD$, where a is the excess relative risk (ERR) per unit dose. Given the total number of cancers in the two groups, the statistical power depends only on the product of a and D and on the ratio of the number of cancers expected in the two groups if there were no elevated risk. In particular, power is calculated here by evaluating the proportion of simulations for which the number of cancers in the exposed group is greater than the value which, if there were no increased risk, would be exceeded only 5% of the time. This represents a one-sided test at the 5% level.

24. An approximate form of the power calculation is as follows. Let N denote the total number of cancers in the exposed and unexposed groups, let p denote the proportion of the total number of cancers expected to arise in the exposed group if there were no elevated risk, and let O denote the observed number of cancers in the exposed group. It can be shown that conditional on the value of N, O has expected value $E = Nq$ and variance $V = Nq(1 - q)$, where $q = p(1 + aD)/(1 + paD)$. Furthermore, provided that Nq and $N(1 - q)$ are reasonably large (at least 20 or so), O is approximately normally distributed. Consequently the statistical power (i.e. the probability that O will exceed the value that would be exceeded only 5% of the time if there were no increased risk) can be approximated using tables for the normal distribution. In particular, if there were no elevated risk (i.e. $a = 0$), then $q = p$, and so O would be approximately distributed normally with mean $E_0 = Np$ and variance $V_0 = Np(1 - p)$. Therefore a one-sided test at the 5% level would signal an elevated risk if $T = (O - E_0)/V_0^{1/2}$ exceeds 1.645, where the probability that a normally distributed variable with mean zero and variance 1 would exceed 1.645 is 0.05. More generally, let C(x) denote the probability that a normally distributed variable with mean zero and variance 1 would exceed x. Then the probability that T exceeds 1.645 would be $C(1.645) = 0.05$ if there were no increased risk. More generally this probability, which equates to the power, can be calculated as $C[(E - E_0 + 1.645V_0^{1/2})/V^{1/2}]$.

25. It should be noted that the power is not zero when there is no increased risk, since there is still a chance that a large number of cases might arise in the exposed group, which would lead to a statistically significant (but spurious) finding. Under the above test, the probability of such a finding is set to 0.05. Also, since this example involves an internal comparison group, it does not rely on the validity of, say, published national or regional baseline cancer rates.

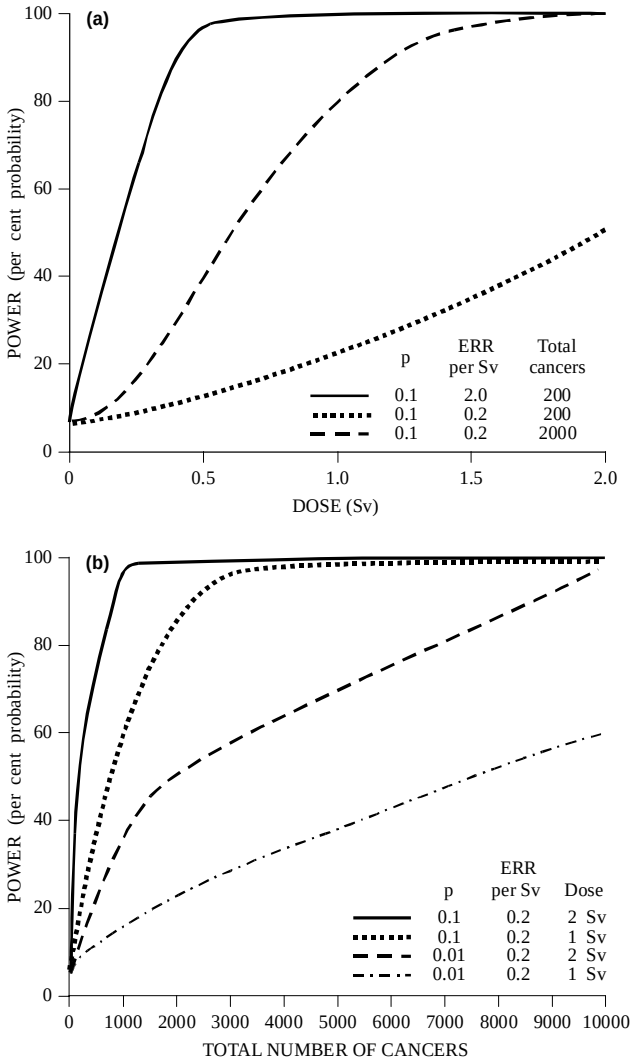

Figure I. Statistical power to detect an increased risk of cancer in an epidemiological study (a) in relation to dose with a baseline cancer incidence of 0.1; (b) in relation to the number of cancers observed with an excess relative risk (ERR) of 0.2 Sv^{-1}.
p denotes the proportion of total cancers expected in the exposed group if there were no raised risk.

26. The upper panel of Figure I shows how the power varies with a and D for various values of the total number of cases in the situation where, in the absence of an elevated risk, the expected number of cancers in the exposed group is 10% of that in the total cohort (i.e. p=0.1). Here the power is expressed as a percentage probability. Usually an analysis with about 80% power would be considered to be quite sensitive in detecting an underlying effect. The first point that should be noted from Figure Ia is the effect of the total number of cancers, N. This number is influenced not only by the size of the combined cohort but also by the baseline cancer rates and the length of follow-up. Thus a study based on a very large cohort may not be particularly informative if a rare cancer is under investigation and the follow-up is short. Conversely, a study based on a fairly small cohort may be quite informative if a common cancer is being considered and the follow-up is long. For the example illustrated in the upper panel of Figure I, if the ERR per Sv, a, is 0.2 and the exposed group received 1 Sv, then the power to detect an elevated risk is 81% if the total number of cancers in the two groups is 2,000 but only 25% if the total number of cancers is 200.

27. The second point to note from the upper panel of Figure I is the effect of the level of elevated risk. If the overall number of cancers is 200 and the exposed group received a dose of 1 Sv, then the probability of detecting an enhanced risk at the 5% level is 25% if a (the ERR per Sv) is 0.2. In contrast, if a = 2, the corresponding probability is nearly 100%. The same probabilities would arise if, say, the dose D is doubled and a is halved. This is because the ERR can be represented by the product of a and D in this example. However, the calculation is more complex under alternative scenarios in which cohort members receive a range of different doses.

28. The two panels of Figure I are similar, except that in the lower panel the ERR per Sv, a, is fixed at 0.2 and the ratio of expected numbers of cancers in the two groups is allowed to vary. It can be seen that for a given total number of cancers and at a given dose, the power decreases with decreasing values for the proportion, p, of cancers expected in the exposed group in the absence of an elevated risk. However, for given values of a and D, the power tends to be similar if the proportion p and the total number of cancers vary in such a way that the expected number of cancers in the exposed group is roughly constant. For example, based either on p=0.1 and a total of 1,000 cancers or on p=0.01 and a total of 10,000 cancers, the predicted number of cancers in the exposed group is about 120 at a dose of 1 Sv (an excess of roughly 20). The lower panel of Figure I shows that the power is similar in the two instances (58% and 60%, respectively). An exception to this arises if p is very high, owing to the difficulty of establishing baseline cancer rates for a relatively small control group.

29. The above example is intended to show how certain factors can influence statistical power. As indicated earlier, the calculations are often more complex, as when the people in the exposed group receive a range of doses rather than the same dose. Indeed, errors in the assessment of individual doses also affect statistical power, as mentioned in the following Section and as Lubin et al. [L10] illustrated for studies of indoor radon. It should be emphasized that summary measures of the doses received by a population, such as collective dose, are not, by themselves, suitable for determining statistical power. For example, if the same dose is received by all the members of a cohort, then the usual form of analysis that looks for a trend or difference in risk according to the level of dose would not be possible. Indeed, it is essential when calculating statistical power to take account of the distribution of dose within the study population.

30. The above considerations indicate that studies such as the Life Span Study of survivors of the atomic bombings [P4, P9, S3, T1], which are based on large cohorts with doses ranging up to several gray and for which the follow-up has extended over several decades, are particularly informative about radiation-induced cancer risks. The same

holds for medically irradiated cohorts that received a wide range of doses and have a long follow-up, such as in studies of women treated for cervical cancer [B1] or given multiple chest fluoroscopies [B3, M1]. While studies of low-dose chronic exposure are of direct relevance to most occupational, environmental, and diagnostic medical exposures, their power is inherently low, owing to the low predicted level of elevated risk [L3]. In such situations, combining studies with similar designs can be very helpful in attempting to increase power. However, the possible influence of residual bias and confounding needs to be borne in mind, since the gain in precision will not lead to a gain in accuracy if bias still exists. Sometimes a meta-analysis is performed based on published findings from several studies. However, as indicated below, it is preferable, where feasible, to combine the original data and to analyse them using a common format. This approach has been used, for example, to analyse data for about 95,000 radiation workers from Canada, the United Kingdom, and the United States [C11, I2]. It has also been used for studies with greater power and large numbers of excess cancers, such as studies of lung cancer in radon-exposed miners [L4], thyroid cancer following childhood exposure [R4], and breast cancer in medically exposed cohorts [L5], to enhance analyses of effect modification as well as to increase precision.

31. In addition to increasing statistical precision, pooled or meta-analyses may be able to resolve apparently conflicting results from different studies [D1]. By aligning the studies in a parallel fashion and analysing them using a common approach, it may be possible to explain such differences on the basis of, for example, different categorizations of the exposure data. One of the main difficulties that can arise in a meta-analysis is a lack of comparability of the studies under consideration, for example because of differences in the form of the data collected on exposures and potential confounders. Summing many studies with potentially biased results may provide a precise but incorrect estimate of risk; consequently, meta-analyses can produce results that are seriously misleading [B28, B29]. Parallel analyses which address the comparability of data and the potential for bias in the various studies under consideration are therefore important in determining whether it is sensible to perform a pooled analysis. Since such an analysis is easier to perform if the individual studies are of a similar design, a prospective approach whereby studies are constructed around a common protocol is more advantageous than a retrospective pooling exercise. The former approach is being taken for a very large international collaborative study of radiation workers that is being coordinated by the International Agency for Research on Cancer (IARC) [C8]. Another potential problem with retrospective pooling is publication bias, i.e. selective reporting of results depending on whether the outcome was judged to be positive or negative. This bias, however, tends to arise for small or ad hoc studies, which would carry less weight in a meta-analysis if a number of large studies with clear, pre-defined objectives are included.

32. In view of limitations that can arise not only through considerations of statistical power but also through residual bias and confounding, the ability to detect small elevated risks using individual or pooled epidemiological studies can be low. This affects the ability to discern whether or not there is a dose threshold for radiation carcinogenesis. Results from epidemiological studies can be used to indicate levels of dose at which elevated risks are apparent, as well as whether the data are consistent with various dose-response trends [N3]. The inability to detect increases at very low radiation doses using epidemiological methods need not imply that the underlying cancer risks are not elevated; rather, supporting evidence from animal studies needs to be utilized in addressing risks from low-dose and low-dose-rate exposures [N3], while recognizing that not all molecular changes result in tumours. Epidemiological studies of such exposures do, however, enable upper bounds to be placed on radiation-induced risks. Risks at low doses and low dose rates are discussed in detail in Annex G, *"Biological effects at low radiation doses"*.

C. ASSESSMENT OF DOSES

33. A key aspect in estimating cancer risks following radiation exposure relates to the assessment of radiation doses. A recent workshop report reviewed sources of uncertainty in radiation dosimetry and their impact on dose-response analyses [N15]. Epidemiological studies of radiation-exposed groups can differ, depending, for example, on the type of information available on radiation exposure; the time between a dose having been received and making the measurement; and the specificity of assessments of doses to particular organs and particular individuals. Depending on the method of dose assessment, doses estimates could be subject to systematic or random errors or both, which could then affect the dose-response analyses. These issues are now considered in more detail.

34. The assessment of doses received by individuals in epidemiological studies may take several forms. In studies of radiation workers, for example, it is possible to utilize measurements made using personal dosimeters (e.g. [C11, G4]). For doses received from some types of medical exposures, it may be possible to reconstruct organ doses based on patient records, perhaps in combination with computer models, as for example, in an international study of patients treated for cervical cancer [B1]. In other instances, information on the past location of individuals has to be utilized together with measurement data, as for the Japanese atomic bomb survivors and, for example, people exposed to radon in dwellings. In the case of the Japanese survivors, there is still uncertainty about neutron doses at Hiroshima and the associated impact on cancer risk estimates, particularly at low doses [K20]. Furthermore, as indicated later, studies of indoor radon are generally hampered by the need to assume that a contemporary measurement of radon concentration can be used to estimate concentrations during the preceding 20 or 30 years.

35. It was emphasized in the UNSCEAR 1994 Report [U2] that the data available for assessing doses were generally not collected with epidemiology in mind. For example, radiation monitoring of workers has often been undertaken to comply with management policies. Consequently, a detailed examination of dosimetry practices, including sources and magnitude of errors, is important in considering whether sufficiently accurate and precise estimates of dose can be obtained for use in an epidemiological study. A recent example is the examination of dosimetry records and practices in Canada, the United Kingdom, and the United States, carried out as part of a study of workers in these three countries [C15]. This addressed issues such as the practices on who should be monitored (e.g. all personnel at a facility or only those workers who were likely to receive doses); how missing dosimeter results should be treated (e.g. by recording zero, the threshold value for the dosimeter, a percentage of the statutory dose limit, or a best estimate of the likely dose); and the recording of a dose near or below the dosimeter threshold (e.g. as zero or by entering a "recording threshold"). Also of relevance is whether data are available on neutron doses and internal exposures. Gilbert and Fix [G4] urged the use of sensitivity analyses to examine the effect of potential sources of bias in dose estimates in epidemiological studies of radiation workers.

36. To examine the risks of specific types of cancer in relation to radiation, it is desirable to use the radiation dose to the organ under study. In some instances, such as external whole-body exposures, it may be possible to use a single value for the dose to an individual and to use this value in analysing the risk for each organ. This approach is commonly used in studies of radiation workers (e.g. [M46]). However, even in the case of external whole-body exposures, attenuation of the radiation may lead to some variation in the absorbed doses to different organs. For example, the DS86 dosimetry system for the Japanese atomic bomb survivors incorporated organ-specific transmission factors to calculate organ absorbed doses [R24]. These factors reflect the circumstances of individual exposures, including posture and orientation of the survivors relative to the explosion hypocentre; average values for the organ gamma-dose transmission factor range from 0.72 for the pancreas to 0.85 for the female breast [S51]. Also, as part of an international study of radiation workers [C15], calculations were made of the ratio of organ to "deep dose" (i.e. dose to 1 cm below the skin [I19]), both for the lung and the red bone marrow, and for various photon energies and rotational exposure geometries. This yielded ratios of approximately 1 for the lung and 0.7–0.8 for the red bone marrow for photon energies between 100 keV and 1 MeV, with the consequence that estimates of the leukaemia risk per unit dose were multiplied by 1.2 whereas no adjustment was made for other cancer types [C15].

37. In situations where the exposure involves radiation over a limited range of energies, it is possible to convert organ absorbed doses (in gray) to organ equivalent doses (in sievert) using the radiation weighting factors cited by ICRP [I1]. For most low-LET radiations, the absorbed and equivalent doses would be numerically equal. In contrast, ICRP recommends, for example, applying a factor 20 to convert organ absorbed doses from high-LET alpha radiation to the corresponding organ equivalent dose. In these situations, it may be more direct to relate organ-specific risks to organ absorbed doses than to include the radiation weighting factor by using equivalent dose. However, if the exposure is totally or virtually all due to low-LET radiation, then the use of absorbed dose or equivalent dose would give the same values for risk per unit dose. Alternatively, if the exposure arises solely from, say, internal alpha irradiation, then estimates of the risk per unit organ absorbed dose can be related by a simple factor to the risk per unit organ equivalent dose. However, if the exposure involves radiations of widely differing energies, including both high- and low-LET radiation, such as arose for workers at the Mayak plant in Russia [K32], then it is desirable to examine organ-specific risks in relation to absorbed doses split by radiation energy. If this information is not available, an alternative may be to use a total equivalent dose, based on applying weighting factors to the component absorbed doses and summing these values. However, it should be recognized that the choice of weighting factors would influence the analysis of risk in relation to dose.

38. An additional difficulty that can arise in studies involving internal high-LET exposure concerns the estimation of organ absorbed (or equivalent) doses. For example, plutonium uptake among potentially exposed workers can be assessed using urine measurements of plutonium excretion, together with information on factors tied to each individual's occupational history [O1, K32]. These assessments are dependent on aspects of the monitoring procedures, such as the level of detection and the sampling periods. To arrive at organ-specific absorbed doses, it is then necessary to use a dosimetric model for the distribution of activity between organs (e.g. [I4]). These calculations depend in turn on factors such as the solubility of plutonium in the workplace at a given time [O1] as well as on physiological factors. It should therefore be recognized that estimates of individual organ-specific doses from internal radiation are subject to uncertainty. However, this may be less of a problem if, as was the case in a study of plutonium workers in the United Kingdom, estimates of organ doses from internal radiation are generally lower than those from external radiation, even after applying a weighting factor to the absorbed doses [O1]. It should also be noted that some epidemiological studies of internal exposures present their results in terms not of organ doses but of some measure of intake (e.g. the amount of thorotrast administered to the patients [V8, V3]) or, say, the plutonium body burden (e.g. [K32]).

39. The use of recent measurements in estimating doses received many years ago, as for example in assessments of indoor radon exposures, carries particular difficulties. Changes in the intervening period (to, say, the structure of the dwelling in the case of radon) may well influence exposure levels. Again, it is important to understand which factors may have a substantial impact on exposure levels and the magnitude of these impacts. For example, investigations have been made of factors affecting temporal concentrations of indoor radon [B7]. Supplementary information may sometimes be available through assess-

ments of contemporary exposures. For example, in the case of radon, there has been interest in whether CR-39 surface measurements using a piece of glass possessed by a person over many years [M7] or *in vivo* measurements of ^{210}Pb in the skull [L25] can assist in assessing cumulative radon exposure. The former approach was used recently in an epidemiological study of indoor radon, alongside traditional track-etch measurements [A24], although further validation of the glass-based approach would be desirable in view of the effects of factors such as smoking [W19]. Furthermore, in contrast to measurements of radon in dwellings, radon exposures to persons can be influenced by occupancy patterns, particle size distributions, and breathing rates, although their effect tends not to be as great as those of factors affecting radon concentrations in houses. In general, it is essential to evaluate in detail the feasibility of estimating exposures accurately enough and precisely enough for the purposes of epidemiology.

40. In addition to the above methods of dosimetry, other biological and physical methods are now being incorporated into epidemiological studies. Such methods include classical cytogenetics for translocations, used for example in a study of women with benign and malignant gynaecological disease [K14]; the glycophorin A mutational assay of red blood cells and the fluorescent *in situ* hybridization (FISH) technique for chromosome stable translocation analysis, used by Bigbee et al. [B19] and Lloyd et al. [L26], respectively, in investigations of Chernobyl recovery operation workers; and electron spin resonance (ESR), also known as electron paramagnetic resonance (EPR), of tooth enamel, used for example in atomic bomb survivors in Japan [I8] and workers at the Mayak facility in Russia [R28]. Several factors can affect the utility of these methods in epidemiology. First, it is generally difficult to evaluate individual doses of less than 100–200 mGy using these methods, although in the case of FISH, for example, it is possible to assess average doses to populations at around these levels. For example, in spite of evaluating more than a quarter of a million metaphases, Littlefield et al. [L31] were unable to detect any increase in chromosome aberrations in lymphocyte cultures from Estonian men who took part in the clean-up of the Chernobyl nuclear power site, compared with men who did not participate in this work. Secondly, it can be difficult and/or expensive to collect, store, and analyse material for thousands or tens of thousand of people. This suggests that collection for only a subgroup of a cohort (e.g. for cancer cases and matched controls) may be a more efficient approach, although the possible effect of cancer treatment on such material needs to be considered. Thirdly, some biological measures can be affected by factors other than radiation. For example, Moore and Tucker [M49] reported that adjusting for age and smoking improved estimates of doses for Chernobyl recovery operation workers based on chromosome translocation frequencies. Fourthly, the effect of radiation on some biological measures, such as dicentric aberrations, is relatively short-lived, so the collection of related materials is unlikely to be useful in studying exposures received many years previously [L26].

41. Provided that assessment of doses is performed "blind" to whether or not the study subjects develop particular diseases, there will not be bias owing to differential misclassification of exposures, as, for example, would arise from selective recall by the subjects of past exposures. However, non-differential misclassification can still lead to bias in estimating dose-response relationships. For example, random errors in individual dose estimates tend to bias the dose response towards the null [A1]. Statistical methods have been developed to allow for such random errors in analyses, based on estimates of the magnitude of the errors, and have been applied to several radiation-exposed groups, such as the survivors of the atomic bombings [P2]. However, such errors can have a profound effect on statistical power, particularly when the predicted elevated level of risk is low [L1].

42. In some studies it is not possible to estimate doses on an individual basis, so average doses for a cohort must suffice. For example, in the study in the United Kingdom of ankylosing spondylitis patients treated with x rays, average doses were estimated for a number of organs, but only for the red bone marrow were doses estimated for a sample of individuals [L2, W1]. However, such studies can still provide information on, for example, the temporal pattern of radiation-induced risks in instances where these risks are large.

D. MORTALITY AND INCIDENCE DATA

43. It is often easier to obtain data on cancer mortality than on cancer incidence, since death certification tends to be more complete than cancer registration. For example, essentially complete follow-up for mortality of the survivors of the atomic bombings can be attained via the compulsory system of family registration *(koseki)* in Japan. Cancer incidence data for these survivors, however, are generally limited to cases arising within the areas covered by the Hiroshima and Nagasaki tumour registries [M2]. It was therefore necessary to allow for migration from these areas when analysing incidence data for the survivors of the atomic bombings [S4]. Elsewhere, complete follow-up for cancer incidence is achievable in several countries; the Nordic countries in particular have long-running cancer registries. Some countries, however, either do not have cancer registries or have strict confidentiality laws that prevent the linkage of names to diagnoses; others, e.g. the United States, have high-quality cancer registries, but only in certain regions [P5].

44. Although mortality data are often more complete, it is well known that the cause of death is recorded incorrectly or with low specificity on a non-trivial proportion of death certificates [H5]. As well as on occasion recording the wrong type of cancer, owing to metastases, there is a general tendency to under-report cancers. This affects estimates of both site-specific and total cancer risks. For example, based on linkage of death certificates to autopsy data for the Life Span Study of survivors of the atomic bombings, Ron et al. [R2] found that 24% of cancers diagnosed at autopsy were missed

on death certificates. Most of these deaths had been assigned to non-neoplastic diseases of the same organ system. Taking account also of non-cancer deaths mistakenly recorded as cancer, Hoel et al. [H5] concluded that total cancer mortality within the Life Span Study had been consistently underestimated by about 18%. Sposto et al. [S5] showed that adjustment for errors in death certification would increase estimates of radiation-induced cancer deaths in the Life Span Study relative to published values by about 10%. In contrast to mortality, there tend to be fewer diagnostic errors in the registration of incident cancers, and histological subtypes of some cancers can be studied using incidence data. However, the proportion of histologically verified cancers varies among registries, and consideration of completeness as well as accuracy is important in judging the value of incidence data.

45. A particular advantage of incidence data over mortality data is the information they provide for cancers that are often non-fatal. Of special interest within the field of radiation carcinogenesis are cancers of the thyroid, skin, and breast. For the first two of these cancers, elevated risks have been demonstrated only in cancer incidence data for the survivors of the atomic bombings and not in mortality data [R1]. While elevated risks of breast cancer mortality are apparent in this cohort, the larger number of incident breast cancer cases both in this group and in other cohorts permits a much more detailed evaluation of risks for this cancer site, particularly because survival rates may have been increasing over time. Another advantage of incidence data is that latency periods may be determined more accurately, given that the time between exposure and death could be affected by aspects of the cancer treatment.

46. It is clear that high-quality data on cancer incidence should be utilized when these are available. However, careful examination of the completeness and accuracy of data on cancer registrations is important, since mortality data are more reliable than incidence data in some countries. Furthermore, data on total mortality are important as an indicator of the overall health of populations, although incidence data can be of value for site-specific examinations. It is therefore worth considering mortality data, not only to compare levels of incidence and mortality but also as an adjunct to incidence data.

E. FACTORS THAT MODIFY RISK

47. Analyses for several cancer sites have shown that the level of the radiation-induced risk is dependent not solely on the magnitude of the radiation dose but can be modified by factors such as age at exposure and time since exposure. For example, data on the survivors of the atomic bombings [P4, P9] and on some other irradiated groups [U2] show that the ERR per unit dose for leukaemia began to decrease approximately 10–15 years after exposure and that the ERR is greater for people exposed in childhood than in adulthood. The Japanese data, in particular, also show that for all solid cancers combined, the ERR decreases with increasing age at exposure and, among those exposed early in life, tends also to decrease with increasing time since exposure [P9, T1]. Based on an earlier version of the mortality data, Kellerer and Barclay [K21] suggested that these age and time trends could be described by a model under which the ERR depends simply on attained age. However, Little et al. [L32] showed that the Kellerer-Barclay model is not sufficient to explain the age and time trends in solid cancer risks based on the most recent Japanese incidence data, in contrast to the earlier mortality data; in particular, it is necessary to take account of both age at exposure and time since exposure when modelling the ERR, rather than just the sum of these quantities.

48. As will be discussed later in this Annex, age and temporal factors can also have a large impact on risks for specific types of solid cancer. In the case of radon-exposed miners, Lubin et al. [L4] showed that the ERR of lung cancer decreases with increasing time since exposure and attained age and is also influenced by exposure rate. For thyroid cancer, there is clear difference between the effects of irradiation in childhood and adulthood [R4]. In some instances, it may be possible to associate the effect of age with a specific biological factor; for example, there does not appear to be an elevated risk of breast cancer following post-menopausal irradiation (e.g. [B3, T1]), showing that hormones can modify the radiation risk. Apart from age, other factors that may affect radiation-induced risks are gender and baseline cancer rates, which are considered in more detail later. Indeed, factors that affect cancer rates generally, such as smoking, diet, and chemicals, may also modify the carcinogenic effect of radiation and so have to be borne in mind when, for example, evaluating probability of causation [N1, I12]. Particular examples are smoking in the case of lung cancer and chemotherapy for patients who are also treated with radiation. The combined effects of radiation and other agents are considered in more detail in Annex H, "*Combined effects of radiation and other agents*".

49. In common with endogenous factors such as gender and age at exposure, the ability to detect a modifying effect of exogenous factors is commonly related to the strength of the separate carcinogenic effects of these factors. For example, studies on smoking among radon-exposed miners [L4] and on chemotherapy for patients treated with radiation, e.g. for leukaemia [C9], are reasonably informative about possible interactions, owing to the high risks associated with both radiation and the other factors on their own. In contrast, epidemiological investigations of the joint effect of radiation and another factor are unlikely to be informative when the effect of either or both is weak, e.g. for a low radiation dose or a weak chemical carcinogen. An exception would be where one agent is a promoter that has an effect only in the presence of a carcinogen; however, such situations are rarely identified in epidemiological studies.

50. In addition to exogenous factors, hereditary factors may affect both baseline and radiation-induced risks. For example, retinoblastoma, a rare cancer of the eye, is frequently caused by inherited mutations of the *RB1* tumour-suppressor gene. Radiation treatment for the disease appears to enhance the inborn susceptibility to development of a second cancer,

particularly osteosarcoma and soft-tissue sarcoma [E1, W11], although this effect is seen only at high therapeutic doses (above 5–10 Gy). The extent to which radiation may modify cancer risks associated with other genetic disorders such as ataxia-telangiectasia and Li-Fraumeni syndrome remains to be determined [L28]. The potential for genetic predispositions to influence radiation-induced risks is addressed further in Annex F, "*DNA repair and mutagenesis*", as well as in recent publications by ICRP [I20] and NRPB [N13].

51. Examination of potential modifying factors may be hampered by the relatively small numbers of excess cancers observed for particular sites. First, a lack of statistical power may prevent some modifying effects from being discerned. Secondly, if separate analyses are performed for a large number of cancer sites, some trends with factors such as age at exposure or time since exposure might appear simply through chance variations. To address these difficulties, Pierce and Preston [P6] recommended joint analysis of site-specific cancer risks. In this approach, a general model is fitted simultaneously to data for each of several cancer sites or groupings of sites. This can be achieved by incorporating cancer type as another factor in the usual cross-tabulation of data for analysis. Some of the parameters in this model may be the same for all cancer types; other parameters may be type-specific. Using this approach, significance tests can be performed to examine the compatibility of parameters in the risk model across cancer types. Furthermore, Pierce and Preston [P6] suggested that such comprehensive models may provide a clearer understanding of modifying factors such as gender, age at exposure, and time since exposure.

52. Pierce and Preston [P6] applied this approach to the atomic bomb survivor mortality data that had previously been analysed by the BEIR V Committee [C1]. BEIR V divided solid cancers into four categories (breast cancer, digestive cancers, respiratory cancers, and other cancers) and analysed them separately. The models derived by BEIR V for these categories had different modifying effects of gender, age at exposure, and time since exposure. For example, the ERR for respiratory, but not digestive and other cancers, decreased with increasing time since exposure. Also, the ERR was higher for females than for males in the case of respiratory cancers but was the same for both genders for digestive and other cancers. However, re-analysing these data using a joint analysis approach, Pierce and Preston [P6] showed that the data were consistent with a common model for the ERR for each cancer group except breast cancer. In the model of Preston and Pierce, the difference in relative risk between genders reflected the corresponding difference in baseline rates, the ERR decreased with increasing age at exposure at a common rate for each cancer grouping, and the ERR did not depend on time since exposure.

53. This joint analysis therefore suggested that some of the differences between the risk models developed by BEIR V might be artefacts arising from overinterpretation of the data for separate cancer groupings. On the other hand, there are prior reasons for considering certain cancer sites. For example, leukaemia and other haematopoietic cancers are normally considered separately from solid cancers (as well as from each other) owing to differences in aetiology, in the level of radiation-induced risk, and in the latency period. Also, gender-specific cancers such as breast cancer should be considered separately from non-gender-specific solid cancers, owing to the differences in factors affecting baseline rates as well as (possibly) differences in the radiation-induced risks. It is therefore intended that any modelling of radiation risks conducted in this Annex should be based on either specific cancer sites for which a large amount of data is available (e.g. breast cancer and lung cancer) or groupings such as digestive cancers. However, attention needs to be given to possible differences among cancer sites within such categories (e.g. stomach, colon, and oesophagus in the case of digestive cancers), which may preclude the modelling of combined data. In this regard, reviews of the information available for some individual sites are important, just as they may be for certain cancer subtypes. For example, observations from studies of cancer incidence among the survivors of the atomic bombings, namely that radiation-induced skin cancers are limited primarily to basal-cell carcinomas [R15, T1] and that chronic lymphatic leukaemia and virus-related adult T-cell leukaemia [P4] do not appear to be radiation-inducible, may have significant implications for biomedical research as well as radiological protection. Furthermore, it would still be possible to derive estimates of measures of risk for an individual cancer site by applying the risk model derived for a wider grouping of cancers to baseline rates for the cancer site of interest. One measure of risk that may be calculated is the risk of exposure-induced death (REID), i.e. the probability that an individual will die from a cancer that arose from an exposure [U2]. The approach just outlined has been used, for example, in applying mainly BEIR V-type models to obtain values of REID for specific cancer sites in the population of the United Kingdom [N2].

54. Another point concerns the data available from various studies. Whereas a complete cross-tabulation by factors such as gender, age at exposure, and time since exposure is available for specific cancer sites in the case of the survivors of the atomic bombings, for most studies only summary values in publications are available. Furthermore, these values are sometimes not given separately for different levels of factors such as age at exposure or time since exposure, particularly in small studies. The comparison of risks across studies can therefore be difficult if the levels of these factors differ between studies. The UNSCEAR 1994 Report presented estimates of the ERR and the excess absolute risk (EAR), i.e. the absolute difference in cancer rates, derived from various studies of external low-LET exposures, generally without adjustment for modifying factors (Table 8 of Annex A [U2]). While such a presentation is useful for comparing the general level of risks seen in various studies, it would be helpful, where possible, to consider results specific to particular ranges for age at exposure (e.g. childhood and adulthood) or to each gender, if these factors are likely to be important in modifying risks. Where such factors are important, results that do not allow for them should be interpreted with caution.

II. EVALUATION OF CANCER RISK

A. MEASURES OF RADIATION RISK, INCLUDING LIFETIME RISKS

55. Analyses of epidemiological data on radiation-exposed groups often yield estimates of ERR or EAR. These terms represent the increased cancer rates relative to an unexposed group, measured on proportional and absolute scales, respectively. For example, an ERR of 1 corresponds to a doubling of the cancer rate, while an EAR may be expressed as, for example, the extra annual number of cancers per 10,000 persons. If these values have been derived from a linear dose-response analysis, they may additionally be expressed as amounts per unit dose, e.g. ERR per Sv; otherwise, they may be quoted for a specific dose, e.g. 1 Sv. As was pointed out earlier, the level of radiation-induced cancer risks, either on a relative or an absolute scale, may vary according to various factors. Therefore, one possibility in presenting epidemiological results is to give values for ERR and/or EAR specific to particular values for these factors, for example, specific to gender and age at exposure or time since exposure, when sufficient data are available.

56. Alternatively, it has become increasingly popular in recent years to present models, based on relative or absolute scales, that describe such modifying effects. Particular examples are the models developed by BEIR V [C1] and the models for cancer incidence among the survivors of the atomic bombings [P4, T1]. These models are generally empirical, in that they attempt mainly to provide a good fit to the relevant data. To some extent they can be related to possible biological mechanisms, in that a roughly time-constant relative risk would be predicted if radiation acted at an early stage in a multi-stage process, whereas the EAR would more nearly be constant over time if radiation acted at a late stage [L7]. However, more recent research has focused on the explicit fitting of mechanistic models for carcinogenesis to data on radiation-exposed groups. For example, Little et al. [L8] analysed data on leukaemia among the survivors of the atomic bombings and cervical cancer patients using the Armitage-Doll multi-stage model [A2] and the Moolgavkar-Venzon-Knudson (MVK) two-mutation model [M11, M12]. This analysis suggested that neither model provided an adequate fit to these data, which led to the development of a generalized MVK model involving more than two mutations [L9]. Another type of mechanistic model has been proposed by Pierce and Mendelsohn [P34], in which it is assumed that cancer is caused by mutations that accumulate in a stem cell throughout life and that radiation can cause virtually any of these mutations. This model, in which the relative risk depends mainly on attained age rather than on age at exposure or time since exposure, yields age-specific risks similar to those in the Japanese atomic bomb survivors for all solid cancers combined [P34].

57. As was indicated earlier, the presentation of ERRs or EARs specific to particular levels of factors such as age at exposure and time since exposure can facilitate comparison across studies. A disadvantage of this approach, however, is that the sampling errors in these values may be high if the data are split finely. On the other hand, comparing models fitted to data from different studies may not be straightforward if the investigators concerned have used different types of models. For example, the respiratory cancer model derived by the BEIR V Committee [C1] for low-LET radiation and the lung cancer models developed by BEIR IV [C2] and BEIR VI [C21] for high-LET radon exposure incorporate different time-since-exposure patterns.

58. If it is desired to make comparisons across studies, one possibility is to incorporate the estimated ERRs or EARs (either specific to certain levels of factors or modelled) into a life-table calculation to produce estimates of the REID, the excess lifetime risk (ELR), or the loss of life expectancy (LLE). These terms, together with a description of their advantages and disadvantages, are given in Annex A of the UNSCEAR 1994 Report [U2]. Some caveats should be attached to this approach, however. First, for the purpose of these calculations it may be necessary to extrapolate beyond the scope of the data, for example, from a limited follow-up period to the end of life, to form a lifetime risk estimate. It is important to be aware of the potential impact of such extrapolations on the comparison of results from different studies. However, lifetime risk estimates such as REID and ELR are of interest in their own right, although additional calculations specific to the types of follow-up periods arising in the studies in question may be desirable. Secondly, it is important to use the same type of life-table calculation for each study, e.g. the calculations must be based on the same baseline cancer rates and survival probabilities. If this is not done, study-to-study differences in values such as REID might arise artefactually as a result of differences in life-tables between countries rather than as a result of variation in radiogenic risks. The aim in these calculations would not, in the first instance, be to derive values of REID etc. that are of general applicability but to provide a basis for inter-study comparison. Thirdly, single values of REID etc. may not encapsulate fully the findings of each study. As a consequence, graphical displays of trends in risk in different studies could usefully complement summary risk estimates.

59. In addition to making comparisons across studies, it would be desirable to compare the main risk estimates calculated in this Annex with those calculated in previous UNSCEAR Reports. This topic is considered in Chapter IV.

B. TRANSFER OF RISKS

60. As indicated earlier, an important factor in the quantification of radiation risks is how to transfer site-specific risks across populations with different baseline rates; in other words, how to take a risk coefficient

estimated for one population and apply it to another population with different characteristics. To give some idea of the likely impact of the method of transfer employed, it is useful to consider variations in baseline rates between different populations. Table 1 builds on the corresponding table in Annex A of the UNSCEAR 1994 Report [U2], showing some of the highest and lowest cancer rates in various populations. Since cancer rates can vary over time, this table is restricted to information over a particular time period (late 1980s and early 1990s) [P5]. Although some of the variation is likely to reflect small numbers and low levels of cancer registration in some areas, broad patterns are discernible. For example, baseline rates for breast and lung cancer are generally higher in North America and western Europe than in Asia, whereas Japan has one of the highest stomach cancer rates in the world [P5]. Even within broad regions, baseline rates may differ in specific areas (e.g. [C22]). For breast, lung, and stomach cancer, Land and Sinclair [L12] showed that, depending on whether the ERR or the EAR (i.e. the multiplicative and additive transfer models, respectively) is assumed to be constant across populations, the values of REID predicted for the United Kingdom and the United States using data on the Japanese atomic bomb survivors can differ by a factor of at least 2. In contrast, differences in the total radiation-induced cancer risk tend to be smaller, reflecting the fact that there is less variation across populations in the baseline rates for all cancers combined. ICRP [I1] compared the risks estimated for five different populations using both of the above approaches in arriving at its most recent risk estimates.

61. To some extent it is possible to investigate methods for transferring risks across populations by studying the modifying effect of factors known to account for at least some of the differences in baseline rates. Particular examples are smoking in relation to lung cancer (e.g. [C21]) and, for persons living near the Techa River in Russia, the effect of ethnicity on cancer rates [K5]. However, in many instances either little is known about the specific factors responsible for differences in baseline rates or there are few data from analytical (i.e. cohort, case-control, or case-cohort) epidemiological studies on the joint effect of radiation and such factors. As a consequence, it is necessary in most cases to directly compare measures of radiation risk, such as ERR and EAR, obtained from studies conducted in different countries on groups known to have different baseline rates. In doing so, care must be taken to ensure that the data being studied are compatible, so as to avoid confounding due, for example, to temporal changes in baseline rates. It should also be recognized that neither the multiplicative nor the additive transfer model is likely to be "correct", for individual cancer types or for groups of cancers, and that the true modifying effect is probably much more complicated. However, the paucity of relevant data imply that only a descriptive approach comparing fairly simple measures of risk is warranted in this Annex, although the presentation of data in parallel across studies can provide some idea of the influence of baseline rates.

C. TYPES OF EXPOSURE

62. In the UNSCEAR 1994 Report [U2], epidemiological studies of radiation carcinogenesis were considered for the following types of exposure:

(a) external low-LET irradiation, subdivided into high-dose-rate and low-dose-rate exposures;
(b) internal low-LET irradiation; and
(c) internal high-LET irradiation, subdivided into radon and other exposures.

63. There are several reasons for considering these studies separately. First, the experimental studies reviewed in Annex F of the UNSCEAR 1993 Report [U3] indicated that the cancer risk per unit dose for external low-LET exposures at high dose rates (taken as >0.1 mGy min^{-1}) tends to be higher than that at low dose rates. Secondly, in addition to being protracted and specific to certain organs, it is important to note that internal exposures generally give rise to heterogeneous irradiation within organs, in contrast to most external instantaneous whole-body exposures. Thirdly, experimental studies as well as some epidemiological results indicate that, relative to low-LET radiation, the relative biological effectiveness (RBE) of high-LET radiation is a complex quantity that depends on radiation type and energy, on the dose and dose rate, and on the endpoint under study [N2].

64. The procedure adopted in the UNSCEAR 1994 Report [U2], which considered the above types of studies separately, will therefore be used in this Annex as well. However, some studies involve more than one type of exposure, e.g. external and internal exposures to workers at the Mayak plant and to the population around the Techa River in the southern Urals; these studies will therefore be considered under the type of exposure that is of greatest relevance to the cancer in question. In addition, there is value in comparing some of the results from studies based on different types of exposure; for example, in the case of external low-LET radiation, the results of high-dose-rate studies to which a dose and dose-rate effectiveness factor (DDREF) has been applied might be compared with the results of low-dose-rate studies. However, the distinction between high-dose-rate and low-dose-rate studies is not always clear. For example, exposures to diagnostic x rays are often fractionated but are delivered at a high dose rate. As a consequence, a comparison of findings from the instantaneous exposure of the Japanese atomic bomb survivors and findings from the fractionated exposures of tuberculosis patients who received multiple fluoroscopies [H7, H20, L39] may be more informative about the effects of fractionation than of dose rate. The main difficulty with this type of comparison, as will be shown, is the relatively low statistical power of studies of fractionated or chronic exposures for most individual cancer sites. While other types of comparison can be made concerning, for example, low- and high-LET studies, the complicating factors described above make this exercise difficult. In general, studies of specific types of exposure, such as exposure to radon, are best suited to estimating the associated risks.

D. RELEVANT STUDIES

65. In this Annex, information is examined from well conducted cohort, case-control, and case-cohort studies of radiation-exposed groups that include some assessment of the magnitude of radiation exposures. In describing and comparing these studies, attention is paid to, *inter alia,* the following:

(a) the potential for bias or for confounding by unmeasured factors;
(b) statistical power;
(c) the quality of estimates of radiation doses;
(d) the availability and quality of data on potential confounders and modifiers of radiation risk; and
(e) the availability and quality of data on cancer incidence and on cancer subtypes.

66. Relevant studies of the effects of exposures to low-LET radiation were listed in Table 2 of Annex A of the UNSCEAR 1994 Report [U2], while the strengths and limitations of these studies were summarized in Table 3 of the same Annex. Tables 2 and 3 of the current Annex expand on the tables in the earlier report by including more recent low-LET studies that incorporate estimates of the magnitude of radiation exposure. Chapter III of this Annex focuses on the more informative of these studies, based on the criteria cited in the preceding paragraph. Of these studies, the extended follow-up of mortality among the Japanese atomic bomb survivors [P9] is particularly important, since one of the main uncertainties in the assessment of radiation-induced cancer risks relates to the pattern of risk with time since exposure. Compared to the follow-up to 1985 [S3], this analysis contains 10,500 additional survivors with recently estimated DS86 doses, plus a further five years of follow-up. About 25% of the excess deaths from cancers other than leukaemia during 1950–1990 in this cohort arose in the last five years, between 1986 and 1990; for those exposed as children, this percentage rises to about 50%.

67. Tables 2 and 3 also cover studies of patients with therapeutic or diagnostic exposures, some of which are extensions of studies considered in the UNSCEAR 1994 Report [U2]. These tables are restricted to studies of postnatal and prenatal exposures. However, pertinent results from investigations of preconception irradiation are mentioned in this Annex. It should also be noted that combined analyses of some studies covered in Tables 2 and 3 of Annex A of the UNSCEAR 1994 Report [U2] were published subsequently; these included, in particular, analyses of nuclear workers [C11, I2] and of the effects of external irradiation of the thyroid [R4]. The results from these analyses are described in Chapter III of this Annex.

68. To complement Tables 2 and 3, which are specific to low-LET radiation, Table 4 lists studies of the effects of exposure to high-LET radiation that attempted to quantify levels of exposure, and Table 5 summarizes the strengths and limitations of the studies. Most of these studies were considered in the UNSCEAR 1994 Report [U2], although not in the same format as for the low-LET studies. It is important to note that, in some cases (e.g. for some of the early uranium miners and for exposures to residential radon many years ago), the exposure assessment was performed in the absence of measurements at the time of exposure. However, this caveat also applies to some studies of low-LET exposures.

E. SITE-SPECIFIC RISKS

69. One objective of this Annex is to derive and compare site-specific risk estimates from information provided in the various epidemiological studies. Relative and absolute risk estimates are presented and discussed in Chapter III. There are inherent differences in the exposure conditions, the study populations, and the evaluation procedures. Where the risk estimates available from various studies are in different formats with respect to the classification by factors such as age at exposure or where only fitted models have been presented, some life-table calculations have been performed to derive summary values that can be compared across studies. These calculations have been performed for three types of cancer, namely stomach, colon, and lung cancer. However, potential difficulties in the interpretation of such values need to be borne in mind. One of these concerns the consistency across studies of trends in radiation risks according to dose or modifying factors, which is examined in the relevant sections of Chapter III. Also, the comparison of summary values from studies in different countries with different baseline rates for certain cancer sites may be used in attempting to assess the appropriate means for transferring risks from one population to another.

70. As mentioned earlier, the main aim of these life-table calculations is to permit comparison across studies. To calculate values of measures such as REID that are of general applicability, it is preferable to use models derived for cancer sites for which large amounts of data are available or, possibly, for certain groupings of cancers, although the validity of this approach requires careful assessment. Clearly, the data on the survivors of the atomic bombings, both for mortality and cancer incidence, play a pivotal role in such an exercise. This topic is considered further in Chapter IV.

71. In assessing uncertainties, attention will be paid not only to sampling errors but also to factors such as dose and dose-rate effects, as well as variation with age, gender, and time. The extent to which such factors can explain differences between studies will be examined by, for example, presenting summary risk values based on a lifetime projection and on a period covered by the most recent follow-up. While it is unlikely that all of the uncertainties can be quantified, it is intended that the largest sources of uncertainty for each cancer site can be identified.

III. SITE-SPECIFIC CANCERS

72. Site-specific cancer risks following radiation exposure are examined in this Chapter. The organs, tissues, or types of cancer considered are those 15 cancer sites for which adequate epidemiological data are available. Each site is discussed in a separate Section, and the summary data and inferred risks are presented in the Tables listed below.

Site of cancer type	*ICD number (9^{th} revision)*	*Table(s)*
Oesophagus	150	6
Stomach	151	7, 22
Colon	153	8, 22
Liver	155	9
Lung	162	10, 22–25
Bone and connective tissue	170–171	11
Skin	172–173	12, 26
Female breast	174	13
Prostate	185	14
Urinary bladder	188	15
Brain and central nervous system	191–192	16, 27
Thyroid	193	17, 28, 29
Non-Hodgkin's lymphoma	200, 202	18
Hodgkin's disease	201	19
Multiple myeloma	203	20
Leukaemia	204–208	21, 30

73. A short description is given of the general epidemiological findings for each cancer site considered, including rates in different countries, trends over time, and factors other than radiation that are known to influence rates. Information on risks in relation to both low-LET and high-LET exposures is then considered in some detail, and conclusions are drawn.

74. The results included in Tables 6–21 are grouped according to the type of exposure (external or internal) and the radiation quality (low-LET or high-LET). Studies that provide very small numbers of cases or that do not quote sufficient detail have not been included in these Tables. Since the conditions of exposure, the characteristics of the study populations, and the extent and quality of the dosimetry, follow-up, etc. differ widely, the risk estimates are not strictly comparable. They do, however, illustrate the range and significance of estimates obtained and give some indication of the influence of the study-specific factors involved. Where possible, the estimates of the excess relative risk and the excess absolute risk in Tables 6–21 have been taken from the original publications. However, for the Life Span Study and for studies for which estimates were not cited in the associated publications, the methods described in Section I.C of Annex A of the UNSCEAR 1994 Report [U2] have been employed. In particular, if O denotes the observed number of deaths or cancer cases in the exposed population, E denotes the corresponding expected number, D the average dose and PY the number of person-years of follow-up, then the excess relative risk at 1 Sv is estimated by $(O - E)/(E \times D)$, and the excess absolute risk per unit dose and per unit time at risk is estimated by $(O - E)/(PY \times D)$. Instances where this approach has been implemented are indicated by a footnote in Tables 6–21. It should be noted that the results based on this methodology might differ from those based on a dose-response analysis, if data subdivided into intervals of dose were available for the exposed population.

75. Lifetime risk estimates for those studies for which estimates of ERR are available are given in Table 22. The values in this table, which are restricted to stomach, colon, and lung cancer, arise from applying the ERR estimates to baseline mortality rates for Japan, as was done in the UNSCEAR 1994 Report, and extrapolating over time both with the ERR remaining constant and with the ERR declining to zero at age 90 years, again in line with the UNSCEAR 1994 Report [U2]. As mentioned earlier, the aim of these calculations is to permit comparison across studies.

A. OESOPHAGEAL CANCER

76. Cancer of the oesophagus is the ninth most common cancer in the world and is characterized by remarkable variations from country to country and among ethnic groups in individual countries [M40]. Oesophageal cancer rates are generally low in many countries. Extremely high rates are observed in China and among Chinese immigrants and in central Asia; intermediately high rates are seen in black populations in Africa and the United States and in some Caribbean and South American areas [M43]. Oesophageal cancer is almost always fatal, so mortality very closely approximates incidence. Heavy consumption of alcohol and tobacco has long been known to increase the risk of oesophageal cancer, and this contributes to the geographic distribution. Secular trends of oesophageal cancer vary among different populations. There has been a marked decrease in China as the lifestyle changes, a steady increase among blacks in the United States, a possible decline in central Asia, and a slow decline in Finland, India, and Latin America [D28].

77. Few epidemiological studies have evaluated the role of radiation in the aetiology of cancer of the oesophagus. The limited data for external and internal low-LET exposures are presented in Table 6.

1. External low-LET exposures

78. Overall, the Life Span Study data do not provide convincing evidence of a link between oesophageal cancer and radiation, although a significant excess in oesophageal cancer mortality occurred in the early years of follow-up, i.e. from 5 to 12 years after exposure. The Life Span Study mortality data also show a higher, although not significant, ERR for this cancer in females than males. Higher relative risks in females have been observed for most other solid cancers [P9]. Cancer incidence data from the Life Span Study, which began 12 years after exposure, do not show a significant excess risk of oesophageal cancer [T1].

79. The ankylosing spondylitis study is the only one to report a significant risk of radiation-associated oesophageal cancer. In contrast to the atomic bomb data, there was no significant variation in risk since first treatment [W1]. Data from other medically exposed populations considered here show no excess oesophageal cancer risk (Table 6).

2. Internal low-LET exposures

80. Very little epidemiological information is available for oesophageal cancer associated with internal low-LET exposures. The data that are available from patients treated with ^{131}I for adult hyperthyroidism [R14] show no increased risk of this cancer, but the doses received by the oesophagus were considered to be small.

3. Internal high-LET exposures

81. Data on oesophageal cancer following high-LET exposures are available from several worker studies, most of which involve small numbers of oesophageal cancers. The most informative studies are those of nuclear workers in the United Kingdom. In a study of the three nuclear industry workforces in the United Kingdom, 23 deaths from oesophageal cancer were observed among plutonium workers when 21.3 had been expected [C33]. An analysis of workers who were monitored for exposures to uranium, polonium, actinium, and other radionuclides (apart from tritium), showed 9 deaths from oesophageal cancer compared with 16.1 expected [C33]. Doses to the oesophagus were not available but are considered to be small.

4. Summary

82. Cancer of the oesophagus has been associated with radiation exposure in some studies. Much of the information is for external low-LET exposures, with few data available for internal high-LET exposures. The results from the Life Span Study of survivors of the atomic bombings indicate an excess risk only in the early period following exposure. The ankylosing spondylitis data show a continuing risk, while other medical studies have not demonstrated excess cases of oesophageal cancer. Very few epidemiological data are available on radiation risks for this type of cancer, which is infrequent in many countries. Since oesophageal cancers are extremely common in some parts of the world and for some ethnic groups (e.g. in China and for Chinese populations), more studies are needed to understand the magnitude and nature of the risk, especially the temporal pattern.

B. STOMACH CANCER

83. Incidence rates for stomach cancer vary considerably throughout the world [P5], with particularly high rates in Japan (Table 1). Many countries, including Japan, have seen decreases in incidence and mortality rates during the past few decades [C14]. These changes are likely in large part to reflect changes in diet, in particular, increases in the consumption of fresh vegetables and fruits and de-creases in salt intake, which case-control studies have shown to be linked to reduced stomach cancer risks [K12]. Infection with *Helicobacter pylori* [S43], which in developing countries can often reoccur rapidly following antimicrobial therapy [R36] and which can lead to gastritis, has been associated with elevated stomach cancer risks in descriptive and cohort studies [C14, K12]. In addition, smoking has been linked to modest excesses of stomach cancer in some cohort studies [D11, H28].

84. Several epidemiological studies have shown enhanced stomach cancer risks following exposure to radiation. Studies of external low-LET, internal low-LET, and high-LET radiation are considered separately in this Section.

1. External low-LET exposures

85. Included in Table 7 are the cohort and case-control studies of low-LET exposure for which radiation doses have been assessed. Among these studies, the Life Span Study of the survivors of the atomic bombings in Japan [T1, P9] has the largest number of observed stomach cancers. This is primarily a reflection of the high baseline rates in Japan, since it has been estimated that fewer than 10% of the cancers among exposed survivors are attributable to radiation [T1, P9]. Indeed, compared with national or regional rates, the estimated excess number of cases in the international cervical cancer study [B1] is larger than in the Life Span Study [T1], owing mainly to the higher mean dose in the former study. However, the large numbers of cancers in the Life Span Study make it possible to examine factors that may modify radiation-induced risks. In particular, based on the cancer incidence data, Thompson et al. [T1] showed that the dose response was consistent with linearity and that the ERR per Sv was higher for females than for males, decreased with increasing age at exposure, and did not vary significantly with time since exposure. The mortality findings up to 1990 [P9], summarized in Table 7, accord with the incidence results up to 1987 [T1].

86. Only a few of the other studies listed in Table 7 have sufficient statistical precision to permit meaningful comparison with the Life Span Study. The case-control study of patients treated for cervical cancer [B1] showed a trend in stomach cancer risk with dose that was of borderline significance. It is notable that the ERR per Sv estimated from this study appears to be consistent with that for female survivors of the atomic bombings irradiated in adulthood and that the estimate from the cervical cancer study of the EAR per Sv is lower than that from the Life Span Study, although the confidence intervals are wide. This might suggest that in transferring radiation-induced stomach cancer risks from Japan (which has high baseline rates) to countries in North America and Europe (which contributed to the cervical cancer study and which have lower baseline rates), it would be better to use a multiplicative than an additive model, that is, to transfer the ERR per Sv rather than the EAR per Sv. This is reinforced by Part A of Table 22, which shows that estimates of lifetime risk based on applying estimates of the ERR per Sv to Japanese baseline mortality rates are similar across the Life Span Study, the cervical cancer study, and other studies. Caution is called for, in that a range of other transfer methods would be consistent with these data. However, it is noteworthy

that the estimates of EAR per Sv from the Life Span Study are higher than those from several of the other external low-LET studies in Table 7, whereas the estimates of ERR per Sv are less variable between the studies with the greatest statistical precision.

87. Another important study that can be compared with the Life Span Study of survivors of the atomic bombings is that of patients in the United Kingdom irradiated for ankylosing spondylitis [W1]. Overall there was no excess of stomach cancer in the latter study, although there was some suggestion of an elevated risk 5–24 years after exposure. While there was no evidence of an increasing trend in risk with the number of treatment courses, data on individual stomach doses were not available [W1], compli-cating the comparison of risk estimates. Another study, that of peptic ulcer patients [G6], showed similar values for males and females of the ERR per Sv, in contrast to the Life Span Study, although the number of cancers in the former study was much smaller and the mean dose (about 15 Sv) was much larger.

88. Studies of occupational exposure to external low-LET radiation may be of value in examining risks associated with protracted or low-dose-rate exposure. In a combined analysis of radiation workers in Canada, the United Kingdom, and the United States, Cardis et al. [C11] found no statistically significant trend in stomach cancer risk with dose. Although the number of stomach cancers in this study was quite high relative to other the studies considered in Table 7, the generally low radiation doses received by these workers meant that the study had low statistical precision to estimate risks for this type of cancer. Similarly, a study of nuclear workers in Japan [E3], where (as just noted) baseline rates of stomach cancer are higher than in other countries, lacked precision because of the small doses. In contrast, a case-control study of stomach cancer among workers at the Mayak plant in Russia included some individuals with doses in excess of 3 Gy [Z1]. Although the number of cases in this dose category was modest (see Table 7), doses of this magnitude were associated with a statistically significant elevated risk. Comparison of these results for protracted exposure with the estimated ERR per Sv from the studies of acute exposure included in this table is made difficult by the lack of details on, for example, the mean doses in the categories considered in the Mayak study [Z1]. In addition, there was no significant dose response over the full range of external doses in this study, whereas there was weak evidence of an elevated risk associated with the level of plutonium body burden and with occupational chemical exposure [Z1]. Stomach cancer risks among these workers were also reported to be positively associated with gastritis and smoking, in line with other studies referenced earlier. In particular, there was some suggestion that external doses above 3 Gy interacted submultiplicatively with gastritis and multiplicatively with smoking in the incidence of stomach cancer, although as already indicated, the numbers in this dose category are not large. Additional details of the study design, for example, the means by which the study subjects were identified and information on factors such as smoking was collected, would have to be known to evaluate these findings.

89. Low-dose, protracted exposure from background radiation has been studied in the Yangjiang area of China [T25, T26]. While this did not show an association with stomach cancer risk (see Table 7), the precision of the study was not great, in common with the low-dose occupational studies mentioned above [C11, E3].

2. Internal low-LET exposures

90. In a study of about 10,000 Swedish patients treated with ^{131}I for hyperthyroidism, raised incidence [H23] and mortality [H24] from stomach cancer relative to national rates were reported (see Table 7). Furthermore, there were indications of an increasing trend in risk with increasing administered activity of ^{131}I, although this trend was not statistically significant. Some caution should be attached to the interpretation of these findings. The authors examined a range of different cancer sites, so it is quite possible that one of them would show a positive finding by chance. However, it is notable that the mean dose to the stomach in this study, namely 0.25 Gy, was higher than that to other organs apart from the thyroid and was similar to the mean stomach dose among exposed atomic bomb survivors (see Table 7). Some other studies of hyperthyroid patients treated with ^{131}I [F8, G10, H25] have not reported raised rates of stomach cancer, although in some instances their statistical precision was low. Statistical precision was also a problem for studies in Sweden [H26], Italy [D15], Switzerland [G13], and the United Kingdom [E2] of thyroid cancer patients treated with ^{131}I, owing to the small number of subsequent stomach cancers; furthermore, risks in these studies were not analysed according to the level of exposure. In contrast, a large study of hyperthyroidism patients in the United States [R14] has reported rates of stomach cancer mortality that are generally consistent with national rates and that do not appear to show a relation with the level of ^{131}I administered, although there was some suggestion of an elevated risk associated with anti-thyroid drugs.

91. The relevant part of Table 7 also shows that the estimate of the ERR at 1 Gy from the Swedish hyperthyroidism study [H23, H24] is consistent with that from studies of external low-LET exposure. However, given the limited number of cases, the study is likely to be consistent with a range of other values. It is therefore difficult, based on this study, to reach a conclusion about how stomach cancer risks from acute, external, low-LET exposure compare with those from protracted internal low-LET exposure.

3. Internal high-LET exposures

92. The studies of patients with exposures to radium and thorotrast listed in Table 7 do not tend to indicate elevated risks of stomach cancer relative to unexposed patients. This probably reflects both the modest numbers of cases and, more particularly, the likely low doses to the stomach compared with some other organs. It should also be pointed out that these studies have not analysed risk in relation to individual exposures.

93. Stomach cancer was one of the cancers studied in a collaborative analysis of data from 11 cohorts of underground miners exposed to radon [D8]. Stomach cancer mortality among this group of over 64,000 men was significantly higher than national or local rates (relative risk = 1.33; 95% CI: 1.16–1.52, based on 217 deaths). However, there was no trend in stomach cancer mortality with the cumulative radon exposure received by these miners [D8]. Furthermore, excesses of stomach cancer have been reported in some other groups of miners, such as gold miners [K13] and coal miners [S25]. This, together with the low doses to the stomach from radon exposure, suggests that exposures in mining environments to agents other than radon or other factors such as smoking habits are responsible for these excesses. Among female radium dial workers in the United States, there was a statistically significant increase, relative to regional rates (SMR=3.89), in mortality from stomach cancer among those who started work in 1930 or later, although this was based on only seven deaths [S16]. The absence of an elevated risk among those who started work before 1930 and whose exposures from radium tended to be higher, suggests that the finding for the later workers is not due to ingested radium [S16].

4. Summary

94. Much of the information on stomach cancer risks following radiation exposure comes from the Life Span Study of survivors of the atomic bombings. This reflects not only the large cohort, long follow-up, and wide range of doses but also the high baseline rates for the disease in Japan. The Life Span Study indicates that the dose response is consistent with linearity and that the ERR per Sv decreases with increasing age at exposure, does not appear to vary with time since exposure, and may be higher for females than for males (although one study of medical irradiation may not agree with the latter finding). Some, but not all, studies of external low-LET medical irradiation also show an association between radiation exposure and stomach cancer risk. In particular, the findings from the Life Span Study and the study of cervical cancer patients suggest that it might be more appropriate to transfer relative risks, rather than absolute risks, from Japan to other countries. Studies of low-dose, occupational, low-LET exposure lack precision; a study of protracted, high dose, occupational exposure did indicate an elevated risk, although it is difficult to use it to quantify a dose or dose-rate-effectiveness factor. Studies of internal low-LET and high-LET exposures generally provide little information on stomach cancer risks.

C. COLON CANCER

95. Incidence rates for colon cancer vary considerably around the world [P5, P17] (see Table 1). The highest rates are mainly in North America and western Europe, although some countries with previously low colon cancer rates, such as Japan, now have rates just as high [P17]. Descriptive studies indicate that these patterns are largely associated with diet. Cohort and case-control studies tend to confirm this, with meat consumption being related to an increased risk and vegetable consumption to a decreased risk [P17]. Studies of this type have also shown colon cancer risk to be related inversely to the degree of physical activity [P17]. In addition to lifestyle factors, several rare, genetically determined conditions affect risks [U15]. In particular, familial clustering of colon cancer is thought to be due to an autosomal recessive gene [M22].

96. Colon cancer risks have been examined in various epidemiological studies of radiation-exposed groups. The findings of these studies, classified according to radiation type, are summarized in Table 8. Although it sometimes can be difficult to distinguish rectal cancer from colon cancer, the role of ionizing radiation appears to differ substantially in the aetiology of the two cancers, with cancer of the rectum rarely showing a link with radiation [T1, P9].

1. External low-LET exposures

97. The Life Span Study shows a clear association between external dose and colon risk to the survivors, based both on incidence [T1] and mortality [P9] data. Detailed analysis of the incidence data shows that the dose response is consistent with linearity [T1]. However, it is noticeable from Table 8 that studies with mean colon doses of several Sv or more, namely those of patients treated for cervical cancer [B1] or peptic ulcer [G6], show little or no evidence of an elevated risk. This suggests a possible cell-killing effect at very high doses. However, an excess of stomach cancer was seen among the peptic ulcer patients [G6], whose mean stomach dose exceeded the dose to the colon, although this might be explained by differences from organ to organ in the degree of cell killing. There is no clear pattern in the ERR per Sv by gender or age at exposure among the atomic bomb survivors, which may reflect statistical imprecision. In contrast, while the incidence data suggest that the ERR per Sv may be decreasing with increasing time since exposure [T1], the corresponding values for mortality in Table 8 would suggest, if anything, a trend in the opposite direction, although the confidence intervals are wide. However, it is clear from Table 8 that the EAR per Sv for mortality is increasing with increasing time since exposure.

98. The comparison of risk estimates across studies, in considering how colon cancer risks should be transferred across populations, is complicated by the changing baseline rates in Japan referred to earlier. Furthermore, the confidence intervals for values of the ERR and EAR per Sv estimated from the studies listed in Table 8 are wide and are consistent with various transfer methods. This is confirmed by Part B of Table 22, which shows lifetime risk estimates (based on an implicit multiplicative transfer across populations) that are fairly similar in the Life Span Study and the study of women in the United States treated for benign gynaecological disease [I16] but smaller in other studies of populations in North America and western Europe. It is therefore not possible to come to a firm conclusion on how to transfer colon cancer risks across

populations. It is also not possible to make a meaningful comparison of risks from high- and low-dose-rate exposures, owing to the large imprecision in estimates derived from studying nuclear workers [C11, E3].

2. Internal low-LET exposures

99. Few data are available on colon cancer following internal exposure to low-LET radiation. Among Swedish patients treated with ^{131}I for hyperthyroidism, the standardized incidence ratio for colon and rectal cancer combined was 1.17 (95% CI: 0.97–1.39) after 10 or more years of follow-up [H23]. However, results for colon cancer alone were not presented or analysed in relation to the level of iodine administered. It should be noted that the mean dose to the colon and rectum from this treatment was estimated to be 0.05 Gy [H23], suggesting that any analysis of risk in relation to the level of exposure would have had low statistical precision. Studies of patients treated with ^{131}I for hyperthyroidism in the United States [G10, H25, R14] and for thyroid cancer in Sweden [H26], together with a study of diagnostic exposures in Sweden [H27], did not report findings specifically for colon cancer. However, a large study of hyperthyroidism patients in the United States provided little indication of an elevated risk of colorectal cancer mortality [R14].

3. Internal high-LET exposures

100. Numbers of colon cancers reported from studies of thorotrast patients are included in Table 8. Here, as in the combined analysis of underground miners exposed to radon [D8] and in studies of radium patients [N4] and radium dial workers [S16], the very low doses to the colon associated with these exposures preclude meaningful inferences.

4. Summary

101. Data on the Japanese atomic bomb survivors are consistent with a linear dose response. The effect of gender, age at exposure, and time since exposure on the ERR per Sv is not clear, although the EAR per Sv does increase with increasing time since exposure in the Life Span Study. Changes over time in baseline rates in Japan make it difficult to decide how to transfer risks across populations. Also, the lack of precision in low-dose studies of external low-LET radiation and of internal low-LET and high-LET radiation do not allow conclusions to be drawn.

D. LIVER CANCER

102. The liver is one of the most frequent sites for metastatic cancer. Since a large proportion (as high as 40%–50%) of liver cancers reported on death certificates are tumours originating in other organs, mortality data are usually a poor measure of the magnitude of primary liver cancer. It is therefore difficult to obtain reliable estimates of the magnitude of liver cancer in many countries and populations. Cancer incidence data, which provide more reliable diagnostic information, are available for various parts of the world, but their quality also varies. Liver cancer is one of the eight most common cancers in the world, accounting for 5.6% of the new cancers in males and 2.7% in females, but there is a wide geographic variation [M40]. Liver cancer is a common disease in many parts of Asia and Africa but is infrequent in the United States and Europe [P29]. The incidence of liver cancer has been increasing in Japan and the Nordic countries [S45], although some of the increasing trends may be explained by changes in disease classification and coding practices.

103. The great majority of primary liver cancers in adults are hepatocellular carcinomas. It has been estimated that about 80% of hepatocellular carcinomas are aetiologically associated with chronic infection with hepatitis B virus [L43]. Infection with hepatitis C virus also plays an important role in some countries, notably in Japan. Alcohol consumption and liver cirrhosis have been shown to increase the risk of hepatocellular carcinoma, but their precise roles have yet to be clarified. In general, hepatocellular carcinoma occurs much more frequently in men than in women (male:female ratio of 4–5:1). Other types of liver cancer include cholangiocarcinoma and angiosarcoma, which are rare in adults. The male preponderance is less pronounced for cholangiocarcinoma (male:female ratio of 1–2:1) than for hepatocellular carcinoma. Liver cancer has been associated with infestations with liver flukes in certain areas as well as with exposure to thorotrast [P29, T1].

1. External low-LET exposures

104. Epidemiological data on liver cancer associated with external exposures to low-LET radiation exposure are limited. Far more information is available on internal high-LET exposure, especially thorotrast (see below). The available data are presented in Table 9. None of the medically and occupationally exposed populations included in this review suggest an association between radiation exposure and liver cancer. Where an increased standardized mortality ratio (SMR) for liver cancer is found, further analyses do not support a dose-response relationship. Furthermore, because a large number of metastatic tumours may be misclassified as liver cancers on death certificates, some of the observed excess liver cancer may be attributable to the inclusion of tumours originating in other organs. The most convincing evidence for excess liver cancer associated with low-LET exposure comes from the Life Span Study. In the latest Life Span Study report [P9], there are 432 deaths from primary liver cancer (939 including those specified as primary and those specified as secondary), the third leading cause following stomach and lung cancers. A significant dose response is found for liver cancer, with an ERR per Sv of 0.52 for males and 0.11 for females, both exposed at age 30 years.

105. Cancer-incidence-based data obtained from the systematic collection of information reported by hospitals to tumour registries have better diagnostic accuracy. The analysis of the Life Span Study cancer incidence data showed for the first time a significantly increased risk of liver cancer associated with radiation exposure from the

atomic bombings. A subsequent study involved 518 cases of liver cancer, mostly hepatocellular carcinoma, verified by a detailed pathology review of each case [C37]. The dose response was linear and an ERR was estimated to be 0.81 per Sv (liver dose). Males and females had a similar relative risk so that, given a three-fold higher background incidence for males, the radiation-induced excess incidence was substantially higher for males. The excess risk peaked for those exposed in the early 20s with essentially no excess risk in those exposed before age 10 or after 45 years.

2. Internal low-LET exposures

106. Epidemiological data are even more sparse on liver cancer and internal low-LET exposures. In the United States thyrotoxicosis study in which about 21,000 hyperthyroid patients treated with ^{131}I were followed up to 45 years, 39 liver cancer deaths were observed with an SMR of 0.87 [R14]. The doses received by the liver were not estimated but are presumably very low.

3. Internal high-LET exposures

107. Thorium-232 is a primordial, long-lived, alpha-emitting radionuclide. Colloidal (^{232}Th) thorium dioxide (thorotrast) was used widely as an intravascular contrast agent for cerebral and limb angiography in Europe, the United States and Japan from 1928 to 1955. Intravascularly injected thorotrast aggregates tend to be incorporated into the tissues of the reticuloendotheial system, mainly the liver, bone marrow, and lymph nodes. Deposition results in continuous alpha-particle irradiation throughout life at low dose rate. The radiation dosimetry is complex because of the non-uniform distribution of thorium dioxide in the liver, bone marrow and lymph nodes and the possible effects of the colloidal material on cancer risk [C2]. It has been estimated that the typical annual dose from alpha radiation following an injection of 25 ml of thorotrast is 0.25 Gy to the liver [K28, M41], but a re-evaluation of liver organ mass has indicated that the annual dose is 0.40 Gy [K41]. A revised whole-body organ partition of ^{232}Th has shown a small reduction in the relative partition to the liver, but the estimated liver dose remains essentially the same [I25]. Patients who were administered thorotrast from the late 1920s through to 1955 have been followed in Germany, Portugal, Denmark, Sweden, Japan and the United States. The total number of people being followed is approximately 5,500, and over 90% of them have died.

108. In Germany, about 5,000 patients treated with thorotrast for cerebral angiography (about 70%) or arteriography of the limbs (about 30%) between 1937 and 1947 at different hospitals were identified [V3, V7, V8]. As controls, a similar number of age- and gender-matched non-thorotrast treated patients were identified among patients at the same hospitals. When the follow-up study was started in 1968, a large number of the patients had already died. The causes of death among those patients were identified from hospital examinations or death certificates. There were 2,326 thorotrast patients (1,718 males and 608 females) and 1,890 controls (1,407 males and 483 females) who survived three years or more after treatment, could be traced. The patients (899 thorotrast patients and 662 controls) who were still alive at that time have since been followed through clinical examination every two years. The latest follow-up data show 48 thorotrast patients and 239 controls who are still alive [V8]. In the deceased patients, the most common neoplastic disease is liver cancer (454 thorotrast patients compared with 3 controls) [V8]. Previous data showed that cholangiocarcinoma and haemangiocarcinoma, which are norm-ally rare types of liver tumour, accounted for about 54% and hepatocellular carcinoma for only 17%; histological types were unknown for the remaining 29%.

109. In the German study, the cumulative rate of liver cancer was correlated with the mean dose of administered thorotrast, although no formal dose-response analyses were performed. No age-at-exposure effect was observed, as the cumulative rate of liver cancer was similar for the three cohorts having different ages at injection (1–14, 15–29, 30–44, and 45–59 years) [V8]. Recent data suggest an increase in liver cancer among those who received less than one ampoule of thorotrast (less than 6 or 6–12 ml thorotrast) [V8]. Although there was no gender difference with regard to age at injection and mean volume of injected thorotrast and exposure time, the cumulative rate of liver cancer was significantly higher in males than in females. As a measure of the total risk, the cumulative rate was calculated using the sum limit method, i.e. by taking the cumulative number of liver cancers after injection (excluding those dying within the first 15 years of exposure as they are not considered to be due to thorotrast) as the numerator and the cumulative dose of all patients up to 10 or 15 years (wasted dose or time) before clinical manifestation of liver cancer as the denominator. The cumulative risk of liver cancer was estimated to be 607 10^{-4} Gy^{-1} (with 10 years wasted dose) and 774 10^{-4} Gy^{-1} (with 15 years wasted dose) [V8].

110. The continuing follow-up of the Danish thorotrast study, although based on a smaller number of patients than the German study, has provided further detailed epidemiological information [A5, A18, A19]. The thorotrast group consisted of 999 neurological patients treated with thorotrast for cerebral angiography between 1935 and 1947. The group has been followed through linkage to the national death register and the cancer registry in Denmark. Previous analyses of cancer incidence data from this cohort study had been based on SIRs compared to the national cancer data. To avoid possible confounding due to the neurological conditions for which the patients were treated, a control group (1,480 persons) was identified from patients who had been examined during 1946–1963 with cerebral arteriography using contrast agents other than thorotrast [A5].

111. The latest analyses of the Danish thorotrast study data are based on 751 deaths in the thorotrast group and 797 deaths in the control group up to January 1992 [A5]. At the end of follow-up, 40 thorotrast patients and 422 controls were still alive. Since the thorotrast and control groups differed with respect to calendar period and were

not matched for gender, age at arteriography, or neurological condition, multiplicative regression models were fitted, allowing the SMR to vary with gender, age at arteriography, and calendar period. For the thorotrast patients, the models included the amount of thorotrast injected (as a measure of dose rate) and the amount injected multiplied by the time since the injection (as a measure of the cumulative alpha-radiation dose). When evaluated in multiple regression analyses, the effect of injected volume was significant for cancer (relative risk per 10 ml = 11.1; 95% CI: 3.5–34.0) and benign liver conditions (relative risk per 10 ml = 1.2; 95% CI: 1.1–1.3). Analyses of specific cancer types were based on cancer incidence cases (315 cases in the thorotrast group and 201 cases in the control group). Primary liver cancer was the most frequent type of cancer among the thorotrast-exposed patients. There were 84 cases reported as primary liver cancer, 16 reported as liver cancer not specified as primary. A significant effect of injected volume of thorotrast was seen for liver cancer (relative risk per 10 ml = 194; 95% CI: 31–1,220) and as a consequence for all cancers combined (relative risk per 10 ml = 14.7; 95% CI: 5.2–41.5). No effect of the surrogate measure of cumulative dose was seen.

112. The earlier analyses of the Danish thorotrast cancer incidence data showed a positive trend in SIR for liver tumours with young age at injection. However, the cumulative frequency of liver cancer relative to the estimated cumulative radiation dose to the liver showed no significant difference between those injected at different ages (0–25, 26–45, 46–59, and older than 59 years). The female:male ratio for liver cancer was 1.6, but the cumulative frequency of liver cancer relative to the estimated cumulative radiation dose to the liver did not differ for males and females. This is in contrast to the German study, which suggested a larger absolute risk for males than females [V8]. In a separate study in Denmark [A18], cases of primary liver cancer were reclassified by a pathology review. As with the German thorotrast series, cholangiocarcinoma (34%) and haemangiosarcoma (28%) were relatively common, while hepatocellular carcinoma accounted for 38% of cases. However, no significant differences were found between three histological types with respect to such factors as age at injection of thorotrast, mean amount injected, mean time from injection to diagnosis, or mean estimated cumulative alpha-radiation dose. The incidence of all histological subgroups was described most simply as a function of the estimated cumulative dose up to 15 years previously.

113. In Japan, two cohorts of thorotrast patients have been followed. An early study initiated in 1963 involves 262 war veterans who received intravascular injection of thorotrast (with a mean of 17 ml per injection) for diagnosis of injuries during 1937–1945 and a control group of 1,630 war-wounded veterans [M42]. As of 1998, 244 (93%) thorotrast patients had died, of whom 79 died from liver cancer [M47]. The second study began in 1979 after a nationwide survey of thorotrast patients with diagnostic x rays, and this cohort includes 150 thorotrast patients [K33]. As of 1998, 132 (82%) patients had died, of whom 64 died from liver cancer. Analyses of combined data from these two cohorts show the rate ratio for all causes, compared to controls, to start to increase after a latency period of 20 years after the thorotrast injection [M14]. The rate ratio is highest for liver cancer (35.9) [M14]. Using previous data, the risk of liver cancer was estimated to be 330 10^{-4} Gy^{-1} with a linear dose-response model [U2]. A study of an autopsied series of 106 thorotrast-related liver malignancies showed that 44 (42%) were cholangiocarcinoma, 42 (40%) were angiosarcoma, 17 (16%) were hepatocellular carcinoma, and three were double cancers [K29].

114. The Portuguese thorotrast study was set up in 1961. It involved about 2,500 patients injected with an average of 26 ml of thorotrast between 1929 and 1955 and 2,000 controls [D27, H46]. They were followed for 30 years. Of 1,244 traced thorotrast patients, 955 had died, 137 of them from malignant tumours, including 87 primary liver cancer. The BEIR IV Committee estimated the risk for liver cancer to be 275 10^{-4} Gy^{-1} [C2]. The follow-up of this cohort was interrupted in 1976, but has recently been reactivated. The results of the follow-up extended through 1996 have been made available [D31]. A total of 1,931 patients who received thorotrast systemically and 2,258 unexposed subjects were initially identified from medical records. Follow-up was possible for 1,131 (59%) of the thorotrast patients and 1,032 (46%) of the unexposed patients. By the end of 1996, 92% of the thorotrast patients and 5% of the unexposed patients had died. The relative risk was significantly elevated for liver cancer (70.8) and for leukaemia (15.2), which accounted for most of the excess mortality from malignancies.

115. Liver cancer mortality has been studied among about 11,000 workers exposed to both internally deposited plutonium and to external gamma radiation at the Mayak nuclear plant in the Russian Federation [G23]. Within this cohort, liver cancer risks were elevated among workers with plutonium body burdens estimated to exceed 7.4 kBq, compared to workers with burdens below 1.48 kBq (relative risk 17; 95% CI: 8.0–36), based on 16 deaths in the former group. In addition, trend analyses using plutonium body burden as a continuous variable indicated an increasing risk with increasing burden ($p<0.001$). However, because of limitations in the current plutonium dosimetry, it was not possible to quantify liver cancer risks form plutonium in terms of organ dose, nor to make a reliable evaluation of the risk from external radiation in this cohort [G23].

4. Summary

116. While an association of liver cancer with radiation exposure has not been demonstrated in medical and worker studies involving external or internal low-LET exposures, the mortality data from the Life Span Study of survivors of the atomic bombings indicate a significant dose response. This relationship is strengthened by the analysis of incidence data based on histologically and clinically

verified primary liver cancer cases. Studies of thorotrast-exposed patients consistently show increased risks of liver cancer from alpha-radiation exposure.

117. While the types of liver cancer associated with thorotrast exposure are typically cholangiocarcinoma, followed by angiosarcoma and hepatocellular carcinoma, the excess risk associated with low-LET exposure in the Japanese atomic bomb survivors is primarily hepatocellular carcinoma. Liver cancer rates are high in Japan, especially in males, and the high rates have been attributed to infection with hepatitis viral infection, particularly hepatitis C virus. In transferring liver cancer risks from one population to another, differences in background liver cancer rates, as affected by the prevalence of hepatitis viral infection, should be considered.

E. LUNG CANCER

118. Although lung cancer was once a rare disease, it is now one of the leading causes of cancer mortality in industrialized countries and is rising in incidence in many developing countries [G1]. Table 1 illustrates the wide variation in rates between different populations. The geographical and temporal differences in incidence and mortality largely reflect cigarette smoking, which has been shown by epidemiological and toxicological evidence to be the main cause of the disease [U17]. Assessments made in the early 1980s indicate that occupational exposures to agents such as arsenic, asbestos, chromium, and nickel may account for 5%–15% of lung cancers in the general population of industrialized countries such as the United States [D6, S6], while outdoor air pollution arising from fuel combustion and industrial sources is thought to be responsible for only a few percent of cases in most areas [D6].

119. In addition to the above factors, ionizing radiation has been shown in numerous epidemiological studies to be a lung carcinogen [U2]. Increased risks have been shown not only with respect to exposure to low-LET radiation but also from exposure to radon and its progeny. Such increases have also been reported in animal studies [C4, U16]. Results from epidemiological studies of low-LET and high-LET exposures are presented in Table 10.

1. External low-LET exposures

120. The results from the latest mortality follow-up of the Japanese atomic bomb survivors [P9] bear out many of the results of the previous mortality and incidence studies. In particular, the dose response is consistent with linearity, and the ERR per Sv is higher for females than for males. However, compared with the previous follow-up, there is more indication now of similarities in the EAR per unit dose for males and females (see Table 10). Taking into account the wide confidence intervals, there is little to suggest that the ERR varies in a consistent fashion with either age at exposure or attained age, either in the incidence [T1] or the mortality data [P9]. In contrast, Pierce et al. [P9] showed that the EAR per Sv for mortality increases sharply with increasing attained age, reflecting the pattern in baseline rates, whereas (after adjusting for attained age) age at exposure does not appear to influence the EAR per Sv.

121. It should be noted that these analyses do not take account of smoking habits. As indicated above, much of the variation in baseline rates between populations reflects differences in smoking habits, so examination of the joint effect of radiation and smoking is highly pertinent to the issue of how to transfer risks across populations. The UNSCEAR 1994 Report [U2] gave some details of a 1986 study of radiation and smoking among a subgroup of the atomic bomb survivors [K8]. The findings from this study may need to be qualified, since they are based on the use of the previous dosimetry system for the survivors and on data on cancer incidence only up to the end of 1980. Furthermore, as in an earlier analysis based on mortality up to 1978 [P13], neither an additive nor a multiplicative model for the joint effect of smoking and radiation was totally inconsistent with the data. However, the suggestions from this analysis of an additive rather than multiplicative effect of low-LET radiation and smoking on lung cancer risk might explain the higher ERR per Sv for females than for males. It is possible that smoking could explain some of the other findings described earlier, such as the lack of trend in the ERR with age at exposure.

122. Further information on the joint effect of radiation and smoking comes from a case-control study of lung cancer incidence among patients treated for Hodgkin's disease in the Netherlands [V2]. In contrast to the Life Span Study findings, there was a statistically significant supramultiplicative effect of radiotherapy dose to the affected lung area and the cumulative amount smoked after diagnosis of Hodgkin's disease. Indeed, a trend in lung cancer risk with radiation dose was evident only among those who had smoked more than a small amount in the period following the original diagnosis. Some caution should be attached to these results. There were only 30 persons in total with lung cancer, of whom 8 were either non-smokers or light smokers. Furthermore, other measures of smoking, such as the number of years smoked before diagnosis of Hodgkin's disease or lifetime consumption, did not show the above supramultiplicative effect. Therefore the possibility of a chance finding cannot be excluded. An alternative interpretation is that smoking may have a strong promoting effect on the induction of lung cancer following an earlier radiation exposure. However, it should be recognized that many of those who smoked after the diagnosis of Hodgkin's disease had also smoked before that time, which makes examination of the interactions even more complicated. A larger, international study of lung cancer incidence following Hodgkin's disease [K9] also collected information on smoking, although this was limited to never/ever smoked and may have been reported more fully for cases than controls. In contrast to some other studies (e.g. [V2]), this international study showed an elevated risk associated with chemotherapy. Risks by type of therapy were reported to be

similar for smokers and for all subjects, although a formal statistical analysis of the joint effect of radiation and smoking was not undertaken. Although, if anything, there appeared to be more evidence of a radiation-induced risk among the patients who did not receive chemotherapy (relative risk = 1.6; 95% CI: 0.66–4.12, for lung doses above 2.5 Gy relative to less than 1 Gy), neither among those patients nor among patients who received chemotherapy did the trend with radiation dose approach statistical significance.

123. The only other study in Table 10 that shows an excess of lung cancer associated with low-LET radiation and that has sufficient numbers to permit examination of modifying factors is that of patients in the ankylosing spondylitis study in the United Kingdom [W1]. It should be borne in mind that, in contrast to other studies, in the ankylosing spondylitis study it was not possible to estimate individual doses to organs other than the bone marrow. This makes it difficult to address the transfer of risks between populations, although it might be worth noting from the above table that the ERR per unit dose estimated for the ankylosing spondylitis study is lower than that from the Life Span Study of the atomic bomb survivors. Indeed, the indications from Part C of Table 22 of higher lifetime risk estimates based on ERR values from the Life Span Study data compared with those from other data sets may suggest that the variation in radiation risks across populations is closer to additive than multiplicative. The latest mortality follow-up of the ankylosing spondylitis study continues to show, in contrast to the Life Span Study, a strong decrease in the relative risk more than 25 years following first treatment. The interpretation of this result is complicated by the absence of smoking data for the ankylosing spondylitis study. However, Weiss et al. [W1] pointed out that relative to national lung cancer rates, the risk among unirradiated patients showed little trend with time since diagnosis of spondylitis. While this suggests that the temporal trend in risk among irradiated patients may not be explained solely by changes over time in smoking habits, the number of lung cancer deaths among unirradiated patients was relatively small.

124. Of particular interest among the low-LET studies is the discrepancy between the lung cancer risks observed among the survivors of the atomic bombings in Japan and the findings from studies of patients who received multiple fluoroscopies in the course of treatment for tuberculosis. Studies of the latter type in both Canada [H7] and the United States (Massachusetts) [D4] found no evidence of a positive association between dose and risk of lung cancer. The Canadian result is particularly important, since it is based on a large cohort of exposed persons (25,000 with lung doses in excess of 10 mSv), while the mean age at exposure, follow-up time, and total number of lung cancer deaths are similar to the corresponding values for the atomic bomb survivors. Table 23 gives details by dose range of lung cancer mortality in both the Canadian fluoroscopy study and the latest follow-up of the atomic bomb survivors. This table clearly shows the lack of evidence for a dose response for lung cancer in the former study, which contrasts with the corresponding results for breast cancer among female members of the cohort [H20] (see Section III.H.1). Furthermore, the large number of deaths means that the discrepancy with the atomic bomb survivor results cannot be explained by a lack of statistical precision.

125. Howe [H7] addressed a number of possible reasons for the difference between the Canadian and Japanese results. He pointed out that the effect of non-differential measurement errors on estimates of risk per unit dose in the Canadian study was likely to be similar in magnitude to that in the Japanese study for solid tumours, i.e. 4%–11% [P2]. Most of the measurement error was associated with estimating the dose per fluoroscopy, which, since it was not performed individual-by-individual, should not bias risk estimates [A1]. In contrast to breast doses [H20], lung doses were similar for anterior-posterior and posterior-anterior orientations and, consequently, were similar in Nova Scotia (where the former orientation predominated) and in the rest of Canada (where the latter orientation predominated). It is difficult to evaluate the potential for systematic errors in dose estimates, but it seems highly unlikely that such errors could explain the discrepancy with the atomic bomb survivor findings. Howe also addressed the effect of possible misclassification of some lung cancer deaths as deaths from tuberculosis. Had the lack of an association between lung cancer and dose been due to differential misclassification concentrated at higher doses, this would have led to an increasing trend with dose in deaths classified as tuberculosis. However, no such trend was apparent, even among those patients at a minimal or moderate stage of tuberculosis, for whom the potential to detect any such effect is likely to have been greatest [H7]. Finally, although individual data on smoking habits were not available for all members of the Canadian cohort, information for over 13,000 of these patients indicated that heavy smokers had not tended to have received lower doses.

126. Several other possible explanations can be considered for the difference between the results of the Canadian and Massachusetts fluoroscopy studies and the Life Span Study. First, the fluoroscopy studies were performed on groups in North America, in contrast to the atomic bomb survivor study in Japan. In particular, baseline rates for lung cancer in North America are higher than the corresponding values in Japan [P5]. However, elevated risks of lung cancer in other groups exposed to low-LET radiation in North America or western Europe are indicated in Table 10, most notably the ankylosing spondylitis study [W1], demonstrating that genetic factors or differences between countries in smoking habits cannot by themselves explain the difference in risks. Secondly, Howe [H7] drew attention to the differences in the fractionation of dose and in dose rate between the atomic bomb survivors and the fluoroscopy patients. Whereas people in the former group received a single dose averaging several hundred mGy in about one second, the latter group received fractionated doses, with an average dose rate of 0.6 mGy s^{-1} to the lungs. In this regard, Elkind [E5] has suggested that complete repair may occur between fractions of sub-effective lung cancer initiation.

It should be noted that, even if fractionation or low dose rate does considerably reduce the risk of lung cancer from low-LET radiation, this need not imply that similar effects would be seen for other cancers or for high-LET exposures, as will be discussed later. Thirdly, the effect of radiation on inducing cancer in the lung may differ between patients with tuberculosis and healthy persons. However, the lack of an association with radiation dose in the Canadian study was observed for those with tuberculosis in its early stages as well as for those with a more advanced stage of the disease [H7]. On the other hand, even within categories of tuberculosis, the severity of the disease was related to the degree of lung collapse, and hence to both the number of fluoroscopies and the degree of surgery [B15]. The latter would have involved the removal of lung tissue and may have affected the lung cancer risk. Consequently, there remains the possibility that the severity of the tuberculosis may have had some confounding effect.

127. Inferences from the other high-dose-rate, low-LET studies listed in Table 10 are limited by the smaller number of lung cancers and the general lack of data on smoking habits. Furthermore, the comparison of risks at high and low dose rates, even in large studies of radiation workers [C11, E3], is made difficult both by the low statistical precision associated with low doses received and by the lack of data on smoking. However, early workers at the Mayak plant in Russia tended to receive higher cumulative doses than many other groups of radiation workers, so data on them may be more informative. For a group of 1,841 men who started working at the nuclear reactors at Mayak between 1948 and 1958 and who had a mean external whole-body gamma dose of 1.02 Gy (low-LET), there was no indication of an increasing trend in lung cancer risk with gamma dose (see Table 10) [K34]. It should be noted that, in contrast to other groups of Mayak workers, described in Section III.E.3 below, these reactor workers did not have potential for plutonium exposure [K34]. A study of natural radiation in the Yangjiang area of China did not indicate an elevated risk associated with low-dose, protracted exposure [T25, T26] (see Table 10). Although the precision of this study was limited, information on smoking habits collected in an associated survey [Z2] suggested that smoking was not associated with dose and therefore might not be a confounder.

2. Internal low-LET exposures

128. Several studies of patients given ^{131}I have examined the risks of lung and other respiratory cancers. Most of these studies were reviewed in the UNSCEAR 1994 Report [U2]. Among Swedish patients treated for hyperthyroidism, Hall et al. [H24] reported increased mortality relative to national rates more than 10 years after treatment (based on 63 deaths, SMR = 1.80; 95% CI: 1.39–2.31). However, there appeared to be no clear trend in the risk of respiratory cancers with the level of ^{131}I administered. It should be noted that the mean lung dose in this study was only 70 mGy. Studies of hyperthyroid patients in the United States [G10, H25] and of thyroid cancer patients in Sweden [H26] treated with ^{131}I did not show raised rates of respiratory cancer, although both studies were based on smaller numbers than the study of Hall et al. [H24]. A larger study of hyperthyroid patients in the United States [R14] provided slight evidence of a trend in lung cancer mortality with increasing administered ^{131}I activity, but this was weaker after allowing for a 10-year latency. A study of Swedish patients with diagnostic exposures to ^{131}I [H27] had more respiratory cancers but lower doses than in the Swedish hyperthyroidism study [H24]; the former study again showed no elevated risk. Bearing in mind not only the low risks predicted in these studies but also the general absence of individual lung dose estimates and smoking histories, it is not possible to compare the risks of protracted internal low-LET exposure with the risks of acute external exposure.

129. Kossenko et al. [K5] drew attention to differences between the Techa River cohort and the Japanese atomic bomb survivors with respect to the proportion of cancers of the lung. In particular, lung cancer accounted for 27% of all cancers among men in the former cohort, compared with 10% in the latter. Conversely, among women the corresponding percentages were 4% and 10%, respectively. While differences in the type of exposure and in ethnic background might be responsible for some of these variations, smoking habits are likely to be of importance. However, the available data did not allow investigating this issue.

130. Wing et al. [W14] reanalysed data on cancer incidence near the Three Mile Island nuclear plant in the United States, originally analysed by Hatch et al. [H37]. These data involve scaled estimates of doses associated with the 1979 accident. Wing et al. [W14] suggested that their results, in contrast to those of Hatch et al. [H14], indicate an increasing trend in lung cancer with the radiation dose estimates; they speculated that this may be due to inhaled radionuclides that might be correlated with external doses. However, Hatch et al. [H38] pointed out that their original analysis did indicate an association for lung cancer, and that many of the differences claimed by Wing et al. [W14] were matters of interpretation rather than new findings. In view of the very low doses received (generally less than 1 mSv), the lack of individual doses, the short follow-up (to the end of 1985), the lack of individual smoking data, and the possibility of chance findings when many different cancer types are studied, these data are not informative on radiation and lung cancer.

3. Internal high-LET exposures

131. Results from various studies of radon exposures are included in Table 10. Particularly informative are the studies of radon-exposed miners, in view of the large numbers of excess lung cancers observed. The joint analysis of 11 miner cohorts by Lubin et al. [L4] permitted detailed examination of factors that may modify the risk of radon-induced cancer. This analysis and the component studies were considered in detail in the UNSCEAR 1994 Report [U2]. In summary, the ERR per working level month (WLM) was found to decrease with attained age,

time since exposure, and time after cessation of exposure to radon, but not with age at first exposure. The joint effect of radon and smoking on lung cancer risk was greater than additive, although it is difficult to quantify this further; in particular, only a small proportion of miners never smoked. Similarly, the modifying effect of exposure to other agents encountered in mines is not clear, although the ERR per WLM was lower after adjusting for arsenic exposure [L4].

132. The exposure-response relationship in the various studies of radon-exposed miners is consistent with linearity. However, at relatively high cumulative exposures, the slope of the exposure-response relationship is steeper at lower than at higher exposure rates [L4, L6]. It should be emphasized that this inverse exposure-rate effect does not imply that low exposures carry a greater risk than higher exposures; rather it suggests that for a given total exposure, the risk is higher if the exposure is received over a longer rather than a shorter period of time. Table 24, based on the analysis of Lubin et al. [L6], shows that this inverse exposure-rate effect (as measured by the modification factor γ) is seen, to varying degrees, in all of the studies except the French cohort; workers in the latter study [T8] often worked for many years at low exposure rates. However, a reanalysis of the Beaverlodge data based on revised exposure estimates [H18] provided no evidence of an inverse exposure-rate effect, in contrast to previous analyses. It should be noted that the highest exposure rates, which generally gave rise to the highest cumulative exposures, occurred in the earliest years of mining, when the fewest measurements were made. Furthermore, concentrations of radon rather than radon progeny were measured in the earliest years in many of the studies, requiring assumptions to be made in calculating working levels (WL). Errors in estimating WL were therefore likely to be greatest in the early years of mining and would have tended to lessen the observed effects of high exposure rates, inducing an apparent inverse exposure-rate effect. However, adjustments by Lubin et al. [L4, L6] by calendar year of first exposure, calendar year of exposure, attained age, and years since the last exposure yielded patterns similar to those in Table 24. It, therefore, seems unlikely that WL measurement errors can explain the entire inverse exposure-rate effect. It is also evident from Table 24 that there is wide variation between studies in the estimate of ERR per WLM at an exposure rate of 1 WL, i.e. β. This variation reflects uncertainty in extrapolating to low exposure rates. Another possible explanation for what appears to be an inverse exposure-rate effect actually may be the effect of cell killing at high doses.

133. The BEIR VI Committee [C21] reexamined the data on the radon-exposed miners of Lubin et al. [L4], adding new data from China, the Czech Republic, France, and the United States (Colorado Plateau). Table 25 describes the mathematical format of the models derived by this Committee. In contrast to the model derived by the BEIR IV Committee [C2], the BEIR VI models include an extra time-since-exposure category, so as to distinguish between exposures received 15–24 years earlier and those received 25 or more years earlier. Furthermore, these models allow for effects of either duration of exposure or average radon concentration, again in contrast to the BEIR IV model. Separate models were derived [C21]: "exposure-age-duration" and "exposure-age-concentration", with no preference being given by the BEIR VI Committee to either. Under these models, the ERR associated with a given cumulative exposure increases as the exposure duration increases or the average concentration decreases.

134. Animal studies using very high exposure rates have shown that a longer duration of radon exposure at a lower rate induces more lung cancers than a shorter duration exposure at a higher rate [C3, C4]. As for possible mechanisms, Moolgavkar et al. [M5, M6] suggested, based on the two-stage initiation-progression model for carcinogenesis, that extended duration allows time for the proliferation of initiated cells and thus for higher disease occurrence rates. Furthermore, by incorporating cell killing into such a model, Luebeck et al. [L23] hypothesized that the inverse exposure-rate effect may be reduced in the absence of ore dust, in view of effects on net cell proliferation. Using a different approach, Brenner [B5] postulated that the inverse exposure-rate effect comes from cell cycling, whereby cells in a particular period of their cycle are more sensitive to radiation than at other times. For the same total dose, a greater proportion of cells is predicted to be exposed during the sensitive period if the dose is protracted rather than acute. Multiple traversals of a cell by alpha particles are necessary for such an inverse exposure-rate effect, although it should be recognized that not all traversals will lead to transformation. At sufficiently low exposure rates, there would probably be at most one traversal of any cell. Consequently the inverse exposure-rate effect would be predicted to disappear, owing to the absence of multiple traversals and their associated interaction. Little [L33] outlined a biological justification for using data from epidemiological studies of miners exposed to high radon levels to estimate risks at low exposure rates. This was based on research by Hei et al. [H34], which showed that traversal by a single alpha particle has a low probability of being lethal to a cell, and that many cells survive traversal by one to four alpha particles to express a dose-dependent increase in the frequency of mutations. In a recent cell transformation study, Miller et al. [M53] found that the oncogenic potential of a single alpha particle, with an energy similar to that of radon decay progeny, was significantly less than that from a Poisson distributed mean of one alpha particle. This finding suggests a non-linear response at low doses of high-LET; however, these results need to be replicated by others.

135. Epidemiological backing for the absence of an inverse exposure-rate effect at low exposure rates comes in particular from the study of miners in western Bohemia, which showed that below 10 WL the ERR per WLM did not appear to depend on duration of exposure [T3]. Furthermore, in their joint analysis of the miner studies, Lubin et al. [L6] concluded that the inverse exposure-rate effect diminishes, and possibly disappears, when the duration of exposure becomes very long. Animal data have also been used to address this issue. In a

study of about 3,000 rats, Morlier et al. [M3] found that lung cancer incidence among rats that received a total of 25 WLM appeared to be lower when the exposure was protracted over 18 months rather than 4–6 months; although the corresponding number of cases was small, the study excluded an inverse exposure-rate effect at this level of exposure. Similar conclusions were drawn from an analysis of another data set, based on more than 4,000 rats with a wide range of exposures and exposure rates; namely, risk per unit exposure decreased with increasing duration of exposure for exposure rates below 10 WL [H41].

136. Results from a meta-analysis of eight case-control studies of residential radon and lung cancer published up to the mid-1990s are summarized in Table 10 [L21], together with the results from some more recent large studies. Lubin et al. [L10] pointed out that the results of these studies appear to be consistent with a wide range of underlying risks. The variability in the findings is likely to reflect, at least in part, the impact of errors in assessing radon exposures. In particular, Lubin et al. [L1, L10] showed that errors due, for example, to the use of recent measurements to characterize past levels and gaps in measurements in previous homes can substantially reduce the statistical power of such studies. As was indicated in Section I.C, it is possible to adjust estimates of the exposure-response relationship to allow for the bias towards the null that tends to arise from random errors in exposure assessment. For example, the central estimate of the ERR per 100 Bq m^{-3} in a study in the United Kingdom increased from 0.08 (95% CI: −0.03–0.20) to 0.12 (95% CI: −0.05–0.33) after adjusting for uncertainties in the assessment of radon exposure, although the width of the associated confidence interval also increased [D30]. Another example of the possible effect of errors in exposure assessment occurs in a study in western Germany [W17]. Here the evidence for an association between radon and lung cancer incidence was stronger in a subanalysis of radon-prone areas than in the analysis of the entire study region (see Table 10); the authors suggested that the latter findings may have been biased by the inclusion of many dwellings with low, but imprecisely estimated, radon levels [W17]. In addition, a recent study in Missouri (United States) showed stronger evidence of an association between radon and lung cancer based on CR-39 surface (i.e. glass-based) measurements rather than on the more traditional track-etch measurements, which has been suggested to reflect the effect of the more precise assessments of cumulative exposure achieved using the surface technique [A24]. However, as pointed out in Section I.C, further validation of glass-based techniques would be desirable [W19]. In addition to the weak indications from some of these recent studies, a meta-analysis of eight earlier case-control studies yielded some direct support for an elevated risk from residential radon exposure [L21]. Based on over 4,000 lung cancer cases, the trend in risk in the meta-analysis was significantly greater than zero (p=0.03) and was consistent with the results from the miner studies, as illustrated in Figure II. In particular, the relative risk estimated at 150 Bq m^{-3} was 1.14 (95% CI: 1.0–1.3). It should be noted that a log-linear model was fitted to the case-control and miner data. Importantly, no single study dominated the overall results, although there were significant differences in the exposure-response trends among the studies considered [L21].

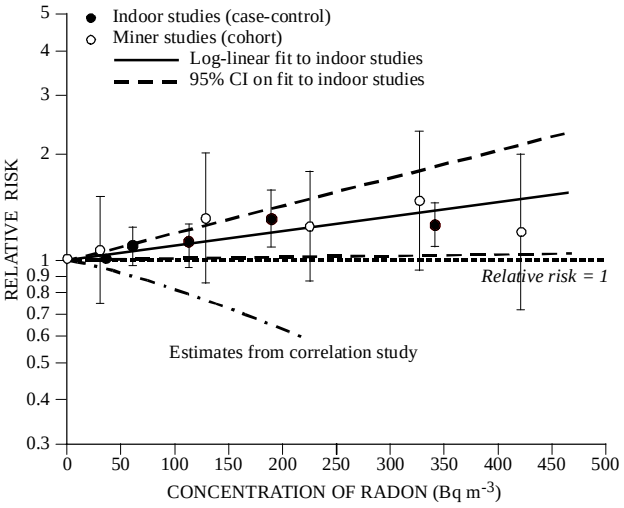

Figure II. Risk estimates of lung cancer from exposure to radon (based on [L21]).
Shown are the summary relative risks from meta-analysis of eight indoor radon studies and from the pooled analysis of underground miner studies, restricted to exposures under 50 WLM [L22] and the estimated linear relative risk from the correlation study of Cohen [C18].

137. Several analyses of lung cancer in the United States in relation to average levels of indoor radon have been published by Cohen (e.g. [C5, C6, C18]). These analyses show decreasing trends in area-specific lung cancer rates with increasing area-averaged radon levels. The findings contrast with those of cohort studies of radon-exposed miners and of case-control studies of indoor radon [L21]. In both the cohort and case-control studies, radon exposures have been estimated for individual study subjects. Furthermore, in the residential studies and some of the miner studies, individual smoking data have been collected. In contrast, the data on radon and the many potential confounders considered in Cohen's correlation studies are averages over geographical areas. Results from such studies are vulnerable to biases not present in results based on individual-level data, such as from cohort or case-control studies. Radon studies are particularly vulnerable to biases associated with the use of geographical area-averaged radon levels because of extreme variation in radon levels within areas. Greenland and Robins [G2] pointed out that a lack of confounding in grouped data need not imply the absence of confounding in data for individuals, and vice versa. This is particularly important in the case of indoor radon, because smoking habits have a much greater impact on lung cancer risk [B35]. Whereas individual smoking habits form the main potential confounder in an individual-level study, the corresponding potential confounder in a geographical correlation study consists of the distribution of all smoking histories across all individuals within each area. Consequently, particularly if the effects of variables such as smoking are non-linear or non-additive at the individual level, the corresponding data available at the area level are unlikely to be sufficiently detailed to adjust for confounding. Furthermore,

the data available in correlation studies do not take account of residential histories. For example, a person who had just moved into an area from another area with different radon levels would be categorized solely by the current area of residence rather than by a time-weighted average exposure. Additionally, residential radon levels often vary widely, even within small geographical areas. On the other hand, Cohen [C7] has drawn attention to the lower statistical uncertainty associated with his studies, relative to case-control studies. However, greater statistical precision needs to be weighed against the potential for substantial bias.

138. The interpretation of geographical correlation studies of radon and lung cancer has continued to be the subject of debate. In examining this issue, it should first be considered whether it is possible mathematically that spurious results could arise from a correlation study. This is possible; there have been numerous mathematical proofs that results from such studies can differ systematically from those based on data for individuals (e.g. [G2, L35]). Secondly, it should be considered whether it is plausible that the results reported by Cohen could be explained simply by the methodological aspects described above. In the absence of data for individuals throughout the regions studied by Cohen, it is difficult to be certain on this point. Lubin [L35] presented examples showing that results of the type described by Cohen can arise even with weak correlations between radon and smoking, but Cohen [C25] stated that correlations far beyond the limits of plausibility cannot explain an appreciable part of the discrepancy with extrapolations from miner data. Smith et al. [S2] reported that a negative correlation seen in the state of Iowa, United States, disappeared when mortality data were replaced by incidence data, although Cohen [C26] was dubious about the value of these data. It should be emphasized that epidemiological studies of all types have their strengths and weaknesses and that none is perfect. As pointed out above, individual residential case-control studies often lack statistical precision, in part because of uncertainties in exposure assessment. However, greater precision should be obtained from planned combined analyses of these studies, which in contrast to the Lubin and Boice's [L21] meta-analysis based on published summary data, will incorporate subject-specific data. For the time being, considering the methodological aspects of the various studies, the data on miners appear to provide the soundest basis for estimating radon-induced risks. Furthermore, it should be noted that risk models based on the full range of miner exposures yield results that are similar to those based on miner exposures of less than 50 WLM [L22].

139. In connection with the development by ICRP of a model for internal doses to the respiratory tract [I4], there has been some interest in comparing risk estimates for lung cancer from studies of low-LET and radon-exposed groups. However, Howe [H7] drew attention to the difficulty of arriving at a single value for the low-LET dose to the lung that could lead to the same lung cancer risk as 1 WLM exposure to radon. In particular, the comparison of data on the Japanese atomic bomb survivors and on fluoroscopy patients referred to earlier suggests a strong fractionation/dose-rate effect for low-LET radiation, while the data on radon-exposed miners indicate a higher risk per unit exposure at low than at high exposure rates. Furthermore, when attention is confined to low-dose protracted exposures, the derivation of a conversion factor between low-LET and radon exposures is complicated by the paucity of data that are directly relevant.

140. Studies of groups with internal exposures from thorotrast and ^{224}Ra generally provide little evidence of elevated risks of lung cancer; see Table 10. In the case of thorotrast, irradiation of the lung arises principally from exhalation of ^{220}Rn (thoron), one of the daughter nuclides of ^{232}Th [H21]. However, the distribution of dose within the lung is different from that in underground miners exposed to radon. The incidence of lung cancer among neurological patients in Denmark given thorotrast was elevated relative to national rates but not relative to a control group of patients not given thorotrast, after adjusting for gender, age at angiography, and calendar period [A5]. In an analysis of the combined series of Japanese patients, Mori et al. [M14] indicated an elevated risk of lung cancer relative to a control group, although this was based on only 11 deaths. Among female radium dial painters in the United States, there was some suggestion of an increasing trend in lung cancer mortality with increasing intake of ^{226}Ra/^{228}Ra, although there were only 6 deaths in that analysis [S16]. In general, the statistical precision of these studies was limited by the relatively low numbers of lung cancers; furthermore, information on individual smoking habits was not always available.

141. Information from studies of workers with high-LET exposures from plutonium, uranium, and polonium was reviewed in the UNSCEAR 1994 Report [U2]. Since then, more information has been published for workers at the Mayak nuclear plant in the Russian Federation, many of whom were exposed to both plutonium and external low-LET radiation. Koshurnikova et al. [K10, K11] showed that relative to a control group of workers, lung cancer mortality was raised significantly among workers at the radiochemical processing plants and at the plant for plutonium production but not among workers at the nuclear reactors at Mayak, who were exposed predominantly to external gamma radiation (see Table 10). The elevated risk appeared to be concentrated among workers with plutonium body burdens. A subsequent, more detailed analysis of lung cancer deaths among 1,479 men who started work at Mayak during 1948–1958 showed a clear trend in lung cancer risk with estimated alpha dose to the lung, consistent with linearity [K34]. In addition, a separate analysis of data for Mayak workers is consistent with a linear dose response from less than 1 Sv to more than 100 Sv, although it was based on a weighted sum of high- and low-LET doses to the lung rather than the high-LET dose alone [K37]. In contrast to these findings, a case-control study of Mayak radiochemical plant workers [T2] appears to indicate a non-linear dose response. The methodology for this study is summarized in Tables 4 and 5. In particular, in addition to individual measurements of plutonium body burden and gamma dose, information on

smoking habits and other potential confounders was utilized in this analysis [T2]. There was a clear excess of lung cancer among workers with a ^{239}Pu body burden in excess of 5.6 kBq (see Table 10). This association was apparent for adenocarcinoma, squamous-cell carcinoma, and small-cell carcinoma. Further analysis found little evidence of an elevated risk for plutonium body burdens below about 3.7 kBq (corresponding to a lung dose of 0.8 Gy), in qualitative agreement with the form of the dose response reported in animal studies by Sanders et al. [S38]. There was some suggestion of an elevated risk for gamma doses in excess of 2 Gy (low-LET) relative to lower doses, although this finding was not statistically significant [T2, T14]. The wide range of internal doses encountered in the Mayak studies, from less than 0.5 to over 120 Sv [K34], together with the individual data on possible confounders in the case-control study [T2], contribute considerably to the potential ability of the studies to provide information on the carcinogenic effects of plutonium in the lung. The reasons for the differences in the dose-response relationship between the cohort and case-control studies are not clear. One possibility is that the cohort findings have been confounded by smoking. Another possibility relates to the fact that the average lung doses to female workers in the case-control study were higher than those to males, whereas virtually all of the male cases and only one of the female cases were smokers [T2]. Based on this, Khokhryakov et al. [K37] have suggested that curvilinearity in the dose response in the case-control study may be an artefact associated with combining two subgroups with different characteristics, whereas the cohort findings are based exclusively [K34] or largely [K37] on data for males. Further investigation may shed more light on the reasons for the apparent differences in the findings.

142. Other studies of plutonium-exposed workers, such as at the Sellafield plant in the United Kingdom [O1] and at the Los Alamos National Laboratory in the United States [W8], did not show statistically significant elevated risks of lung cancer relative to other workers at the same plants (see Table 10). The internal exposures in these studies were generally much lower than those to Mayak workers; as well as which it was not possible to control for smoking.

4. Summary

143. Results from the Japanese atomic bomb survivors and from several groups of patients with acute high-dose exposures show elevated risks of lung cancer associated with external low-LET radiation. The risk for the atomic bomb survivors is consistent with a linear trend. These data also show similar values for the ERR per Sv by age at exposure and for the EAR per Sv by gender, although without taking account of smoking habits. Indeed the large influence of smoking on lung cancer risks is likely to be of great importance in determining how radiation-induced risks differ from one population to another. There is some suggestion that the joint effect of low-LET radiation and smoking is closer to an additive than a multiplicative relationship, although the data are sparse and not entirely consistent. Studies of tuberculosis patients who received multiple chest fluoroscopies have not demonstrated increased risks of lung cancer, in spite of the large number of patients with moderate or high lung doses. The fractionation of these exposures, compared with the acute doses received by the atomic bomb survivors, may explain the difference in findings. However, the severity of tuberculosis may have confounded the results for some of the patients with this disease.

144. In contrast to internal low-LET irradiation, there is a substantial amount of information on lung cancer in relation to internal high-LET exposure. Most of this information comes from studies of radon-exposed miners. In particular, the risk appears to increase linearly with cumulative radon exposure, measured in WLM, but the ERR per WLM decreases with increasing attained age and time since exposure. Furthermore, at high cumulative exposures, the ERR per WLM appears to increase with decreasing exposure rate, but both epidemiological and experimental evidence indicate that this phenomenon does not arise at low exposures. Findings from case-control studies of domestic radon exposure have been variable but are consistent with predictions from the miner studies. Among studies of other types of high-LET exposure, the most informative are those of workers at the Mayak plant in the Russian Federation, which show an elevated risk for high lung doses from plutonium; further investigation of the shape of the dose-response relationship would help to understand apparent differences in findings for different groups of workers.

F. MALIGNANT TUMOURS OF THE BONE AND CONNECTIVE TISSUE

145. Malignant tumours of the bone account for about 0.5% of malignant neoplasms in humans [M39], while soft-tissue sarcomas, which include connective tissue malignancies, account for about 1% of all malignancies [Z3]. Among bone sarcomas, dissimilarities in cell type between oesteosarcoma and Ewing's sarcoma indicate that these tumours have different origins. The role of genetic susceptibility has been identified through molecular and cytogenetic studies of the gene loci for these types of sarcomas, as well as by the linkages of osteosarcoma with hereditary retinoblastoma and the Li-Fraumeni syndrome [M39]. Li-Fraumeni syndrome has also been investigated together with connective tissue malignancies [Z3]. As will be described below, a variety of studies with external low-LET and internal high-LET studies exposures have established that bone sarcomas can be induced by radiation. Human and animal studies have suggested a possible association between exposure to chromium and the risk of bone and soft-tissue malignancies [M39].

1. External low-LET exposures

146. The results from studies of bone and connective tissue malignancies following external low-LET exposures are given in Table 11. Among the Japanese atomic bomb survivors overall, the estimated trend in risk per unit dose

is positive but is not statistically significantly greater than zero [P9, R1, T1]. However, there is an indication that the risk is higher for exposure in childhood than in adulthood, although this finding is based on small numbers. Statistically more powerful information comes from studies of patients treated for cancer in childhood. Three studies with reasonably large numbers of cases [H44, T17, W11] have reported a statistically significant increasing trend in risk with dose, based on mean doses between 10 and 30 Gy; another such study reported similar results, although with fewer details [D33]. While the high doses contributed to the detection of an elevated risk, these studies are less informative about risks at doses of a few gray or less, although no excess is apparent at these levels. Compared with some other cancer types, the estimated ERR per Sv of around 0.1–0.2 for bone malignancies and/or soft-tissue sarcomas is not large. A notable finding from the study of Wong et al. [W11] of retinoblastoma patients was that the risk of bone and soft-tissue sarcomas was concentrated among those with hereditary retinoblastoma. Tucker et al. [T17] reported a similar result, and found that the relationship between relative risk and dose was similar for retinoblastoma and other patients; the retinoblastoma patients had a higher absolute excess risk by virtue of their higher baseline risk. These results suggest that genetic predisposition may modify the radiation-associated risk at high doses.

147. Few studies of adult exposure are informative, owing in part to the rarity of malignant tumours of the bone or connective tissue. However, the study of cervical cancer patients involved mean doses comparable to those in the above childhood cancer studies [B1]; in that instance, no significant increasing trend in risk with dose was found. Among ankylosing spondylitis patients in the United Kingdom, the total number of deaths was significantly greater than expected from national rates, but the data were not analysed in relation to estimates of dose [W1]. In a group of over 120,000 women in Sweden treated for breast cancer, the incidence of soft-tissue sarcomas was about double that expected from national rates [K35]. In a case-control study based on this Swedish cohort, which analysed information on the energy imparted from radiotherapy (i.e. the product of the mass of the patient and the dose absorbed) because organ dose estimates were not available, angiosarcoma was not found to be related radiotherapy energy, whereas the risk of other types of soft-tissue sarcomas was found to increase with increasing energy [K35]. A review of medical records at a cancer centre in the United States indicated that fewer than 3% of cases of bone and soft-tissue sarcoma had previously received radiotherapy [B40]. In a study of over 50,000 men in the United States who had received radiotherapy for prostate cancer, the proportion who subsequently developed sarcomas was also low, although there was an elevated risk for sarcomas at sites within the treatment field, in contrast to more distant sites that received lower doses [B42]. An analysis of 53 cases of soft-tissue sarcomas that were identified following radiotherapy showed no definite relation with age at exposure, although there was some suggestion of a shorter latency for therapy involving higher doses [L48].

2. Internal low-LET exposures

148. Studies of groups with medical exposures to radioactive iodine are uninformative about the risks of bone malignancies, owing to the low doses to bone surfaces from this type of exposure and to the rarity of the disease. Even in a large study of patients treated for hyperthyroidism in the United States, deaths from bone malignancies were not listed separately [R14]. More information may be obtained from studies of bone-seeking radionuclides. Residents of the area around the Techa River in the Southern Urals received internal exposures, mainly from ^{90}Sr, which has been shown to induce osteosarcomas in rats [N18, S55], as well as external exposures. In the period 1950–1989, 12 deaths from bone malignancies were observed in a cohort of 26,485 residents in the Techa River region [K5]. This represents about 1% of all cancer deaths in this cohort [K5], compared with a corresponding value of 0.4% in the Life Span Study [P9]. Risk estimation using the Techa River data is made difficult by the absence of information on vital status for over a third of the cohort and by uncertainties in the estimates of individual doses. However, a major dose reconstruction project is in progress that aims to provide more reliable individual dose estimates for cohort members [D37]. Direct measurements of ^{90}Sr have already been made for about half of the population exposed in the Techa River region, either using a whole-body counter or by *in vivo* measurements of teeth. These measurements have shown a clear correlation with year of birth [D37]. Total doses to soft tissue, from external and internal exposures, are likely to be less than 0.1 Sv for most Techa River residents, although a small proportion is estimated to have received doses in excess of 1 Sv [K5]. With further improvements in the quality of the dosimetry and the follow-up, this cohort has the potential to provide quantitative estimates of risks from chronic exposures.

3. Internal high-LET exposures

149. Most of the information on bone tumour risks and internal high-LET irradiation comes from studies of intakes of radium. Data from medical intakes of ^{224}Ra and occupational intakes of predominantly ^{226}Ra are considered in turn.

150. In the early 1950s, Spiess initiated a follow-up study in Germany of 899 patients with ankylosing spondylitis, tuberculosis, or a few other diseases who had received multiple injections of ^{224}Ra [S14]. Up to the end of 1998, a total of 56 malignant bone tumours had occurred in 55 of these patients [N14], whereas less than one tumour would have been expected. Most of the tumours occurred within 25 years of the first ^{224}Ra injection [N14]. Among those cases for which histopathology information was available, about half of the cancers were osteosarcomas. However, there was a relatively high proportion of fibrous-histiocytic sarcomas, compared with spontaneous bone tumours [G22]. In particular, the ratio of osteosarcomas to fibrous-histiocytic sarcomas in this study, 1.8, is similar to that in other groups where radiation-related excesses have been seen, such as the radium dial painters [G22].

151. Bone sarcoma risk among these ^{224}Ra patients was recently analysed [N14] taking into account revised dosimetric calculations [H8]. In particular, these calculations indicate that doses to the bone surface for those exposed at young ages are smaller than had previously been estimated. As a consequence, the new risk analysis indicates that absolute risks of bone tumours decrease with increasing age at exposure [N14]. Nekolla et al. modelled the absolute excess risk in terms of attained age, age at first injection, duration of treatment, and mean absorbed dose to the bone surface; no effect of gender was seen [N14]. A linear dose-response model provided a good fit to the data, although models involving a quadratic component in dose could not be excluded. Also, while the risk for a given cumulative dose was higher if the dose was protracted rather than acute, this difference was estimated to be small for cumulative doses below about 10 Gy. In addition, the excess absolute risk decreased from about 12 years following exposure onwards. Based on this model, the lifetime risk of bone sarcoma incidence for an acute exposure up to several gray (high-LET) of a population aged 0–75 years was estimated to be 1.8 (0.6–2.4) 10^{-3} Gy^{-1}. This value is similar to estimates made previously by, for example, the BEIR IV Committee [C2]. However, as indicated earlier, the new calculations indicate that risks are higher for exposure at younger ages. In particular, the lifetime risk for the incidence of bone sarcomas was estimated to be 4 10^{-3} Gy^{-1} for an acute exposure up to several gray (high-LET) at age 15 years, compared with 0.8 10^{-3} Gy^{-1} for an acute exposure at age 45 years [N14]. It should also be noted that, while these absolute risk coefficients are small, the corresponding estimates of the ERR per Sv (based on a radiation weighting factor of 20), between about 0.45 and 0.04, depending on age at exposure, are consistent with those seen for many other solid tumours [N14].

152. Nekolla et al. [N14] drew attention to uncertainties in the extrapolation of their findings to low doses. In particular, they compared their findings with those of Wick et al. [W20], who studied a more recent group of about 1,500 patients in Germany treated for ankylosing spondylitis with lower activities of ^{224}Ra than patients in the Spiess study. The model of Nekolla et al. [N14] predicts 7.8 excess bone sarcomas in the study of Wick et al. up to 1995, whereas only four malignant tumours of the skeleton, none of them osteosarcomas, have been observed, compared with 1.3 expected spontaneous cases [W20]. Since the mean dose to the bone marrow in [W20] is lower by a factor of about five than that in [N14], the results of this comparison suggest that the linear extrapolation in [N14] may overestimate risks at low doses.

153. Studies of over 4,000 radium dial painters, radium chemists, and patients given ^{226}Ra or ^{228}Ra therapeutically in the United States were reviewed in the UNSCEAR 1994 Report [U2] and by the BEIR IV Committee [C2]; Fry [F9] recently published a detailed history of the radium dial painter studies. Some of these individuals had been internally contaminated with pure ^{226}Ra, which has a half-life of 1,620 years, whereas others received a mixture of ^{226}Ra and ^{228}Ra, which has a half-life of 5.75 years. The BEIR IV Committee reported 87 bone sarcomas in 85 of 4,775 persons whose vital status had been ascertained on at least one occasion [C2]. Among those 2,403 individuals for whom there was an estimate of skeletal dose, 66 sarcomas in 64 persons were reported, whereas fewer than 2 cases of sarcomas would have been expected from national rates [C2]. The elevated risk in dial workers was particularly evident among women who entered the industry before 1930 and whose exposures were higher than those for later workers; among those early workers there were 46 bone sarcoma deaths up to the end of 1990 [C27, R35].

154. Various attempts have been made to model the risks of bone sarcoma in the United States series. Based on 1,468 female radium dial workers who entered the dial industry before 1950 and who were followed to the end of 1979, Rowland et al. modelled the annual rate of bone sarcoma as $(\alpha + \beta A^2)\exp(-\gamma A)$, where A is the activity of radium that entered the blood during the exposure period [R33]. In a later analysis with follow-up to the end of 1990, Rowland suggested that the exponent of A was nearer to 3 than to 2 [R35]. Marshall et al. developed a two-target model, proposing that two successive initiating events are required for osteosarcoma induction and also allowing for the effects of cell killing [M51, M52]. Using information on time to death and average skeletal dose, Raabe et al. drew attention to the effects of dose rate in both human and animal data on bone sarcomas following intakes of ^{226}Ra, in particular to the finding that risks may not be elevated at low dose rates [R34]. More recently, Carnes et al. analysed data on 820 women who started radium dial work before 1930 and who were followed for mortality through to 1990 [C27]. In contrast to some other analyses, the models of Carnes et al. took account of time distributions for both risk and exposure and examined ^{226}Ra and ^{228}Ra separately [C27]. Their preferred model for the excess absolute risk of bone sarcoma consisted of the sum of a quadratic term in the accumulating skeletal dose from ^{226}Ra and a linear term in the accumulating skeletal dose from ^{228}Ra. In addition, the excess relative risk was higher for exposure at ages associated with active bone growth than at older ages, when the skeleton was fully developed, although the excess absolute risk did not appear to vary by age at exposure [C27]. However, all of these analyses should be interpreted with caution: the intake of radium was estimated many years after the event and may be inaccurate; the distribution of radium in the bone is probably non-uniform and hot spots capable of extensive cell killing may have occurred; the continuous receipt of dose makes it difficult to separate out the fraction of dose associated with cancer induction; the contributions from alpha emitters and other radiations accompanying radium decay cannot be separated; and the fraction of the total dose to the endosteal cells cannot be specified precisely [B47].

155. In a group of about 1,200 women in the United Kingdom who worked with paint containing radium from 1939 to 1961, one fatal bone sarcoma occurred up to the end of 1985, compared with 0.17 expected [B14]. The difference between these findings and those from the United States series can be explained by the much lower radium exposures received by the United Kingdom

workers, although it should be noted that both groups would have also received external exposures from the proximal containers of radioactive paint. The results from the United Kingdom study, the models fitted to the United States data that are at least quadratic in dose at low doses, and the findings from animal studies have prompted the suggestion that there is a "practical threshold" of about 10 Gy for the induction of bone sarcomas. However, the UNSCEAR 1994 Report drew attention to a few cases of bone sarcomas and head sinus carcinomas that had arisen at lower doses, down to about 1 Gy, in the United States series [U2]. Furthermore, the bone sarcoma case observed in the United Kingdom study was in a worker with an estimated skeletal dose of 0.85 Gy. It would appear, therefore, that any practical threshold, if it exists, is unlikely to be greater than about 1 Gy [U2].

156. Some studies of thorotrast patients, such as the one in Portugal [D31], have indicated elevated risks of bone sarcomas (see Table 11). However, the numbers of cases in these studies were smaller than among the ^{224}Ra patients and the United States radium dial workers. Based on thorotrast studies, the BEIR IV Committee assessed the lifetime risk of bone cancer to be 1 10^{-2} Gy^{-1} (high-LET) [C2]. This value is somewhat higher than that derived by Nekolla et al. from the ^{224}Ra patients [N14]. However, the estimate based on the thorotrast studies is likely to be more uncertain, because these studies had fewer cases than the studies of the ^{224}Ra patients and because dose estimation may have been more difficult in the thorotrast studies.

157. Studies of workers from the United Kingdom and the United States monitored for exposure to plutonium have reported few if any cases of bone malignancies (e.g. [W8, O1]). In contrast, bone tumour deaths were significantly elevated among plutonium-monitored workers at the Mayak plant in the Russian Federation [K42]. Bone tumour mortality increased with increasing levels of plutonium body burden ($p<0.001$); however, additional plutonium dosimetry is needed before reliable risk estimates can be calculated.

4. Summary

158. Studies of patients treated for childhood cancer demonstrate an increasing risk of bone sarcomas with dose, over a range of several tens of gray (low-LET). These studies are not informative about risks at doses below a few gray, but a study of retinoblastoma patients in particular indicates that genetic predisposition may affect risks associated with high dose therapeutic radiation exposure. Other studies of external low-LET exposure are less informative, although there is some suggestion that the relative risk is lower for exposure in adulthood than in childhood. Studies of the population living near the Techa River in the Russian Federation may in the future provide more information on bone cancer risks following internal low-LET exposures.

159. There is extremely strong evidence that large intakes of radium have induced bone sarcomas in a group of patients in Germany and in radium dial workers in the United States. Because of the long half-lives of ^{226}Ra and ^{228}Ra (the source of the high-LET exposures in the United States study) relative to the half-life of ^{224}Ra (the source of exposure in the German study), it is easier to model risks using the latter study. Analysis of the ^{224}Ra data indicates that the excess absolute risk decreases with increasing time since exposure (beyond about 12 years) and age at exposure, and that the effect on risks of exposure rate is small at doses below around 10 Gy. The ^{224}Ra data are consistent with a linear dose response over a range up to more than 100 Gy, although there is uncertainty in extrapolating the findings down to doses of a few gray. The United States study on ^{226}Ra and ^{228}Ra offers little evidence of an elevated risk at these lower doses, although it is difficult to evaluate the dose associated with any "practical threshold" in risk.

G. SKIN CANCER

160. Non-melanoma skin cancers are extremely common in light-skinned populations but relatively rare in populations with highly pigmented skin [A9, S26]. Malignant melanoma incidence is also strongly correlated with skin pigmentation, but it is about 10 times less common than non-melanoma skin cancer. Annual incidence rates for melanoma vary from about 0.5 per 100,000 persons in Asia to over 20 per 100,000 in Australia, whereas rates for non-melanoma skin cancers range from almost 5 per 100,000 in Africa to about 200 per 100,000 in Australia [P5]. Non-melanoma skin cancer incidence rises rapidly with age, with such cancers being common among the elderly. Over the past decades, there has been a dramatic increase in the incidence of both non-melanoma and melanoma skin cancer [A10, M24]. Much of the increase in incidence appears to be due to sun exposure. Total accumulated exposure appears to be the main risk factor for non-melanoma skin cancer [S26], but for melanoma this relationship is not a simple one and may be related to intermittent sun exposure of untanned skin [N8]. Survival for melanoma depends on stage. Non-melanoma skin cancer is a treatable malignancy with a very high cure rate.

161. From a histological standpoint, the two most common types of non-melanoma skin cancer are basal-cell and squamous-cell carcinomas. They are substantially different with respect to demographic patterns, survival rates, clinical features, and aetiological factors. The incidence of both types is higher among males than females [S26].

1. External low-LET exposures

162. Since publication of the UNSCEAR 1994 Report [U2], additional information from the Life Span Study of atomic bomb survivors has become available [R15, Y3]. Data from this and other studies are summarized in Table 12 and Table 26.

163. An association between external ionizing radiation and non-melanoma skin cancer risk has been demonstrated in the Life Span Study of atomic bomb survivors [L29,

R15, T1, Y3], the New York and Israeli tinea capitis studies [R16, S27], the Rochester thymus study [H31], patients irradiated for enlarged tonsils [S28], patients irradiated for various benign head and neck conditions [V4], and the American and British radiologists [M25, S41]. No such relationship has been observed for melanoma, but the number of cases in each study was extremely small. Most of the significantly increased risks observed for non-melanoma skin cancer occurred among people irradiated as children (Table 12).

164. In the latest data from the Life Span Study of atomic bomb survivors, a strong dose-response relationship was demonstrated for basal-cell carcinoma (ERR at 1 Sv = 1.9; 90% CI: 0.83–3.3) (Table 26), but not for squamous-cell carcinoma or melanoma [R15]. There was non-linearity in the basal-cell carcinoma dose response. A dose-response curve having two slopes (with the change in slopes at 1 Sv) marginally improved the fit (p=0.09); a linear model with a threshold at 1 Sv did not fit the data. In earlier evaluations of skin cancer in the Life Span Study, non-linearity was found for all non-melanoma skin cancers combined [L29, T1].

165. For basal-cell carcinoma in the Life Span Study, the ERR decreased substantially with increasing age at exposure, but gender, time since exposure, and attained age had little influence on the risk [R15]. Skin tumour prevalence was assessed among a subgroup of atomic bomb survivors who were clinically examined. A dose-response relationship was found for basal-cell carcinoma and precancerous lesions [Y3]. Consistent with the results from the larger study of all Life Span Study members, age at exposure was predictive of developing a skin neoplasm but gender was not.

166. The substantial increase in skin cancer incidence rates and reporting, as well as the wide variation in incidence depending on region and ethnicity, suggests that relative risks are more suitable than absolute risks for describing radiation-induced skin cancer risks. Analyses of skin cancer conducted by the National Radiological Protection Board in the United Kingdom indicate that a generalized relative risk model describes the data more parsimoniously (i.e. with fewer model parameters) than an absolute risk model [N10]. As seen in Table 12, the ERR at 1 Sv for persons exposed medically ranges from no risk for cervical cancer patients [B1] to 1 for infants treated for enlarged thymus gland [H31, S30]. In the two studies of patients receiving scalp irradiation for tinea capitis, the ERRs were about 0.5 [R16, S27, S30]. For children between the ages of 1 and 15 years, a significant decrease in the ERR with increasing age at exposure was demonstrated in the Israeli tinea capitis study [R16].

167. Several recent studies of medical exposures add to what is known about ionizing radiation and the risk of skin cancers of different histological types. Associations between basal- and squamous-cell skin carcinoma and a history of therapeutic x-irradiation were reported from a case-control study of male skin cancer patients conducted in Alberta Province, Canada [G14]. Most of the exposure was from treatment for benign skin disorders. This is one of the few studies reporting an excess risk for squamous-cell carcinoma. Recall bias or misclassification of the skin disease being treated might account for this finding. The development of a new basal-cell or squamous-cell carcinoma subsequent to therapeutic radiation was evaluated in a study of 1,690 patients diagnosed with an earlier non-melanoma skin cancer in New Hampshire, United States [K16]. A history of radiotherapy was associated with basal-cell carcinoma (relative risk = 2.3; 95% CI: 1.7–3.1) but not squamous-cell carcinoma (relative risk = 1.0; 95% CI: 0.5–1.9). The risk of a second non-melanoma skin cancer was higher among persons exposed early in life.

168. In a follow-up study of bone marrow transplantation patients, an eightfold risk of melanoma was observed among patients treated with high-dose, total-body irradiation [C16]. This finding was based, however, on only nine melanomas. Among Swedish patients treated with ionizing radiation for skin haemangioma, the observed number of melanomas was close to what had been expected [L16], but no data on non-melanoma were available since follow-up was based on the Swedish Cancer Registry, which does not register basal cell carcinomas.

169. Several studies of radiation-exposed medical and nuclear workers have been conducted, but most do not have individual doses. These studies mainly evaluated mortality, so they are not very informative for assessing skin cancer effects. A significantly increased risk of skin cancer mortality was reported for radiologists in the United States [M23] and in the United Kingdom [S41]. The risks were larger for radiologists practicing in the early years, when exposure is thought to have been highest, than for those practicing later. Among radiological technologists in the United States, skin cancer mortality was significantly lower than expected compared with national rates (SMR = 0.62; 95% CI: 0.44–0.84) [D23]. Skin cancer incidence was elevated (SIR = 2.8, $p<0.05$) among Chinese diagnostic x-ray workers [W10], particularly those who had been employed for 15 years or more. Among 4,151 medical workers in Denmark, whose mean cumulative dose was very small (18.4 mSv whole-body dose equivalent), skin cancer risk was not significantly elevated [A15]. The difference in these findings is probably due to the longer duration of employment among the Chinese workers (69% of the Chinese workers had been employed for five or more years compared with slightly more than 15% of the Danish workers) or their exposure to higher doses during the early years. Although the mean radiation dose is not known for the Chinese workers, it is assumed to be relatively high, since improvements in radiation safety practices were introduced only in the mid-to-late 1960s.

170. The results for nuclear workers are similarly inconsistent. An increased incidence of melanoma was associated with working with radiation sources at the

United States Lawrence Livermore National Laboratory in some studies [A14, S40] but not in others [M34], and no association was observed at the sister laboratory, Los Alamos National Laboratory, or at most other nuclear facilities [W13].

171. Using data from the American Cancer Society database, the frequency of various occupational exposures was evaluated in 2,780 cases of malignant melanoma and approximately three times that number of matched controls. A history of occupational exposure to x rays was significantly more frequent among the cases than the controls [P26]. This study did not, however, distinguish between medical and nuclear workers, and it was not possible to control for confounding due to social class.

172. In a summary of the literature through the late 1980s, Shore [S30] suggested that there is an interaction between ultraviolet and ionizing radiation. One reason for this hypothesis was the fact that black patients treated in New York City with scalp irradiation for ringworm did not develop skin cancer on the scalp or face, while white patients demonstrated a significantly increased risk for developing basal-cell carcinoma [S27]. A recent National Radiological Protection Board publication reported that radiation-associated non-melanoma skin cancer generally develops on areas of the skin exposed to ultraviolet radiation [N10]. It was estimated that for the population of the United Kingdom, the lifetime risk for non-melanoma skin cancer is $2.3\ 10^{-2}\ Sv^{-1}$. The report concluded that ultraviolet-shielded and heavily pigmented skin would have lower risks than ultraviolet-exposed or lightly pigmented skin. The latest Life Span Study data for basal-cell carcinoma do not support this hypothesis [R15]. First, the ERR for the atomic bomb survivors, who have moderately pigmented skin and very low natural rates of non-melanoma skin cancer, was extremely high; second, the ERR was not larger for ultraviolet-exposed parts of the body than for parts of the body that are generally ultraviolet-shielded [R15]. Yamada et al. [Y3] reported a high risk for the development of skin neoplasia among people with occupational exposure to ultraviolet rays, but they did not report which parts of the body had higher risks. In the New Hampshire study, there did not appear to be a higher risk for ultraviolet-exposed parts of the body compared with ultraviolet-shielded parts [K16]. Thus, the question of a possible interaction between ionizing radiation and ultraviolet radiation remains unresolved. Possibly, ultraviolet radiation exposure plays a less important role in inducing skin cancer in individuals whose skin has a relatively high melanin content, but more data are needed to fully understand this complicated relationship.

2. Internal low-LET exposures

173. Studies of patients receiving ^{131}I diagnostic examinations [H27] or ^{131}I treatment for hyperthyroidism [G18, H23, H25] or thyroid cancer [D15, E2, G13, H26] do not indicate any significantly increased or decreased risks of skin cancer associated with this exposure. Although the amount of ^{131}I administered varies from about 2 to 500 MBq for hyperthyroid treatment to 5.5 GBq for thyroid cancer treatment, the dose to the skin would be relatively small.

3. Internal high-LET exposures

174. A large, significantly elevated risk of non-melanoma skin cancer was observed among uranium miners in Czechoslovakia [S29]. In contrast, neither mortality from melanoma nor non-melanoma skin cancer was significantly elevated or related to cumulative exposure in an international pooled analysis of 11 studies of underground miners [D8]. Although the radon levels in the air were high and the study population large (64,209 miners), the latter study is hampered by the fact that mortality does not reflect the true risks of skin cancer.

175. The major studies of patients treated with internal high-LET exposures were summarized at two international meetings [D31, N4, V1, V8, W20]. These results, as well as results from the Danish thorotrast study [A5], do not suggest that skin cancer is related to exposure from ^{224}Ra, ^{226}Ra, ^{228}Ra, or thorotrast.

4. Summary

176. Ionizing radiation can induce non-melanoma skin cancer, but the relationship is almost entirely due to a strong association with basal-cell carcinoma. To date, there has been little indication of an association between ionizing radiation and malignant melanoma or squamous-cell carcinoma, but the data are sparse. When radiation exposure occurs during childhood, the ERR for basal-cell carcinoma is considerably larger than when the exposure occurs during adulthood. A very strong trend for a decreasing risk of basal-cell carcinoma with increasing age at exposure was observed in the Life Span Study. Data on the dose-response relation for basal-cell carcinoma suggest non-linearity, but more data are needed to better characterize the shape of the dose response, to further evaluate the role of ionizing radiation in the development of squamous-cell carcinoma and melanoma, and to clarify the role of ultraviolet radiation in relation to ionizing radiation.

H. FEMALE BREAST CANCER

177. Breast cancer is the most commonly diagnosed cancer and cause of cancer mortality among women in many countries in North America and western Europe; incidence rates are lower by a factor of 5 or more in Asian countries (see Table 1) [P5]. Breast cancer incidence rates have increased since 1960 at all ages in many countries throughout the world [U14]. In some countries this increase may be explained in part by changes in screening practices. However, particularly outside western Europe and North America, the bulk of the increase is likely to be due to risk factors for the disease. Known risk factors include age, family history of breast cancer, early menarche, late age at first birth, nulliparity, late age at menopause, height, postmenopausal weight, and a history

of benign breast disease [K3]. A recent analysis of more than 50 studies indicated that there is a small increased risk of breast cancer while women are taking combined oral contraceptives, although this does not appear to persist more than 10 years after stopping use [C12]. The potential role of other possible risk factors, such as birth weight [M19], which may be a marker of intrauterine factors, and some components of diet [H19], is still unclear.

178. Ionizing radiation is well documented as a cause of breast cancer in women [U2]. Mammary tumours have also been induced in several studies of mice exposed to radiation (e.g. [S11]). Table 13 presents results from epidemiological studies that have incorporated some assessment of the level of low-LET or high-LET doses.

1. External low-LET exposures

179. Most of the external low-LET studies listed in Table 13 were reviewed in the UNSCEAR 1994 Report [U2]. New findings include those from the extended follow-up for mortality of the Japanese atomic bomb survivors [P9]. However, as a consequence of the high cure rate for this type of cancer, the results for cancer incidence in this cohort [T1] are probably of greater importance, despite the slightly shorter follow-up period for incidence than for mortality. New results have also been reported from a number of studies, including the extended follow-up of Swedish patients irradiated for skin haemangioma in infancy [L46]; this study also incorporated individual estimates of organ doses [L14] and patients from both Stockholm [L17] and Gothenburg [L15].

180. Much of the information that has accumulated since the UNSCEAR 1994 Report relates to exposure in childhood. For example, Bhatia et al. [B16] reported a very high standardized incidence ratio in an international study of breast cancer among patients treated for Hodgkin's disease in childhood, as shown in Table 13. Similar results were reported in studies in the Nordic countries [S23], in France and the United Kingdom [D33], and in the United States [T9]. Furthermore, Bhatia et al. reported evidence of a dose-response trend with relative risks of 5.9 (95% CI: 1.2–30.3) at 20–40 Gy and 23.7 (95% CI: 3.7–152) at more than 40 Gy, relative to those with doses to the mantle region of radiotherapy of less than 20 Gy [B16]. While the study of Hodgkin's disease patients by Hancock et al. [H2] gave a lower ratio of observed to expected breast cancer cases, fewer than 10% of these patients were less than 15 years old when originally diagnosed, and there was no elevated risk among women treated at ages above 30 years. However, as mentioned in Section I.A, there is the possibility in the hospital-based study of Bhatia et al. [B16] that patients with a second cancer were more likely to return to hospital than those who were disease-free [D25]. There is some suggestion of an elevated breast cancer risk following scattered radiation received from radiotherapy for retinoblastoma during infancy [W11], while in a study of patients who underwent bone marrow transplantation (primarily given during childhood to treat leukaemia and lymphoma) inferences are hampered by the limited period of follow-up (mean of 4.5 years) [C16]. It should be noted that the number of cases in these studies is fairly small, and that the possible role of both chemotherapy and genetic susceptibility in the development of the tumours is unclear. However, from a clinical viewpoint these findings are extremely important, because Bhatia et al. estimate that around 35% (95% CI: 17–53) of the female patients in their study will have developed breast cancer by the age of 40 years [B16]. Although other studies, such as those of the survivors of the atomic bombings in Japan [P9, T1] and of patients who received thymic irradiation [H10], have reported lower risks than that of Bhatia et al. [B16], both the former studies and the latter indicate that the relative risks for females exposed to radiation in childhood are higher than for those exposed in adulthood. In particular, studies of women irradiated after age 40 years [B3, B10, H20, P9, S20, T1] generally show low values for the ERR per Sv. For exposure within childhood, there has been some variation in the findings; for example, the estimate for the ERR per Sv in Swedish skin haemangioma study [L46] is lower than in some other studies (see Table 13), possibly owing to the high proportion of children in the Swedish study who were irradiated in infancy [L46] or to the lower dose rate in this study. A recent follow-up of scoliosis patients in the United States irradiated during childhood and adolescence indicated a relatively high value for the ERR per Sv (see Table 13), although potential confounding associated with the severity of disease and hence reproductive history may explain part of this increase [D34].

181. Several of the studies of medical exposures have a longer follow-up than the Life Span Study. The latest results from an extended follow-up of the Canadian fluoroscopy study [H20] suggest that, after allowing for age at exposure, the ERR per Sv may be lower between 40 and 57 years following exposure compared with the earlier period; however, this difference is not statistically significant. In the Massachusetts fluoroscopy study [B3] the ERR appears to be constant up to 50 years or more after exposure, again after adjusting for age at exposure. A reanalysis of data on women in Sweden irradiated for benign breast disease found no persistent heterogeneity in the ERR over the period up to more than 40 years after exposure [M20]. In contrast to the original analysis [M8], this analysis involved more detailed modelling of internal baseline rates and of age and calendar period effects [M20]. The study of Swedish skin haemangioma patients [L46] also showed that risks were still elevated more than 60 years after exposure. Thus, these studies indicate that, in common with the Life Span Study [T1], the ERR per unit dose is approximately constant up to at least 40 years following exposure, and indeed may be constant at follow-up times of 50–60 years.

182. Howe and McLaughlin [H20] reported results from an extended follow-up of breast cancer mortality among tuberculosis patients in Canada who received multiple chest fluoroscopies. In common with other studies (e.g. [B3, S15, T1]), this study showed a linear dose-response

relationship, although there was some indication of non-linearity in an earlier analysis of this cohort [M1]. As before, the slope of the dose trend was greater for patients in Nova Scotia than that for patients in other parts of Canada. The reason for this difference is not clear. One factor that may be pertinent is the higher doses for the exposures in Nova Scotia. However, Howe and McLaughlin noted that on both a relative and an absolute scale, the risk among Nova Scotia patients appeared to be higher than that among the survivors of the atomic bombings in Japan. Furthermore, the risk per unit dose among the non-Nova Scotia patients is similar to that among the patients in the Massachusetts study [B3]. The quality of the dosimetry for the various sanatoria may also be relevant, although Howe and McLaughlin emphasized that identical protocols were used to estimate doses. It should also be noted that the Nova Scotia findings are driven by data at doses in excess of 10 Gy, so the non-Nova Scotia findings may be more representative of risks at lower doses.

183. As indicated earlier, comparison of the risks seen in studies of the Japanese atomic bomb survivors and of populations elsewhere who received medical exposures may be of value in deciding how to transfer risks across populations. One complication, however, is the different degree of fractionation and radiation quality in the two studies. A parallel analysis of earlier data on breast cancer among the atomic bomb survivors and patients in several of the North American studies indicated that the ERR per unit dose is higher in the latter group, whereas absolute risks are more similar [L5]. Similar results were found by Little and Boice [L39], who analysed more recent incidence data for the Japanese atomic bomb survivors and the Massachusetts cohorts. Little and Boice concluded that these data provide little evidence for a reduction in breast cancer risk after fractionated irradiation [L39]. However, Brenner [B33] has interpreted these findings as being consistent with a lower risk for fractionated compared with acute exposure, based on differences, by a factor of about 2, between the number of *in vitro* cell transformations observed for the relatively soft x rays received in fluoroscopy and other medical exposures and the number observed for the higher energy gamma rays received by the atomic bomb survivors. On the other hand, there is little evidence from animal studies to indicate a difference between x rays and gamma rays in inducing breast cancer [U3]. Also, Elkind [E5] has interpreted the results of Little and Boice [L39] as indicating that breast cancer target cells may be deficient in repair, in line with a radiobiological model that he has proposed [E6]. It should also be emphasized that the comparison of the Japanese and North American cohorts is also influenced by the method of transferring risks across populations. Since the disparity in the ERR per unit dose between the Japanese and Massachusetts cohorts [L39] would be greater rather than smaller if the possible effects of photon energy suggested by Brenner [B33] were allowed for, it would appear to be more appropriate to transfer age-specific absolute (rather than relative) risk coefficients for breast cancer from Japan to North American and possibly other populations.

184. It has been claimed by Gofman [G8] that about 75% of current breast cancer cases in the United States are due to ionizing radiation exposure, mostly from diagnostic medical procedures. This claim is based not on new epidemiological findings but on his estimation of medical doses and breast cancer risk factors. There are a number of flaws and questionable assumptions in his calculations. For example, the risk estimates are based on old mortality data for all cancers among the Japanese atomic bomb survivors, using the previous T65D dosimetry and follow-up to the end of 1982, rather than on recent incidence or mortality data for breast cancer specifically, using the DS86 dosimetry system. The extrapolation to low doses was based on an analysis that failed to take account of competing causes of death in the calculation of cancer rates and that did not adjust for age and gender [M17]; also, a factor introduced into the calculations to allow for a multiplicative transfer of risks from Japan to a United States population was too high and, in the light of the above findings, probably not necessary. Furthermore, while Gofman multiplied the risks from gamma-ray exposure of the atomic bomb survivors by two, in order to arrive at a risk estimate for x-ray exposure, it was noted above that relative risks are lower among women in the United States with x-ray exposures [B3, S15, L39] than among atomic bomb survivors exposed predominately to gamma rays, whereas absolute risks are similar. Given all these considerations, it is likely that Gofman's breast cancer risk estimate is too high by a factor of between 7 and 60 approximately [M18]. Furthermore, doses from past medical practices in the United States are also likely to have been overestimated. Calculations made by Evans et al. [E4] based on scientifically sounder approaches to the estimation of doses and radiation risk factors indicate that the proportion of breast cancers in the United States attributable to diagnostic radiography is closer to 1% than to the much higher values suggested by Gofman [G8].

185. Most of the studies of occupational exposure to low-LET radiation have not been informative about the risks of female breast cancer, owing to the small proportion of women in these studies. The largest amount of information concerns radiation workers in the medical field. Based on a survey of about 79,000 female radiological technologists who had worked in the United States since 1926, Boice et al. [B6] conducted a nested case-control study for 528 women with breast cancer. The study demonstrated associations with known risk factors, such as early age at menarche and family history of breast cancer but did not find correlations with number of years worked or with jobs involving radiotherapy, radioisotopes, or fluoroscopic equipment. However, dosimetry records were available for only 35% of the study subjects, mainly those who had worked in more recent years. Owing to the low level of doses received by these workers (generally below 0.1 Gy), the statistical power to detect an elevated risk was weak. As mentioned, dose data were lacking for earlier workers, whose cumulative doses may have been up to about 1 Gy. A subsequent mortality analysis based on a larger version of the cohort of radiological technologists showed a relative

risk of 1.5 ($p<0.05$) compared with national rates for women certified before 1940, whereas no enhanced risk was evident for more recent workers [D23]. This might reflect the higher doses received by early workers compared with later workers. However, the early workers were also more likely to be nulliparous than later workers, which may indicate a confounding effect. An elevated risk of breast cancer has also been reported among radiological technologists and radiologists in China; the doses are not known, although measured decreased blood counts suggest that they were generally high [W10].

2. Internal low-LET exposures

186. Several studies of patients given ^{131}I have examined breast cancer risks. Most of these studies were reviewed in the UNSCEAR 1994 Report [U2]. While a study in Massachusetts in the United States showed a higher risk of breast cancer among women treated for hyperthyroidism with ^{131}I compared with patients treated by other methods, there was no consistent trend in risk with the amount of ^{131}I administered [G10]. Similar conclusions were reached in a larger study including this and other hyperthyroid patients in the United States [R14]. In addition, a study of patients treated for hyperthyroidism in Sweden [H23, H24] did not show an elevated breast cancer risk overall, nor did it indicate a trend in risk according to the level of activity administered. It should be noted that the mean dose to the breast in the Swedish study was estimated to be 0.06 Gy [H23], indicating that such studies are unlikely to have sufficient statistical precision to detect an elevated risk. This problem also applies to studies of patients given diagnostic exposures to ^{131}I, where the number of cases was larger but the doses substantially smaller [H27], and of patients treated with ^{131}I for thyroid cancer, where the doses were higher but the number of breast cancers was lower [H26]. In neither of the last two studies were breast cancer rates raised significantly relative to national rates.

187. Among people residing on the banks of the Techa River who received both internal and external low-LET exposures as a consequence of radionuclide releases from the Mayak facility in the southern Urals, the proportion of female cancer deaths from breast cancer (4%) is similar to that among the Japanese atomic bomb survivors [K5]. However, without information on the breast doses in the Techa River cohort, it is difficult to make inferences.

3. Internal high-LET exposures

188. Continued follow-up of the early cohort of ^{224}Ra patients in Germany [N4] has indicated an excess of female breast cancers compared with the general population, as shown in Table 13. Calculations [H8] have yielded estimated breast doses from ^{224}Ra of several milligray to about 0.45 Gy [N19], with an average of about 0.1 Gy (high-LET). Analyses of these data indicated that the best fit was with a model in which the relative risk varied linearly with dose and decreased with increasing age at exposure [N4]. In particular, the estimate of the ERR per Sv was 2.9 among females treated at ages less than 21 years, compared with an ERR per Sv of 0.9 for the full cohort, although these estimates are based on small numbers of cases. To identify potential confounders, a control group was constructed based on 182 patients who had not been treated with ^{224}Ra. In this group, 7 female breast cancer cases were observed, compared with 3.8 expected. Although the numbers were small, there was a suggestion that some of the cases in the control group may have been associated with repeated fluoroscopic x-ray examinations in the course of pneumothorax therapy [N4]. In contrast, the patients in the ^{224}Ra cohort had not in general received pneumothorax therapy, so this may not explain the excess seen in this group. Another possible reason for the excess is that patterns of reproductive risk factors may differ between these patients and the general population. In view of the results for the control group of patients, it seems unlikely that this could explain all of the excess, although the severity of the original disease may have affected whether or not radium was used, as well as the patient's subsequent reproductive history (and hence the risk of breast cancer). It may be that a combination of factors has led to the observed increase.

189. The study of neurological patients in Denmark [A5] gave some suggestion of an elevated breast cancer risk among women exposed to thorotrast for cerebral angiography relative to unexposed women, although this increase was not statistically significant (relative risk = 2.1; 95% CI: 0.8–5.7). Autopsy findings suggest that the dose to the breast from thorotrast is likely to be lower than that to many other organs [M21]. There is also some indication of an excess of breast cancer among female dial painters in the United Kingdom who had used a paint containing radium [B13, B14]. While there was no significant excess of breast cancer relative to local rates among radium dial workers in the United States, the cohort included not only dial painters but also women who carried out other tasks in this workplace [S16]. In contrast, a study restricted to the dial painters in the United States provided some suggestion of a raised breast cancer rate [R11]. However, as described in the UNSCEAR 1994 Report [U2], any effect of radiation is more likely to be due to external irradiation of the breast from paint in containers than to exposures arising from intakes of ^{226}Ra. In addition, reproductive risk factors may be of relevance to the breast cancer findings in these studies.

190. In view of the uncertainties in quantifying breast doses and cancer risks in studies of women exposed to high-LET radiation, it is not possible to directly compare the risks of female breast cancer associated with low-LET and high-LET radiation.

4. Summary

191. Extensive information from the Japanese atomic bomb survivors and several medically exposed groups demonstrates elevated risks of female breast cancer following external low-LET irradiation. The trend in risk with dose is consistent with linearity, and the ERR per Sv is particularly high for exposure

at young ages. In contrast, there is little evidence of increased risks for exposure at ages of more than 40 years. While the ERR per Sv seems to be fairly constant with time since exposure, the EAR per Sv appears to be more stable across populations with differing baseline rates. Examination of data for the atomic bomb survivors and some of the medical studies tend to suggest that dose fractionation has little influence on the risk per unit dose, although different interpretations have been placed on these analyses.

192. Data from studies of low-dose chronic external low-LET irradiation and of internal low-LET and high-LET exposures are limited. The interpretation of some reports of increased risks is complicated by the potential for confounding as a consequence of reproductive factors or other exposures.

I. PROSTATE CANCER

193. Worldwide, prostate cancer is one of the most common malignancies in men, but with wide variations in rates between countries [P5]. Specifically, incidence rates are highest in North America and some European countries and lowest in China and Japan. However, there is less international variation in prostate cancer mortality than in incidence [R32]. Studies of migrants suggest that the variations between countries cannot be explained solely on the basis of genetic predisposition [R32]. Both incidence and mortality rates have increased over the past few decades in many countries, although a substantial proportion of these increases may reflect improved detection of the disease [W6].

194. Prostate cancer is rare before 40 years of age, following which incidence rates double for each subsequent year of life, such that the age-specific curve has a steeper slope than for any other cancer [R32]. Survival rates are related strongly to the stage of the disease at diagnosis. The aetiology of prostate cancer is largely unknown. However, there is some evidence of effects associated with hormonal factors (e.g. levels of testosterone), family history of the disease, and dietary factors (e.g. possibly, fat intake [R32]).

1. External low-LET exposures

195. As indicated in Table 14, there is little evidence of an association between radiation and prostate cancer in the Life Span Study of the Japanese atomic survivors [T1]. In other studies, the point estimate of the ERR per Sv from the study of ankylosing spondylitis patients in the United Kingdom coincides with that for the atomic bomb survivors, but with a tighter confidence interval that excludes values below zero [W1]. However, the latter finding should be viewed cautiously, in that it is based on a combination of the number of x-ray treatments and mean organ dose rather than on individually-based estimates of doses, as in the Life Span Study. Among patients in the United States treated for peptic ulcers, raised mortality from prostate cancer relative to the general population was observed for both those who received radiotherapy and those who did not; rates in the two groups did not differ significantly [G6]. An international study of patients treated for testicular cancer, many of whom received mean doses of several tens of gray, indicated an elevated risk of prostate cancer (SIR = 1.26, 95% CI: 1.07–1.46). However, this increase was apparent even in the first few years after treatment, and, in the absence of individual dose data, it might be surmised that this result was due to heightened medical surveillance of genitourinary conditions [T21]. Studies of medical exposures in childhood have thus far yielded little information on prostate cancer risks, mainly because a very long follow-up is required to obtain sufficient cases (given that this disease occurs predominantly in older persons).

196. Large studies of radiation workers generally do not show elevated risks of prostate cancer in relation to external low-LET radiation (e.g. [C11, M46]). Instances of worker studies in which increases have been reported may reflect chance variations (e.g. [A15]) or possibly other types of exposure (e.g. [B45, F6, R26], described in more detail below).

2. Internal low-LET exposures

197. In a large study of hyperthyroidism patients in the United States [R14], mortality from prostate cancer among patients treated with ^{131}I was significantly lower than would have been expected from national rates (SMR = 0.68). Furthermore, there was no indication of a trend in risk with the level of ^{131}I administered, although it should be noted that doses to the prostate are likely to have been low. Studies in Sweden of patients with medical exposures to ^{131}I have tended not to present results for prostate cancer specifically [H23, H24, H26, H27]. However, the findings given in these Swedish studies for all male genital cancers combined, most of which are likely to have been prostate cancers, showed overall incidence and mortality to be consistent with national rates. Furthermore, among the group of Swedish patients treated for hyperthyroidism, there did not appear to be a clear trend in mortality from all male genital cancers combined related to the amount of ^{131}I administered [H24]; however, in common with the corresponding study in the United States [R14], the prostate doses are unlikely to have been high.

198. A cohort study of employees of the United Kingdom Atomic Energy Authority showed that while prostate mortality among all radiation workers was consistent with national rates, mortality was raised among those workers who had experienced higher external doses and who had been monitored for internal radiation exposure [B45, F6]. Based on this cohort, a case-control study was conducted that looked at individual assessments of exposure to radionuclides and other substances in the workplace, as well as socio-demographic factors, for 136 workers with prostate cancer and 404 matched controls [R26]. Analyses were conducted for various radionuclides; however, the results were often correlated, because there was simultaneous exposure to some radionuclides in certain working environments. Rooney et al. [R26] reported significantly

elevated relative risks associated either with documented exposure to ^{51}Cr, ^{59}Fe, ^{60}Co, ^{65}Zn, or ^{3}H or with working in environments potentially contaminated by at least one of these radionuclides. The latter finding in particular was based largely on men who worked on heavy water reactors. Exposure to other radionuclides or to chemicals was not associated with an elevated risk. While it was difficult to distinguish the findings for the above five radionuclides, particular attention was paid to ^{65}Zn, because zinc is concentrated in the prostate gland and Auger electrons emitted from ^{65}Zn may give rise to high doses at short range. However, studies of biokinetics and dosimetry [A7, B46] indicate that even with pessimistic assumptions about the uptake of zinc in the prostate and the relative biological effectiveness of Auger electrons, the dose to the prostate from occupational exposures is likely to be 0.1–0.2 Sv at most and, taking account of the findings from the Japanese atomic bomb survivors [T1], would not be sufficient to explain the findings of Rooney et al. [R26].

3. Internal high-LET exposures

199. Few studies have reported results for prostate cancer in relation to internal high-LET exposures. As shown in Table 14, there is little indication of elevated risks among patients with intakes of ^{224}Ra [N4] or thorotrast [V8], although the numbers of cases are not very large. Furthermore, information has rarely been presented about level of exposure. An exception concerns a study of plutonium workers in the United Kingdom, in which there was no increase in risk with the sum of the cumulative organ-specific dose from plutonium and the external dose [O1]. However, in common with many other studies of workers high-LET doses to the prostate are likely to have been low.

4. Summary

200. Data for the Japanese atomic bomb survivors and from most other studies provide little evidence of an elevated risk of prostate cancer following radiation exposure. Elevated risks have occasionally been reported, but it is not clear whether these represent chance findings or facets of particular types of exposure in the workplace, either from radiation and other factors. It should be noted that the statistical precision of some of the medical and occupational studies is limited by small numbers of cases and/or low doses. Also, because prostate cancer is predominantly a disease of the elderly, follow-up studies of exposure in childhood have not been informative to date.

J. CANCER OF THE URINARY BLADDER

201. Bladder cancer accounts for less than 5% of cancer incidence and less than 2% of cancer mortality in industrialized countries. There is wide international variation in bladder cancer incidence, with high rates in Europe and North America and low rates in Latin America and Asia. Incidence increases steeply with age and is more common among men than women. In some countries the gender ratio can reach 5:1 [H47, P5]. The incidence increased from the 1960s to the 1980s, but recently the rates have begun to stabilize. Mortality has been decreasing in both men and women and at all ages. The temporal trends are influenced by changes in detection and improvements in survival.

202. Cigarette smoking is a leading cause of bladder cancer. In Western countries, approximately 50% of the cancer in men and 30% in women have been attributed to smoking. Occupational exposures, particularly to aromatic amines, are also well known bladder cancer risk factors. Urinary tract infections are also associated with an increased risk of bladder cancer, especially among women. Use of phenacetin-containing analgesics and cyclophosphamide, as well as exposure to *S. haematobium* infection, are also suspected bladder cancer risk factors [H47, M45, S48].

1. External low-LET exposures

203. Estimates of risk for bladder cancer from several studies are given in Table 15. Statistically significant excess risks have been derived for incidence [T1] and mortality data [P9, R1] from the Life Span Study, the cervical cancer case-control study [B1], the anklylosing spondylitis study [W1], the metropathia haemorrhagica study [D7], and the benign gynaecological disease study [I16]. Although the doses are considerably higher in the last two studies (~6 Gy), the risk estimates are about the same as the risk estimate in the ankylosing spondylitis study [W1]. In the Life Span Study, the effects of age and gender on the risks are unclear. In particular, the incidence data exhibit a statistically significant gender difference, with the ERR for females exceeding that for males by a factor of about 5 but the average EAR showing no significant difference [T1]; in the mortality data, the point estimates of the ERRs and EARs for males are higher than those for females, although the differences are not statistically significant [P9]. Neither the mortality data [S3, P9] nor the incidence data [T1] in the Life Span Study exhibit statistically significant variation with age at exposure for either the ERR or the EAR. There is, however, a suggestion of some variation with age in the cervical cancer case-control study [B1].

204. Although individual organ doses frequently are not available, several, but not all, studies of second cancers have reported an association between bladder cancer risk and high therapeutic radiation doses. A non-significant increased risk of bladder cancer was associated with radiotherapy in a large cohort of non-Hodgkin's lymphoma patients [T19] and in a European nested case-control study of 63 women with bladder cancer who had previously been treated for ovarian cancer and 188 ovarian cancer patients who did not develop bladder cancer [K30]. Compared with surgically treated patients, the relative risks were 1.9 (95% CI: 0.77–4.9), 3.2 (95% CI: 0.97–10), and 5.2 (95% CI: 1.6–16) for radiotherapy only, chemotherapy only, and radiotherapy and chemotherapy combined, respectively. Of 32,251 ovarian cancer patients, 20 of the 65 women who developed bladder cancer were treated solely with

radiation, resulting in a significantly increased risk (O/E = 2.1; 95% CI: 1.6–2.6) [T20]. The risks increased with time since exposure, until they were six times greater at 15 or more years. These results are very consistent with those for cervical cancer patients who were treated with similar radiation doses [B1]. Risk was not significantly elevated among ovarian cancer patients treated with chemotherapy only [K30].

205. Among men treated for testicular or prostate cancer, enhanced risks of bladder cancer have been observed. Among testicular patients with seminoma treated with radiotherapy (mean dose = ~22 Gy), a two- to threefold greater risk was found five or more years after treatment. More than 20 years after treatment, the risk rose to 3.2 [T21]. Among non-seminoma patients receiving radiotherapy (mean dose = 45 Gy), the risks were elevated but not statistically significant. Among men treated with high-dose radiotherapy for prostate cancer, a statistically significant 40% increased risk was noted five or more years after therapy [N11]. No excess risk was found among patients treated surgically. In a reanalysis and update of these data, Brenner et al. [B42] reported a 15% (95% CI: 1.02–1.31) elevated risk of bladder cancer among over 50,000 men treated with high-dose radiotherapy compared with over 70,000 patients who underwent surgery. Risks were much higher, however, for long-term survivors, with radiotherapy patients surviving 10 or more years having a risk of 1.77 (95% CI: 1.14–2.63).

2. Internal low-LET exposures

206. High doses of ^{131}I are often used to treat thyroid cancer. The bladder is one of the organs that concentrate iodine [U2]. The ^{131}I dose to the bladder from treatment for thyroid cancer is about 2 Gy. An excess risk of bladder cancer has been reported in one small study of thyroid cancer patients [E2] but not in two others [D18, H26]. Patients treated with ^{131}I for hyperthyroidism receive 100–200 mGy to the bladder. No significantly increased risks were noted in two studies with a combined study population of about 30,000 patients [H23, H24, R14]. In a recent study of hyperthyroid patients treated with ^{131}I in the United Kingdom, there was a significantly lower risk of bladder cancer than in the general population, but bladder cancer incidence increased (p=0.005) with increasing levels of administered activity [F8].

3. Internal high-LET exposures

207. The recent follow-up of a cohort of German patients treated with ^{224}Ra has demonstrated an excess relative risk of bladder cancer compared with the general population (ERR per Sv = 0.4) [N4]. The relative risk was higher for patients who were older at diagnosis. No excess of bladder cancer has been reported in another cohort of patients treated with ^{224}Ra [W20] or among patients receiving thorotrast as a contrast medium for arteriography [A5, D31, M14, V8].

4. Summary

208. Statistically significant excess risks of cancer of the urinary bladder are seen in several populations exposed to low-LET radiation. The Life Span Study risk estimates are somewhat greater than those seen for cancer patients; however, since the cancer patient studies involve extremely high doses, the differences may reflect cell killing. In addition, second cancer register-based cohort studies often obtain information on initial treatment only. Subsequent treatments can lead to exposure misclassification, which in turn can lead to underestimation of exposure effects. Potential interactions between smoking and radiation remain to be studied.

K. BRAIN AND CENTRAL NERVOUS SYSTEM TUMOURS

209. Depending on tumour location, benign and malignant tumours of the central nervous system (CNS) can have similar symptoms and outcomes. As a result, the two types of tumours are not always easily distinguished, and many tumour registries routinely include both histological types in their CNS incidence rates. [I11, P18]. Annual incidence rates for CNS cancers range from about 1.0 to about 10 per 100,000 persons, but since the quality of medical care varies from country to country and reporting of benign tumours is inconsistent among registries, international comparisons of CNS tumours can be misleading [P5]. The fact that the lower incidence rates are reported primarily from cancer registries with uncertain completeness of ascertainment suggests that country-to-country variation is probably considerably less than current reporting indicates. Over the last few decades, brain tumour incidence and mortality have increased, especially among the elderly, but whether this is a real increase or a result of better diagnosis and reporting is controversial [I11, P18]. With the exception of meningiomas, CNS tumours occur more frequently among men than women [P5]. This Section will consider both benign and malignant CNS tumours occurring within the cranium (brain, cranial nerves, cranial meninges), spinal cord, spinal meninges, and peripheral nervous system because of the potential problem of misclassification by tumour behaviour. In addition, since the comparison rates used in some studies are derived from tumour registries that combine all CNS tumours in one category, results are reported for all CNS tumours and not for malignant tumours only.

210. While the aetiology of CNS tumours remains elusive, therapeutic irradiation of the head and neck during childhood is an established risk factor, and social class, trauma, diet, and some chemicals have been identified as potential risk factors [B43, D35, I11, P18]. Primary malignancies of the central nervous system are among the most lethal of all cancers. In the United States, five-year survival for malignant CNS tumours is approximately 30% and shows little relation with stage at diagnosis [K17]. Survival for benign meningiomas has improved

considerably over the last few decades, but depending on tumour size and location, the quality of life can be severely impaired [L30].

1. External low-LET exposures

211. As summarized in Table 16, the epidemiological literature provides evidence for an association between ionizing radiation and tumours of the CNS. Since publication of the UNSCEAR 1994 Report [U2], additional information on the incidence and mortality of CNS tumours in the Life Span Study of atomic bomb survivors has become available [P9, P19]. As in earlier reports, the most recent mortality data from the atomic bomb survivors provide no evidence of a radiation effect for brain tumours but do show a non-significant excess risk for tumours of the CNS outside the brain [P9]. New incidence data that assess histologic types separately demonstrate a strong dose response for neurilemmomas (ERR at 1 Sv = 4.0) and a moderate dose response for meningiomas (Table 27) [P19]. The excess risk for neurilemmomas was observed for persons of all ages at the time of the bombings. Other studies of atomic bomb survivors in Hiroshima and Nagasaki show an association between meningioma incidence and radiation exposure [S33, S39, S42].

212. A significant relationship between radiation dose and CNS tumour risk was demonstrated in the Israeli tinea capitis study [R17]. An average dose of 1.5 Gy from childhood radiotherapy to the scalp was associated with an increased incidence of CNS tumours in the head and neck (relative risk = 8.4). The relative risks ranged from 2.6 for gliomas to 9.5 for meningiomas to 33 for neurilemmomas. Large relative and absolute risks for CNS tumours were also observed in the New York tinea capitis study [A15, S31]. Similarly, an association between radiotherapy and benign CNS tumours was reported following childhood irradiation for inflamed tonsils and other benign head and neck conditions [S28, S46] and irradiation in infancy for an enlarged thymus gland [H31]. Following low doses of radiation from ^{226}Ra treatment for haemangioma during infancy in Stockholm, intracranial tumours were not elevated [L16]. In contrast, the incidence of gliomas and meningiomas was significantly greater in 1,805 infants treated with similar doses of ^{226}Ra for haemangioma in Gothenburg, Sweden, but no clear dose response was observed [K22, L15]. In a recent pooled analysis of the two studies, 86 patients with intracranial tumours were observed among exposed and unexposed patients compared with 61 expected (SIR = 1.42; 95% CI: 1.13–1.75) [K23]. A linear dose-response relationship fit the data best (ERR at 1 Gy = 2.7), and within the narrow age-at-exposure range (0–81 months) the risk increased with decreasing age at exposure. In a small cohort of children treated with nasopharyngeal radium implants to prevent deafness, three adult brain cancers occurred [S32]. Although the incidence was raised, chance could be one explanation for the increase [S47]. CNS mortality was not elevated in a larger study of children treated with smaller doses [V5].

213. A higher-than-expected number of second primary CNS tumours among survivors of childhood cancers has been noted in several studies. Neglia et al. [N9] demonstrated that radiotherapy during childhood was a significant factor in the excess of CNS tumours occurring among acute lymphoblastic leukaemia patients. A cohort of 4,400 childhood cancer survivors in France and the United Kingdom has been followed to evaluate the risk of developing second cancers [D19, L32, L36, L37]. Based on 12 cases with malignant brain tumours and an equal number of cases with benign brain tumours, each matched to 15 controls, a significant dose response was demonstrated for both types of tumours. The risk was higher for benign tumours (ERR = 3.15; 95% CI: 0.37–n.a.) than for malignant tumours (ERR = 0.12; 95% CI: n.a.–0.55), and no modifying effect of age at exposure was found. This pattern of a higher risk for benign tumours has been seen in other studies [P19, R17]. Eng et al. [E1] reported that bilateral retinoblastoma patients treated with radiation had a large excess of mortality from benign and malignant neoplasms of the brain and meninges. More recently, an increased risk of CNS tumour incidence was found among these patients [W11]. In a small study with limited statistical power, no excess risk was observed among retinoblastoma patients [M26]. Young children who received cranial irradiation as a conditioning regimen before bone marrow transplantation were found to have a significantly elevated relative risk of developing brain or other CNS cancers; however, it was likely that earlier cranial radiotherapy to treat acute lymphocytic leukaemia prior to bone marrow transplantation (and associated total-body irradiation) played an important role in the development of these neural malignancies [C16].

214. Data on adult exposures are considerably more limited. Following high-dose (~40 Gy) fractionated radiotherapy, an excess risk of CNS tumours was observed among pituitary adenoma patients [B22, T11]. In several case-control studies of patients with CNS tumours of various histological types, a history of diagnostic x-ray examinations [H32] or x-ray treatments to the head was more often reported for cases than for controls [B23, P20, P21]. In contrast, a mean brain dose of about 0.6 Gy was not associated with an increase in CNS tumour incidence or mortality in two small cohorts of infertile women irradiated to the pituitary gland and ovaries [R18, R30], and ankylosing spondylitics did not have an excess of mortality from spinal cord tumours after being exposed to high radiation doses to their spinal cords [W1].

215. Dental diagnostic x-ray exposures have been assessed in several studies conducted by Preston-Martin et al. in relation to various types of CNS tumours [P20, P21, P22, P23, P24]. They found associations between meningiomas and frequent annual full-mouth x-ray examinations and x-ray examinations performed many years ago, when radiation doses were relatively high. Risks were higher when exposure occurred during childhood. In other studies, however, brain tumour cases did not have a history of dental x-ray exposure significantly more often than controls [K18, M27, R19].

216. Radiation workers in general receive low, fractionated doses with relatively little exposure to the brain. To date, most occupational studies have been negative with respect to this site of cancer [C11, M46, W10]. Brain cancer incidence and mortality rates were elevated among airline pilots in a few studies [B48], but no dose-response relation was observed and confounding due to non-ionizing radiation and socio-economic status has been postulated [G15].

217. The issue of whether CNS tumours are related to fetal exposure to radiation remains controversial. Most recently, Doll and Wakeford [D17] carefully reviewed the literature and concluded that *in utero* exposure to a mean dose of approximately 10 mGy increases the risk of childhood cancer. This conclusion was largely based on the Oxford Survey of Childhood Cancers. In the Oxford Survey, mortality from childhood CNS tumours was associated with fetal irradiation (relative risk = 1.4; 95% CI: 1.2–1.7) [B2]. Miller and Boice [M31] expressed concern about the Oxford Survey results, noting that all childhood cancers were increased about 40%, whereas such commonality is not seen in either animal or human studies. Among atomic bomb survivors exposed *in utero*, an association between dose and cancer mortality has not been found, but the *in utero* survivor cohort is small, and the negative result is compatible with a wide range of risks [D14].

2. Internal low-LET exposures

218. Little is known about brain and CNS tumours following internal exposure to low-LET radiation. A small increased risk of CNS tumours was observed among 35,000 Swedish patients receiving diagnostic ^{131}I examinations (SIR = 1.19; 95% CI: 1.00–1.41) [H27]. Since the dose to the brain was <10 mGy, the observed excess is not likely to be due to the radiation exposure. Significant excess risks were not demonstrated among patients receiving ^{131}I therapy for hyperthyroidism [H23, H24, R14] or thyroid cancer [D15, E2, G13, H26]; however, among ten-year survivors, brain tumour incidence was significantly elevated in the Swedish hyperthyroid patients [H23].

3. Internal high-LET exposures

219. Danish patients exposed to thorotrast had a significantly elevated incidence of brain tumours, but the fact that these tumours developed very soon after the thorotrast examination suggests that they are related to the underlying disease or better ascertainment rather than to the thorotrast itself [A5]. Thorotrast was given in conjunction with cerebral angiography because of a suspected brain disorder. Often this disorder was later found to be a brain tumour, especially among epileptic patients. Brain malignancies and other CNS tumours have not been linked to exposure to radium [S34] or to radon among miners [D8].

4. Summary

220. Ionizing radiation can induce tumours of the CNS, although the relationship is not as strong as for many other tumours, and most of the observed radiation-associated tumours are benign. Indeed, neurilemmomas, which are highly curable, are the only tumours that consistently exhibit high risks. Overall, exposure during childhood appears to be more effective in tumour induction than adult exposure, but the data on adult exposure are fairly sparse, and the most recent study of atomic bomb survivors demonstrated an excess relative risk for neurilemmomas following exposure at all ages. Little is known about other factors that modify risk. The association between benign tumours, particularly meningiomas and neurilemmomas, and radiation appears to be substantially stronger than with malignant tumours. Malignant brain tumours are seen only after radiotherapy. Additional data are needed to better characterize the dose response for CNS tumours of various histological types.

L. THYROID CANCER

221. Thyroid cancer is one of the less common forms of cancer [P5]. Unlike most cancers, its incidence is relatively high before age 40 years, increases comparatively slowly with age, and is about three times higher in women than men. This female predominance is also observed for benign thyroid tumours. The degree of malignancy varies widely with histological type, ranging from the rapidly fatal anaplastic type to the relatively benign papillary type [F2, R13]. Data from most countries suggest that mortality is falling while incidence is increasing [F1]. Ionizing radiation is a well documented cause of thyroid cancer. The relative risk of thyroid cancer is also substantially increased among persons with a history of benign nodules and goitre. There is some evidence that elevated levels of thyroid-stimulating hormone, multiparity, miscarriage, artificial menopause, iodine intake, and diet also may be risk factors for thyroid cancer[F2, R13].

222. Shore [S8] reviewed the epidemiological studies of radiation and thyroid cancer conducted through the early 1990s. Since then, more information has become available from continued follow-up of some cohorts and from a pooled analysis of seven studies of external radiation [R4]. Additional data on the occurrence of thyroid cancers among children living in radiation-contaminated areas in Belarus [D13], the Russian Federation [I23], and Ukraine [T23] as a result of the Chernobyl nuclear power plant accident have recently been published. New data on Chernobyl recovery operation workers ("liquidators") have also been published in the last few years [K15]. These results are discussed below and in more detail in Annex J, "*Exposures and effects of the Chernobyl accident*".

1. External low-LET exposures

223. The results for thyroid cancer incidence that were presented in Table 8 of Annex A in the UNSCEAR 1994 Report [U2] are updated here in Table 17. This Table contains findings from a pooled analysis of studies of external irradiation of the thyroid [R4]. This analysis,

which included seven studies and was based on almost 120,000 people with about 700 thyroid cancers and 3 million person-years of follow-up, allowed a more detailed evaluation of the dose-response relationship and of modifying factors than had previously been possible. Nearly 500 thyroid cancers occurred in the half of the study population exposed during childhood or adolescence.

224. In the analysis of the five cohort studies of persons irradiated before age 15 years, 436 thyroid cancers were diagnosed among the exposed population. The pooled ERR per Gy was 7.7 (95% CI: 2.1–28.7). No single study was found to have an undue influence on the overall estimates of risk. The ERR per Gy for females was nearly twice that for males, but the results were not consistent [R4]. Since thyroid cancer naturally occurs two to three times more frequently among females than males, the absolute radiation-induced risk was correspondingly higher among women. Even within the narrow range of ages at exposure, there was strong evidence of a decrease in the ERR with increasing age at exposure, which suggests that the thyroid is particularly sensitive to tumour induction at the time of rapid cell proliferation. The ERR per Gy was highest 15–29 years following childhood exposure, but it remained high for more than 40 years after exposure [R4]. While the latter finding was also reported from an extended follow-up of the Stockholm skin haemangioma cohort [L13], few other studies have more than 40 years of follow-up. In contrast to the well described carcinogenic effects of childhood exposure, there is little evidence of an excess of thyroid cancer associated with external exposure after age 20 years. Among atomic bomb survivors exposed after age 40 years, the ERR was negative [R4, S8, T1].

225. Each of the studies in the pooled analysis was consistent with a linear dose-response relationship, although the range of doses varied considerably among studies [R4]. In the childhood cancer study [T5], which was the only study with doses over 6 Gy, there was some indication that the effects of cell killing flattened the dose response at high doses. Exposures were received in fractions, from all in one day to several years apart in three of the studies included in the pooled analysis. There was very weak evidence that for the same total dose, exposures received in two or more fractions were less carcinogenic than acute exposures by an estimated factor of 1.5, with wide confidence limits [R4]. Although no formal assessment of risk by histology type was conducted, the risk for papillary carcinomas appeared to be higher than for follicular cancer in the individual studies. To date, no clear association between ionizing radiation and either medullary cancer or anaplastic carcinoma has been observed, although there have been reports of anaplastic carcinoma occurring after medical irradiation.

226. An elevated risk of thyroid cancer was reported for patients treated with high-dose radiotherapy for Hodgkin's disease [D33, D36, H9, T5] and for childhood cancers [H30, T5]. New studies emphasize that Hodgkin's disease survivors have a high risk of thyroid cancer if they received radiotherapy as children [B16, S23]. Recently, a large increased risk of thyroid cancer was reported among bone marrow transplantation patients treated with high-dose, total-body irradiation, especially during childhood (4 cases observed compared with 0.02 expected); however, radiotherapy received before bone marrow transplantation might have played a role in the development of these malignancies [C16].

227. Information on fractionated and low-dose-rate exposures mostly comes from studies of high-background areas, diagnostic radiation procedures, and occupational exposures. Studies of residents living in areas of high natural background radiation were conducted in China [T25, T26, W9] and India [P3]. They did not show an association between the prevalence of thyroid nodules and lifetime exposure to elevated background radiation. However, since the doses received in childhood generally were only a few tens of milligray, the statistical power to detect a radiation effect was low. Diagnostic x rays, even those resulting in higher thyroid gland doses or those occurring during childhood, were not linked to thyroid cancer in a study in Sweden [I9]. This study is unique because the ascertainment of diagnostic x-ray procedures was based not on personal recall but on a search of hospital radiation records.

228. While early mortality studies of radiation workers provided no evidence for an elevated risk of thyroid cancer [M23], there have been reports of an increased risk of thyroid cancer among x-ray technologists. Among 27,000 x-ray workers and a similar number of non-radiation medical workers in China, 8 thyroid cancers were found compared with 4.5 expected [W10]. The relative risk was larger for personnel working at relatively early ages and during the period when exposures were greatest. In the United States, a twofold greater risk of thyroid cancer incidence was reported in preliminary results from a survey of over 100,000 predominately female x-ray technologists [B20]. These preliminary results were based on self-reported diagnoses on questionnaires and might have included benign nodules or adenomas. In a recent mortality study of the x-ray technologists, no excess of thyroid cancer deaths was noted [D23]. Consistent with the incidence results are findings from a Swedish record-linkage study in which x-ray technicians had double the risk of thyroid cancer compared with the general population of Sweden [C17] and from a small Italian study in which male hospital radiation workers had a higher prevalence of thyroid nodules than comparable non-exposed workers [A8]. Based on only nine thyroid cancer deaths, a significantly elevated mortality, but no dose response, was observed in mostly male nuclear workers in the United Kingdom [L20]; the evidence for an excess diminished with longer follow-up [M46]. No association was reported for nuclear workers in the United States [G12] or in the combined international analysis of nuclear workers from Canada, the United Kingdom, and the United States [C11]. Since adult, acute radiation exposures have not been linked to thyroid cancer, the reports of excesses are surprising. Each of these studies, however, has methodological weaknesses for studying

thyroid cancer that might have influenced the findings. For example, except for the nuclear worker studies, individual doses were not available; multiple comparisons were tested in most studies; and the number of cases was generally small, which produces unstable risk estimates. Furthermore, the well known association between radiation and thyroid cancer may have led to more complete case ascertainment for radiation workers.

229. As a consequence of the Chernobyl accident, large numbers of men from all over the former Soviet Union were brought in to participate in recovery operations at the reactor and in the surrounding areas. Altogether approximately 600,000 workers were involved, about 240,000 of them during 1986 and 1987. Most of the exposure of the workers came from external gamma and beta irradiation. Internal exposure from radionuclides was minor after the first few weeks [U4]. Several investigations of recovery workers from the Baltic countries have been conducted. In a systematic clinical evaluation, including palpation and ultrasound, of the nearly 2,000 Chernobyl recovery operation workers from Estonia, no excess of thyroid nodularity or cancer was detected [I10]. Doses were estimated for each worker based on medical records, responses to a questionnaire, and biodosimetry. Film badges suggested that workers had been exposed to a mean dose from external sources of approximately 100 mGy, but biodosimetry indicated that the doses might have been considerably lower [L31]. Thyroid cancer incidence and mortality were evaluated in a cohort of nearly 5,000 Estonian workers [R20]. No thyroid cancers were observed, whereas 0.21 would have been expected based on age, gender, and calendar-specific cancer rates in Estonia. In a cohort of Lithuanian Chernobyl workers, the three observed thyroid cancers did not significantly differ from the expected number based on Lithuanian cancer rates [K39]. Given the low dose and late age at exposure, these negative findings are consistent with data from the Life Span Study of atomic bomb survivors [T1].

230. In a much larger study of 168,000 Russian recovery operation workers, Ivanov et al. [I13, I18] reported an increased risk of thyroid cancer compared with the population of Russia. Comparing cancer incidence in these workers to that in a general population is questionable, because the recovery operation workers had a higher level of medical surveillance, especially of their thyroid glands [B4]. However, Ivanov et al. [I17] noted that they adjusted for a screening effect. Further data regarding these findings are needed.

2. Internal low-LET exposures

231. Studies of medical exposures to ^{131}I were reviewed extensively in the UNSCEAR 1994 Report [U2]. Since then, further information has become available from three large follow-up studies of ^{131}I-exposed patients. In addition to an extended period of follow-up (as much as 40 years following exposure), the Swedish study of over 34,000 patients administered ^{131}I for diagnostic purposes now incorporates individual estimates of thyroid doses [H4]. Dose quantification was based on the amount of ^{131}I administered and the 24-hour thyroid uptake. Information on the size of the thyroid gland was available for nearly half of the patients, and adjustments to dose estimates on the basis of these data did not affect the results. Basic details of the study cohort are given in Table 2, Table 3, and Table 17, while Table 28 presents thyroid cancer incidence in relation to dose. Although overall incidence, after excluding the first five years following exposure, was greater than that in the general population, there was no indication of a dose-response trend. Furthermore, analyses based on the reason for the initial referral showed that incidence was higher than expected only among those referred for suspicion of a thyroid tumour. Among those referred for other reasons, thyroid cancer incidence was lower than expected compared with national rates. Among the 34,000 patients evaluated by Hall et al. [H4], 7% were under 20 years of age at the time of exposure and less than 1% were under 10 years of age. Among the 2,408 adolescents and young adults (average thyroid dose of 1.5 Gy), 3 thyroid malignancies were observed compared with 1.8 expected based on national rates (SIR = 1.69; 95% CI: 0.35–4.9). These data do not allow inferences about childhood exposures. No excess of thyroid nodules was detected when 1,005 women who had been examined years before with ^{131}I (mean thyroid dose of 0.54 Gy) and 248 non-exposed women were screened for thyroid disorders [H36]; however, among the exposed women the prevalence of thyroid nodules was correlated with dose.

232. Studies of patients treated with ^{131}I for hyperthyroidism have dealt almost entirely with adults. Although individual thyroid doses have not been calculated, the intention is to deliver 60–100 Gy to the thyroid [B21]. At doses of this magnitude, the ERR per Gy for children receiving external radiation begins to level off, probably due to cell killing [R4]. Among 10,000 Swedish patients, 18 thyroid cancers were observed, yielding a standardized incidence ratio of 1.29 (95% CI: 0.76–2.03) [H23]. Among 23,000 patients evaluated in a new follow-up of the thyrotoxicosis study in the United States, an increased risk of thyroid cancer mortality was observed [R14]. The excess risk was primarily due to a large risk during the first five years following treatment and was higher among toxic nodular goitre patients than Graves' disease patients. Franklyn et al. [F8] reported an elevated incidence of thyroid cancer and thyroid cancer deaths in a follow-up of 7,417 hyperthyroid patients treated with ^{131}I in England. Compared with the population of England and Wales, both the SIR (3.25; 95% CI: 1.7–6.2) and the SMR (2.78; 95% CI: 1.2–6.7) were elevated, but no dose response was demonstrated. These findings suggest that some of the excess may be due to the underlying thyroid disease.

233. While the data from the medical radioiodine studies are informative, the uncertainties associated with estimating thyroid doses from ^{131}I, especially in persons with thyroid abnormalities, reduce the precision of the risk estimates. The non-uniformity of the dose distribution in the thyroid gland results in some areas of tissue receiving

such high doses that cell killing could occur and other areas receiving extremely low doses [N7]. Thus, the tumorigenic effects of the exposure might be lower than would be expected based on the average dose. Nevertheless, ^{131}I dose estimation in medical studies is far better than for the studies of environmental ^{131}I exposure.

234. Four years after the 1986 accident at the Chernobyl nuclear plant, a substantial increase in childhood thyroid cancer was observed in contaminated regions of the former Soviet Union [S49]. For a more detailed discussion of thyroid cancer risk following the Chernobyl accident, see Annex J, "*Exposures and effects of the Chernobyl accident*". In Belarus, and particularly in the Gomel region to the north of Chernobyl, the number of childhood thyroid cancers diagnosed between 1990 and 1992 was much higher than in 1986–1989 [K6]. The diagnoses of most of the thyroid cancers were confirmed by an international pathology review [W5]. An unusually high frequency of thyroid cancer continues to occur in Belarus [B49, D13] and in heavily contaminated areas in Ukraine [L19, T23] and the Russian Federation [T10, I23, I24] among persons who were less than 15 years of age at the time of the accident. Childhood thyroid cancer rates in these areas in 1991–1994 were higher by a factor of almost 10 than in the preceding five years (Table 29). The number of cases identified among persons born less than 17 years before the accident reached about 1,800 in 1998 (Annex J, "*Exposures and effects of the Chernobyl accident*"). Risk appears to increase with decreasing age at exposure [A3, K31, P31, W16]. Recent data from Belarus suggest that while increases in thyroid cancer incidence are still occurring among individuals who were less than 5 years of age at the time of the accident, rates for older children might be stabilizing [K31]. In the Ukraine, rates are still rising for persons less than 14 years of age, but a similar leveling off of the risk among those 14–18 years old at the time of the accident was observed [T23]. Age-at-exposure effects warrant further investigation.

235. Following early reports of an increased frequency of thyroid cancer, questions were raised about the effects of screening the exposed population [B8, R3, S22]. While the screening programmes being conducted in the contaminated areas are responsible for some increases in thyroid cancer ascertainment, the majority of tumours reviewed by an international panel were not microcarcinomas. In fact, many showed direct invasion of extrathyroidal tissues and lymph node spread [W5].

236. A study of 107 thyroid cancer cases and 214 matched controls was conducted in Belarus [A26]. Taking into account the reason for diagnosis, a strong dose response was demonstrated. Although the estimated doses in the study have considerable uncertainty, the results indicate that the excess of thyroid cancers is related to the radiation exposure.

237. A strong correlation between estimated exposure from ^{131}I and thyroid cancer rates has been reported in several studies [J4, J5, L19, L51]. In a well designed correlation study, Jacob et al. [J5] compared average thyroid doses from ^{131}I exposure in many regions in Belarus and the Russian Federation with 1991–1995 incidence rates for the 1971–1986 birth cohort. A linear dose-response relationship was found (EAR per 10^4 PY Gy = 2.3; 95% CI: 1.4–3.8; ERR per Gy = 23; 95% CI: 8.6–82). Likhtarev et al. [L51] also conducted a correlation study using recent data (1990–1997) from the Ukraine. They reported an EAR per 10^4 PY Gy of 1.6 (95% CI: 0.7–3.4) and an ERR per Gy of 38 (95% CI: 16–97) for the 1971–1986 birth cohorts. While these studies provide reasonable risk estimates, they are based on geographical correlations and are subject to the limitations inherent in such evaluations.

238. No radiation-associated thyroid malignancies have been observed less than five years after external exposure [R4]. Despite some early occurrence of childhood thyroid cancers after the Chernobyl accident, most cases were diagnosed after 1991 (Table 29). A minimal latency period for radiation-induced thyroid tumours of four years might have resulted from the ability to detect an effect because of the millions of children exposed to radiation from the Chernobyl accident or because of the advancement of time to diagnosis due to screening.

239. A high frequency of *RET/PTC* oncogene rearrangements is found in the thyroid cancers occurring in the Chernobyl area. Some studies have reported specific types of *RET/PTC* in Chernobyl cases [B25, K24] compared with tumours associated with external radiation [B26]; however, findings have not been consistent [W4]. Both *RET/PTC1* and *PTC3* rearrangements have been reported in Chernobyl-related patients, and recent research suggests that age at exposure, time since exposure, and morphology may be important in determining the type of PTC rearrangement [P10, S13, T34].

240. Taking all of the data together, screening and other selection effects may explain some of the increase in thyroid tumours seen among the children living around Chernobyl, but radiation exposure from the reactor accident clearly plays a major role. The associated mechanism is not yet well understood, and the magnitude of the risk from ^{131}I *per se* remains uncertain. The geographical distribution of these tumours coincides more closely with the areas of ^{131}I contamination than with the areas of ^{137}Cs contamination, but there is also a correlation with the distribution of shorter-lived radioisotopes (e.g. ^{132}I, ^{133}I, and ^{135}I) [A3]. Other factors that might influence radiation risks have been identified. Many of the regions around Chernobyl are iodine-deficient [G20, P37], and iodide dietary supplementation had been terminated before the accident [W5]. Although large amounts of stable iodine were distributed to the population living near the plant as prophylaxis shortly after the accident, the distribution was incomplete and is thought not to have been very effective [M32]. Genetic susceptibility to radiation-associated thyroid cancer also has been suggested as a potential modifier of risk [C36]. Finally, other potential environmental contaminants need to be investigated.

241. The health effects of exposure to ^{131}I fallout from atmospheric nuclear tests conducted at the Nevada test site in the 1950s have been studied for the last four decades. In the most recent follow-up, 2,500 children were examined and individual doses to the thyroid reconstructed. Nineteen neoplasms, of which eight were malignant, were diagnosed. The ERR per Gy was about 7 (p=0.02). When the analysis was restricted to malignancies, the ERR per Gy was 7.9 but was not statistically significant [K36]. The ^{131}I doses from weapons testing at the Nevada Test Site were assessed by the United States National Cancer Institute [N12]. Iodine-131 is the radionuclide of main concern because it is the principal radionuclide in fallout and is ingested by drinking contaminated milk. Approximately 5.6 EBq of ^{131}I were released into the atmosphere, resulting in radioiodine deposition throughout the United States. Iodine-131 thyroid doses were estimated for each county in the continental United States by age group, gender, and level of milk consumption.

242. The average thyroid dose to the approximately 160 million people living in the United States at the time of testing was 20 mGy. The estimated dose varied substantially depending on geographic location, age at the time of exposure, and quantity, source, and type of milk intake. Doses were highest east of the test site in Nevada and Utah and in some counties in Idaho, Montana, New Mexico, Colorado, and Missouri and were lowest on the West Coast, on the border with Mexico, and in parts of Texas and Florida. Owing to geographic differences, doses ranged from 0.01 to 160 mGy. The average dose to young children was approximately 10 times higher than the estimated adult dose, because the thyroid gland of small children concentrates more iodine and because children drink much more milk than adults. While the uncertainty associated with estimating the average thyroid dose to the population of the United States is about a factor of 2, the uncertainty in dose estimates for individuals is about a factor of 3.

243. Gilbert et al. [G19] related age-, calendar year-, gender-, and county-specific thyroid cancer mortality and incidence rates in the United States to ^{131}I dose estimates, taking geographic location, age at exposure, and birth cohort into account. Neither cumulative dose nor dose received between 1 and 15 years of age was associated with thyroid cancer incidence or mortality, but an association was suggested for dose received before 1 year of age (ERR at 1 Gy = 10.6; 95% CI: 1.1–29 and ERR at 1 Gy = 2.4; 95% CI: 0.5–5.6 for mortality and incidence data, respectively).

244. From 1949 to 1962, the former Soviet Union conducted 133 atmospheric nuclear tests at the Semipalatinsk test site in Kazakhstan [B44, R31]. Local fallout was particularly high from tests carried out in 1949, 1953, and 1962. Approximately 10,000 persons living near the test site and 40,000 living in the Altai region in the Russian Federation were exposed to over 250 mSv effective dose. Effects on the health of populations living near Semipalatinsk in Kazakhstan and in the Altai region are currently being studied. An excess of benign and malignant thyroid tumours has been reported for the Kazakhstan population [B44, R31]. It is expected that new data from the ongoing studies in both Kazakhstan and the Russian Federation will become available soon.

245. Between 1944 and 1957, the Hanford Nuclear Site in Washington State, United States, released 20–25 PBq of ^{131}I into the atmosphere. In January 1999, the results of the Hanford Thyroid Disease Study were released to the public [D29]. In total, 5,199 people born between 1940 and 1946 in seven counties in eastern Washington State were identified for study. Ninety-four percent were located, 4,350 (84%) were alive, and 3,441 (66%) agreed to participate in the study. Study participants provided information on place of residence, consumption of milk and other relevant foods, occupational history, selected lifestyle factors, and medical history. Thyroid doses were estimated for the 3,193 study participants who had lived near Hanford at the time of atmospheric releases based on individual characteristics, e.g. level and type of milk consumption and dosimetry information from the Hanford Environmental Dose Reconstruction project. The other 248 participants had moved from the Hanford area and were considered to have received no exposure. The mean and median doses were 186 mGy and 100 mGy, respectively. The distribution of dose was skewed (range 0 to 2,840 mGy), with a high percentage of participants having low doses and only a small percentage having high doses. Each participant was evaluated clinically by two study physicians. The examination included ultrasound, thyroid palpation, and blood tests. Eleven categories of thyroid disease, ultrasound-detected abnormalities, and hyperparathyroidism were evaluated in terms of estimated ^{131}I radiation dose to the thyroid.

246. A total of 19 participants were diagnosed with thyroid cancer and 249 with benign thyroid nodules. No evidence of a dose-response relationship was found for malignant or benign nodules or any of the other outcomes studied. The final report is yet to be published, and there has been criticism of the large degree of uncertainty in the dose estimates. Nevertheless, the results do not provide evidence that ^{131}I doses on the order of 100 mGy increase the risk of developing thyroid neoplasia.

247. Although some animal studies have suggested that ^{131}I may be less carcinogenic than external radiation [N5], a large study of rats found similar carcinogenic effects for ^{131}I and external radiation [L11]. The strain of rat used has a high rate of developing follicular thyroid carcinomas, yet Royal [R22] noted that the study is particularly relevant, since it was well designed and the rats were the equivalent of young adolescents at the time of exposure and were exposed to low as well as moderate and high radiation doses. In summary, the very limited human data on childhood exposure to ^{131}I and adult exposure to external radiation are insufficient for concluding that there are significant differences between these types of radiation with regard to thyroid cancer induction.

3. Internal high-LET exposures

248. Radium is primarily a bone seeker, and the development of thyroid cancer has not been associated with exposure in most studies, but a statistically significant elevated risk, based on a small number of cases, was observed among radium dial painters in the United States who worked before 1940 [P27] and among patients treated with ^{224}Ra in Germany [N4].

249. Neither thyroid cancer mortality nor incidence was elevated among Danish thorotrast patients [A5]. Radon exposure in mines did not increase the risk of thyroid cancer mortality in a pooled analysis of 11 studies of underground miners [D8].

4. Summary

250. The thyroid gland is highly susceptible to the carcinogenic effects of external radiation during childhood. Age at exposure is an important modifier of risk, and a very strong tendency for risk to decrease with increasing age at exposure is observed in most studies. Although thyroid cancer occurs naturally more frequently among women, the ERR does not appear to differ significantly for men and women. Among people exposed during childhood, the ERR of thyroid cancer is highest 15–29 years after exposure, but elevated risks persist even 40 years after exposure. The carcinogenic effects of ^{131}I are less well understood. Most epidemiological studies have shown little risk following a wide range of exposure levels, but almost all of them looked at adult exposures. Recent results from Chernobyl indicate that radioactive iodine exposure during childhood is linked to thyroid cancer development, but the level of risk is not yet well quantified.

M. NON-HODGKIN'S LYMPHOMA

251. Non-Hodgkin's lymphoma (NHL) is a collection of distinct disease entities that are malignant expansions of lymphocytes. The lymphomas that make up this grouping can generally be separated into those with B-cell or T-cell lineage. The precise definition of NHL has varied over time; a recent classification that is widely used is the Revised European American Lymphomas classification [H42].

252. Rates of NHL have increased in many countries over the past few decades, particularly at older ages [H39]. In part this is likely to be due to changes in the definition of NHL and to improved ascertainment, although these factors are unlikely to explain all of the increases [H39]. Epidemiological studies have shown associations with chronic immunosuppression, for example, among transplant recipients and other patients who received immunopressive therapy [H43, K26]. Associations with certain viruses, such as Epstein-Barr [M37] and HIV [S44], have also been identified. Some studies suggest elevated risks for those employed in agriculture, particularly those working with pesticides (e.g. [C31]), although other studies have not shown such a link (e.g. [W15]).

1. External low-LET exposures

253. Information on incidence and mortality from NHL following external exposure to low-LET radiation is presented in Table 18. As can be seen from this Table, the results are mixed, with many of the studies listed having failed to show a statistically significant association with radiation exposure. The Life Span Study of survivors of the atomic bombings falls into this category, although Preston et al. [P4] reported some evidence of an increasing dose response for males ($p=0.04$) but not for females, among whom, if anything, the trend is negative. The latter findings might appear to contradict those for the cervical cancer patients, where there is borderline evidence of a positive dose response; however, among exposed patients, there was little indication of an increasing trend with increasing dose [B1]. Furthermore, studies of women treated for benign gynaecological disorders [D7, I6] have not suggested associations with radiation. Comparison of the Life Span Study findings for males with those findings for the ankylosing spondylitis patients might be informative, given that most of these patients were male. Weiss et al. [W1] reported that NHL mortality among spondylitis patients was raised significantly compared with national rates (relative risk = 1.73; 95% CI: 1.23–2.36), and that this elevated risk appeared to disappear more than 25 years after exposure; however, no dose-response analysis was performed. In another study of a mostly male population, Cardis et al. [C11] did not find an association between NHL and external radiation among nuclear industry workers, although the precision of the study was limited by the generally low doses. The same limitation affected a study of diagnostic x-ray procedures [B39], which also did not show an association when based on a two-year lag; however, this study used numbers of x-ray procedures rather than doses.

254. The Life Span Study also provided no evidence that any elevated risk would be greater for exposure in childhood than in adult life [P4]. There are few other data on childhood exposure. The study of Swedish children treated for benign lesions in the locomotor system [D12] showed rates of NHL incidence and mortality similar to national values, although no dose-response analyses were reported.

2. Internal low-LET exposures

255. There are few data that allow examining the risks of NHL specifically in relation to internal low-LET radiation. The data that are available are for groups with medical exposures to ^{131}I (see Table 18). Among over 35,000 patients with diagnostic exposures, Holm et al. [H27] reported an SIR of 1.21. This value was not significantly different from 1 (at the 5% level), although the SIR of 1.24 for all lymphomas was significantly raised. However, while total cancer risk was

analysed in relation to level of the activity of iodine administered, no results were reported for NHL. Furthermore, doses to this cohort were generally very small (mean bone marrow dose = 0.19 mGy). Doses were higher in a study of Swedish patients treated for hyperthyroidism [H23]. In this instance, the observed number of cases was less than expected from national rates, significantly so after omitting the first 10 years of follow-up (SIR = 0.40, although based on only seven cases). Again, however, NHL incidence was not analysed in relation to level of exposure. Ron et al. [R14] studied NHL mortality among hyperthyroidism patients in relation to estimated bone marrow dose from ^{131}I therapy; most of the patients were from the United States but for this analysis some patients from the United Kingdom were included. There was no evidence of a trend in risk with dose, although the generally low doses limited the precision of the analysis [R14].

3. Internal high-LET exposures

256. There is limited information on NHL risks among groups exposed internally to high-LET radiation. Relevant findings are summarized in Table 18. Among German patients who received thorotrast, van Kaick et al. [V8] reported 15 cases among 2,326 patients, which represented a relative risk of about 2.5 compared to a group of unexposed patients. However, there was no analysis in relation to the level of exposure. Among thorotrast patients in Denmark [A5] and ankylosing spondylitis patients in Germany treated with ^{224}Ra [W3], the numbers of cases were too small to permit detailed inferences. Larger numbers arose in the combined analysis of radon-exposed miners [D8]; here the total number of deaths observed was, if anything, less than that expected from national and regional rates (SMR = 0.80, 95% CI: 0.56–1.10), but no analysis was conducted according to the level of exposure.

4. Summary

257. Results from studies of NHL risk among groups exposed to external low-LET radiation are mixed. The Japanese atomic bomb survivors as a whole do not show an association, although there is some evidence of an increasing trend in incidence with dose among males (but not females). Findings from other studies are variable, with no clear consistency. Overall, there is little evidence of an association between NHL and external low-LET radiation.

258. There is limited information on NHL risk in relation to internal low- or high-LET radiation. The general absence of analyses in relation to level of exposure and the limited statistical precision of one such analysis that was conducted hinders interpretation of the data that are available.

N. HODGKIN'S DISEASE

259. Hodgkin's disease is distinguished from other lymphomas mainly by the presence of giant Reed-Sternberg cells [B34]. While changes over time in the classification of Hodgkin's disease are likely to have had some effect on analyses of trends in rates, there are indications from various countries of a slight decrease in incidence rates [H39]. More pronounced decreases have been seen in mortality rates during recent decades, reflecting improved treatment [H39]. Internationally, incidence rates tend to be much higher in North America and Europe than in Asia [P5] (see also Table 1). Clustering of cases of Hodgkin's disease has been reported in some studies (e.g. [A17]), and a viral origin has been suggested by associations with certain childhood environments, such as small family size and uncrowded conditions, that could reduce or delay infections [G18]; Epstein-Barr virus has been cited as possibly being relevant [M36].

1. External low-LET exposures

260. The studies of external low-LET radiation included in Table 19 have not always reported estimates of trend based on dose-response analyses but have, at least in some instances, indicated whether there were any statistically significant trends with dose. For the Japanese atomic bomb survivors, Preston et al. [P4] found no evidence of a dose response, although the confidence intervals were fairly wide owing to the small number of cases (see Table 19). Studies of patients treated for benign gynaecological disease [I6] and of nuclear workers [C11] also showed no trend with dose, although based on small numbers of deaths in the former instance and low doses in the latter. For the other studies of external low-LET exposure listed in Table 19, the observed number was sometimes greater than the number expected, although not to a statistically significant extent.

2. Internal low-LET exposures

261. There are few data that allow examining the risks of Hodgkin's disease specifically in relation to internal low-LET radiation. The data that are available concern groups with medical exposures to ^{131}I (see Table 19). Among over 35,000 patients with diagnostic exposures, Holm et al. [H27] reported an SIR of 1.35. This value was not significantly different from 1 (at the 5% level), although the SIR for all lymphomas, 1.24, was significantly raised. However, while total cancer risk was analysed in relation to the activity of iodine administered, no results were reported for Hodgkin's disease. Furthermore, doses to this cohort were generally very small (mean bone marrow dose = 0.19 mGy). Doses were higher in a study of Swedish patients treated for hyperthyroidism [H23]. However, the small number of cases observed, while consistent with national rates, limited inferences. Furthermore, the incidence of Hodgkin's disease was not analysed in relation to level of exposure [H23]. Ron et al. [R14] studied Hodgkin's disease mortality among hyperthyroidism patients, mostly from the United States, in relation to estimated bone marrow dose from ^{131}I therapy. There was no evidence of a trend in risk with dose, although the small number of deaths and the generally low doses limited the precision of the analysis [R14].

3. Internal high-LET exposures

262. Relevant findings are summarized in Table 19. Studies of German [V8] and Danish [A5] thorotrast patients, while not indicating elevated risks, are based on very small numbers of cases. A combined analysis of radon-exposed miners [D8] reported an SMR for Hodgkin's disease of 0.93 (95% CI: 0.54–1.48), but the 17 deaths were not analysed in relation to level of exposure.

4. Summary

263. While dose-response analyses have not always been performed in the relevant studies and the numbers of cases have sometimes been fairly small, the available data do not indicate an association between Hodgkin's disease and radiation, either for external or internal exposures.

O. MULTIPLE MYELOMA

264. This group of conditions consists of plasma cell malignancies, which include Waldenstrom's macroglobulinaemia as well as multiple myeloma [H48]. It is more common among men than women and is rare, particularly at young ages [C23]. Mortality rates have been increasing during the past few decades in various countries, but this increase has largely been confined to older ages and may be due in large part to earlier incompleteness in ascertainment [C23]. Some case-control studies have indicated associations between myeloma and employment in agriculture or in the food industry [B30, B31, C24].

1. External low-LET exposures

265. Table 20 contains information on multiple myeloma following exposure to external low-LET radiation. Of particular note is the discrepancy between the findings for mortality and incidence among the Japanese atomic bomb survivors. The most recent mortality follow-up [P9], in common with an earlier analysis of mortality in this population [S3], showed a statistically significant association between myeloma risk and dose. However, data on myeloma incidence yield a much lower estimate for the trend in risk with dose; furthermore, it is consistent with there being no effect of dose [P4]. The authors of the incidence report noted that the mortality findings appeared to be heavily dependent on the inclusion of questionable diagnoses and on both second primaries and cases above 4 Gy that were excluded from the incidence analysis [P4]. In view of the care taken to review the myeloma diagnoses in the incidence analysis, it seems reasonable to place greater weight on these findings.

266. Results from the other studies of external low-LET exposure cited in Table 20 are mixed. Some, e.g. the international study of cervical cancer patients [B1], provide no evidence of an elevated risk. On the other hand, Darby et al. [D7] reported a significant elevated risk of myeloma mortality among metropathia patients in the United Kingdom, although there was less evidence of an association from a similar study in the United States [I6]. The number of myeloma deaths among ankylosing spondylitis patients in the United Kingdom was significantly greater than that expected from national rates but was not analysed in relation to dose [W1]. An international study of cancer mortality among nuclear workers found a significant association with dose [C11], although this finding was influenced strongly by just a few cases with doses above 0.4 Sv. In a study of diagnostic x rays, Boice et al. [B39] found that the risk of myeloma incidence was similar among those who had and those who had not received x rays under two health plans; however, there was some evidence of an increasing trend in risk with an increasing number of x-ray procedures, although actual dose estimates were not available.

267. It is noticeable that of the studies of external low-LET exposures listed above and in Table 20, those that suggest an elevated risk of myeloma tend to be studies of mortality, in contrast to the few studies of incidence. Indeed, in common with the atomic bomb survivors study, the Swedish study of treatment for benign lesions of the locomotor system indicated an elevated risk of mortality relative to national rates, but not of incidence [D12]. It is unclear whether these findings might be due to differential recording of myeloma on death certificates, based on knowledge of prior radiation exposure. However, in view of the greater accuracy in diagnoses of incident cases of myeloma, inferences from incidence data are likely to be more sound.

2. Internal low-LET exposures

268. There are few data on multiple myeloma risks in relation to internal low-LET radiation. In studies of Swedish patients with exposure to ^{131}I for diagnostic purposes [H27] and as treatment for hyperthyroidism [H23], the observed numbers of incident cases were close to those expected from national rates. However, the risk of myeloma was not analysed in relation to level of exposure. Indeed, the bone marrow doses were generally low in the two studies (means of 0.19 mGy and 60 mGy, respectively). Ron et al. [R14] studied myeloma mortality among hyperthyroidism patients, mostly from the United States, in relation to estimated bone marrow dose from ^{131}I therapy. Although the estimated trend was greater than zero, it was not significantly different from zero ($p=0.3$); the small number of cases and the generally low doses limited the precision of the analysis [R14].

3. Internal high-LET exposures

269. Relevant findings are shown in Table 20. There is some evidence of an excess of myeloma incidence among Danish thorotrast patients, relative both to national rates and to an unexposed control group [A5], although based on only four cases. Among German thorotrast patients, van Kaick et al. [V8] reported ten cases of plasmacytoma among 2,326 patients, which represented a relative risk of about 4.1 compared to a group of unexposed patients.

Among patients in Germany treated with ^{224}Ra, two plasmacytomas were cited in the Spiess study [S14], and one medullary plasmacytoma was reported in the study of Wick et al. [W20]. In the combined analysis of radon-exposed miners [D8], there was an indication of elevated mortality from myeloma relative to national and regional rates, although the difference was not significant (SMR = 1.30; 95% CI: 0.85–1.90); however, the risk of myeloma was not analysed in relation to level of exposure. For a subgroup of these miners, namely uranium miners in western Bohemia, Tomášek et al. [T16] reported a statistically significant positive trend in myeloma risk with increasing cumulative radon exposure, but based on only three deaths. Similarly, while there was a statistically significant excess of multiple myeloma deaths among radium dial workers in the United States (SMR = 2.79; 95% CI: 1.02–6.08), this was based on only six deaths, and the risk did not appear to be related to internal radium body burden [S16].

4. Summary

270. Several mortality studies have indicated an increasing trend in the risk of multiple myeloma with increasing dose from external low-LET radiation. However, such associations are not generally apparent in studies of myeloma incidence, even for groups (such as the atomic bomb survivors) where the corresponding mortality data point towards an elevated risk. This suggests that the classification of myeloma on death certificates may have been conducted differentially, according to whether there was a past radiation exposure, although it is difficult to be certain. Given the generally better quality of diagnoses recorded in incidence data, the findings from the atomic bomb survivors, in particular, would suggest that there is little evidence of an association with low-LET radiation.

271. There is limited information on internal low- and high-LET exposures. Some studies have suggested an elevated risk, but based on small numbers of cases.

P. LEUKAEMIA

272. Although one of the rarer cancers, leukaemia is of particular interest because there is substantial information, both epidemiological and experimental, on the effects of ionizing radiation. In terms of its general epidemiology, it can be seen from Table 1 that the variation in rates between different populations is not as great as for most solid tumours. In considering trends and aetiological factors, it is important to take account of the various subtypes of leukaemia and their different age-specific rates. Modern classifications of leukaemia and other lymphatic and haematopoietic malignancies (e.g. [B32]) are based on cytogenetic and molecular principles that do not always coincide with the International Classification of Diseases. Three main subtypes will be considered here: acute lymphatic leukaemia (ALL), which is a leukaemia of precursor cells of either B-cell or T-cell origin; acute myeloid leukaemia (AML), whose lineage and subtype are generally defined according to the FAB system [B32]; and chronic myeloid leukaemia (CML), whose predominant haematological feature is an elevated white cell count in the peripheral blood and which is characterized cytogenetically by the Philadelphia chromosome [L52]. Reference will also be made to chronic lymphatic leukaemia (CLL), which has a B-cell or a T-cell lineage [L52].

273. Most leukaemia cases in childhood are ALL, whereas CML and CLL make up a high percentage of cases in adulthood. In the case of childhood ALL, the most striking and consistent trend in different countries since 1950 has been the decline in mortality [K1], reflecting the introduction of effective chemotherapy and cranial radiotherapy. Childhood ALL incidence, in contrast, has been fairly constant or has perhaps shown a small increase over the same period [D2]. Apart from ionizing radiation, risk factors for childhood ALL include alkylating chemotherapeutic agents and genetic factors such as Down's syndrome. Greaves [G5] suggested that the increase in rates during this century would be consistent with many acute lymphatic leukaemias in children being due to delayed exposure to childhood infections. Kinlen suggested, however, that a specific infective agent (or agents) underlies childhood leukaemias, as is true for several animal leukaemias [K1].

274. For adult leukaemia, rates at ages 75–84 years have increased in several countries since 1950 [K1]. These trends are consistent with improvements in cancer registration and in the detail of death certification. Ionizing radiation, benzene, and cytotoxic agents are known causes of leukaemias in adults; there is also some evidence that cigarette smoking is a risk factor, particularly for myeloid leukaemia [K1].

275. Information on the induction of leukaemia by the irradiation of laboratory animals was reviewed in the UNSCEAR 1977 and 1986 Reports [U5, U7]. A variety of lymphatic and myeloid leukaemias have been induced in different animals, although with differing dose-response relationships. However, studies of myeloid leukaemia in mice are consistent in showing a lower risk for a given total dose when exposure to low-LET radiation is protracted rather than acute [U3].

1. External low-LET exposures

276. Risk estimates for leukaemia are presented in Table 21. For the Life Span Study of atomic bomb survivors, only the leukaemia incidence results are shown, because larger numbers are involved relative to the corresponding mortality data [P9]and because the diagnoses of the incident cases have been reviewed [P4]. In the review in the UNSCEAR 1994 Report [U2], it was concluded that the incidence of acute leukaemias or of chronic myelogenous leukaemia exhibits strong associations with exposure to external low-LET radiation. In contrast, several large studies of groups with medical exposures (e.g. [B12, C9, C10, W2]) show no association between radiation and CLL. Although the Life Span Study of atomic bomb survivors also fails to show an association with CLL, the medical studies provide much stronger evidence,

owing to the low baseline rates in Japan. Furthermore, for leukaemia other than CLL, the temporal pattern of radiation-induced risks differs between exposures in childhood and adulthood, although in both instances the minimal latency period is less than for most solid cancers. Further data on the modifying effects of age and time have become available from the extended mortality follow-up of the atomic bomb survivors [P9]. These data show that, whereas both the ERR and EAR decrease soon after exposure in childhood, the decline in risk tends to be less pronounced for exposures in adulthood. Additional information on temporal trends comes from studies of medical exposures in adulthood, such as therapy for cervical cancer [B12], cancer of the uterine corpus [C10] (in this cohort, a considerable number of women were exposed at ages over 65 years), benign gynaecological disease [I6], and ankylosing spondylitis [W2]. The first and last of these studies found the ERR to decrease substantially about 10 years after exposure. However, as in the study of patients with benign gynaecological disease, most of the evidence for this decrease related to CML, whereas the ERR for acute leukaemia (principally AML) was more stable with time since exposure. These results are generally in accord with findings for CML and AML incidence among the atomic bomb survivors [P4], as confirmed by a parallel analysis [L47] of these data in combination with data from the cervical cancer [B12] and ankylosing spondylitis [W2] studies. The combined analysis showed some evidence overall of a decrease in the ERR for AML with increasing time since exposure, but to a lesser extent than for CML [L47]. In connection with this, it can be noted that acute leukaemias formed the majority of the non-CLL leukaemias in the study of uterine corpus patients, for whom there was no clear trend in ERR with time since exposure [C10].

277. Interpretation of the dose-response relationships in studies of groups exposed in adulthood to at least several gray is complicated by the effect of cell killing at high doses. The degree of partial-body irradiation, fractionation, and dose rate may also be relevant, while there is some suggestion (although based on small numbers) that, for example, the joint effect on leukaemia risk of total-body irradiation and chemotherapy may be more than additive [C9]. Table 30 presents results from modelling of the dose response for leukaemia (other than CLL) in four large, well conducted studies with individual dosimetry. These studies are based on patients treated for cervical cancer, uterine corpus cancer, and ankylosing spondylitis, plus the Japanese atomic bomb survivors. The latter study accords with a linear-quadratic dose response over the range 0–3 Gy, such that the risk per unit dose at low doses is lower than at higher doses. Most of the evidence for this non-linearity arises for AML [P4]. However, a parallel analysis of the atomic bomb data and those from the cervical cancer and ankylosing spondylitis studies [L47] showed that the data for CML and ALL were also consistent with a curvilinear dose response over doses less than 1 Gy (see Figure III). At doses above 3–4 Gy, the risk per unit dose subsequently decreases. This effect is seen at lower doses in the three studies of medical irradiation listed in Table 30. However, while it appears to be particularly strong among the ankylosing spondylitis patients (whose exposures were from x rays given in fractions) and those uterine cancer patients who received brachytherapy (radium implants) alone, it was weaker for the cervical cancer patients, most of whom received a mixture of brachytherapy and external radiation. In addition, Table 30 shows that the estimated ERR at 1 Gy is reasonably similar in the studies of the atomic bomb survivors, the ankylosing spondylitis patients, and the uterine corpus cancer patients given brachytherapy only, but higher than the ERR at 1 Gy for the cervical cancer patients or for the uterine cancer patients treated with external radiation. The risk estimates included in Table 21 from three other large studies of medical exposures in adulthood, namely of breast cancer patients [C9], patients treated for benign lesions in the locomotor system (e.g. arthrosis and spondylosis) [D12], and patients treated for benign gynaecological disease [I6], are also variable, although they are lower than the risk estimates for the atomic bomb survivors.

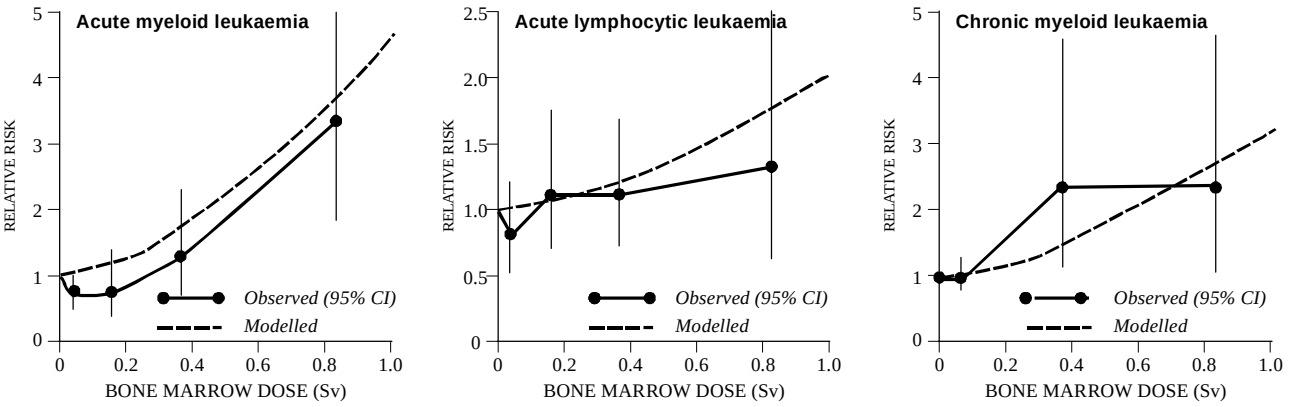

Figure III. Observed and modelled relative risk of acute myeloid, acute lymphocytic and chronic myeloid leukaemia in a combined analysis of data for the Japanese atomic bomb survivors, women treated for cervical cancer, and patients treated for ankylosing spondylitis [L47].

The values are specific to an attained age of 50 years, after exposure at 25 years, and depict the dose-response at doses less than 1 Sv.

278. Reconciling these results is not straightforward. The differing results on the effect of external irradiation and lower-dose-rate brachytherapy make it difficult to explain the findings solely on the basis of dose rate. The possible effect of errors in assessing bone marrow doses should also be borne in mind. However, one potential explanation relates to the degree of partial-body irradiation. Most of the marrow doses for the cervical cancer and uterine corpus cancer patients were to the pelvis, sacrum, and lower lumbar vertebra only. However, a subgroup of the externally irradiated women in the uterine corpus study who received substantial doses to the bone marrow in both the central trunk of the body and the pelvic marrow (as did the ankylosing spondylitis patients) had a greater risk (relative risk = 5.5; 95% CI: 2.0–15.1) than women with more non-uniform exposures (relative risk = 1.90; 95% CI: 1.1–3.2) (p-value for difference = 0.04) [C10]. Furthermore, the estimated ERR per Gy from the study of Swedish patients treated for benign lesions in the locomotor system [D12], in which exposures of the bone marrow were highly non-uniform, appears from Table 21 to be lower than that from the studies of more uniform exposure, although no confidence interval for the former estimate was given. Another important factor concerns differences between leukaemia subtypes. In a parallel analysis of the atomic bomb survivor, cervical cancer, and ankylosing spondylitis studies, Little et al. [L47] showed that there were statistically significant study-to-study differences in the model fitted to data for all leukaemia other than CLL, but that the models fitted to AML, ALL, and CML separately were consistent across the studies. Therefore differences between studies in range of ages at exposure and length of follow-up may explain at least some of the variation in the observed risks.

279. Occupational studies have the potential to provide information on how dose rate influences the risk of leukaemia. In spite of leukaemia being one of the less common cancers, the high ERR per unit dose and the often shorter induction time relative to many other cancers means that the comparison of leukaemia risks among radiation-exposed workers with the risks in groups such as the atomic bomb survivors may well be informative. The UNSCEAR 1994 Report [U2] drew attention to the reports of an association between leukaemia and radiation exposure among workers at the Mayak facility in the Russian Federation, some of whom received substantial bone marrow doses from external gamma irradiation several decades ago [K7]. It can be seen from Table 21 that most of the evidence for an elevated leukaemia risk relates to workers at the radiochemical plant [K10]. Koshurnikova et al. [K11] quoted a preliminary lifetime radiation risk coefficient for men who started work at this plant before 1954 that was similar to that given by ICRP [I1] for workers, although no confidence interval was given for the former value. In interpreting these findings, it should be borne in mind that 10% of the cohort had been lost to follow-up as of the end of 1994, although the cause of death is known for 97% of deaths [K32]. Also, bone marrow doses from plutonium have yet to be calculated for these workers, although they are likely to be lower than those from external gamma radiation [K32].

280. In contrast to the radiation doses received by early Mayak workers, occupational exposures received in various countries in recent years have tended to be low. As a consequence, studies of small groups of such workers have tended to produce varying results, reflecting their low statistical power to detect small increases in risk. To obtain greater statistical precision, it is therefore necessary to assemble as large a cohort with as long a follow-up as possible. In Japan a cohort of nearly 115,000 nuclear industry workers was identified [E3], but it could be followed-up for at most five years, limiting the inferences that could be drawn about leukaemia risks. More powerful information was derived from an international combined study of nuclear industry workers in Canada, the United Kingdom, and the United States [I2, C11]. This study was based on a cohort of over 95,000 workers with individual dosimetry for external radiation and over 2 million person-years of follow-up. As indicated in Table 21, the total number of leukaemias is larger than in many of the other studies listed but the mean dose is lower. Analysis of mortality from leukaemia (other than CLL) showed a statistically significant increasing trend in risk with dose. The central estimate of risk per unit dose corresponded to 0.59 times the value estimated from the atomic bomb survivors based on a linear dose-response model and 1.59 times the value based on a linear-quadratic model fitted to the bomb survivor data; the corresponding 90% confidence interval ranged from about zero up to four times the value from the linear-quadratic bomb survivor model. The evidence for a trend with dose was particularly strong for CML, as has also been reported in a large study of workers in the United Kingdom [M46, L20], some of whom were included in the international study.

281. Several points should be noted when interpreting the results of the international worker study [C11, I2]. First, the statistical significance of the trend in the worker data is based largely on a few cases with cumulative doses above 400 mSv [S24]. Dose-response analyses restricted to lower doses do not show a significant trend, although the estimated trend from these analyses is compatible with that from the full analysis [C11, C13]. However, the small total number, nine, of estimated excess leukaemias should be noted. Secondly, much of the evidence for a trend is based on workers at a reprocessing plant at which there could have been internal exposures not only to radionuclides but also to chemicals. However, excluding workers judged to have potentially received more than 10% of their dose from exposure to neutrons or from intakes of radionuclides did not affect the trend with dose. Indeed, while inspection of the point estimates of the ERR per Sv from the various facilities included in the study might suggest variability [S24], the findings are statistically consistent [C13]. This again reflects the limited statistical precision of the individual studies. Thirdly, dosimetry is an important consideration in a study that draws on data from different countries and in which dosimetry practices have varied over time. A dosimetry committee assembled for the purposes of this study judged that the dose estimates were generally compatible, although bone marrow doses may

have been overestimated by about 20%, implying a slight underestimation of the risk per unit dose [C11]. In addition, as pointed out previously, random errors in ascertaining doses are more likely to bias risk estimates towards the null than away from it. To conclude, this international study of radiation workers is valuable in addressing the risks associated with low-dose and low-dose-rate exposures, and additional investigations of this type should help to reduce uncertainties further.

282. Workers who took part in the recovery operations following the Chernobyl accident often received doses of 0.1–0.2 Gy, i.e. greater than those currently being received by many nuclear industry workers but lower than those of the early Mayak workers. The study of recovery operation workers from Estonia lacked statistical precision, owing to the small cohort and limited follow-up; indeed no leukaemia cases were identified, although one had been expected from population rates [R20]. Further information has been reported from studies of much larger numbers of workers from the Russian Federation. As previously noted in Section I.A, the interpretation of these findings depends on the type of comparison. Ivanov et al. [I13] cited an excess of leukaemia among these workers relative to rates for the general Russian population; however, in a case-control analysis based on comparisons among recovery operation workers, no significant correlations with dose or other aspects of their work were found [I14] (see Table 21). This difference is likely to be due to differences in methodology; in particular, to a probable bias in the cohort study [B27].

283. The study of natural background radiation in the Yangjiang area of China did not show a statistically significant association with leukaemia over all ages [T25, T26] (see Table 21). A subgroup analysis based on an earlier follow-up suggested an excess of leukaemias in the first year of life, but based on very small numbers (three observed compared with 0.4 expected from population rates) and on mortality rather than incidence data [A11]. A small study in Italy found no positive association between adult myeloid leukaemia and levels of background gamma radiation measured in homes, in contrast to earlier suggestions of such an association based on geological inferences of the natural radiation dose levels [F7].

284. Information on the incidence of leukaemia among people living near the Techa River was considered in the UNSCEAR 1994 Report [U2]. Both external and internal exposures were received by these individuals. As indicated previously, these investigations are potentially important sources of risk estimates, particularly for leukaemia. Emigration from this area, the possibly confounding effects of toxic chemicals around the Techa River, and the reconstruction of individual doses are issues pertinent to realizing this potential. Kossenko et al. [K5] noted that the fraction of the total number of deaths due to leukaemia in the Techa River cohort is slightly higher than the corresponding fraction in the Life Span Study. While this result may reflect differences between the cohorts in the level and type of exposure, the inclusion in the former cohort of leukaemias identified from a wide range of sources may also have influenced the finding [K5]. Studies relating to contamination as a result of the Chernobyl accident are addressed in the Section on internal exposures, although again, both internal and external exposures were received. In contrast, doses to persons exposed to nuclear weapons test fallout in southwestern Utah in the United States were mainly from external radiation. The study of this group, which was discussed in the UNSCEAR 1994 Report [U2], found an association between bone marrow doses from fallout and leukaemia mortality [S17]. This association was restricted primarily to acute leukaemia before the age of 20 years following the period of highest exposure, although the indication of a similar level of risk for CLL in adults may suggest caution in interpreting these findings.

285. Findings from another study at low doses were reported by Boice et al. [B39], who undertook a case-control study of diagnostic x-ray procedures. Relative to persons for whom no such procedures were recorded within two health plans, the relative risk of leukaemia (other than CLL) associated with diagnostic x rays was 1.42 (95% CI: 0.9–2.2), based on a two-year lag. There was no significant trend in risk with the number of procedures, although individual estimates of organ doses were not available [B39].

286. Information on the risks of leukaemia and other cancers from irradiation *in utero* was summarized in the UNSCEAR 1994 Report [U2]. The topic is considered in more detail in Annex G, "*Biological effects at low radiation doses*". Briefly, various case-control studies of childhood cancer, including leukaemia, have shown elevated relative risks associated with obstetric x-ray examinations of pregnant women of the order of 1.4–1.5 [D17]. Although the relative risk from the Oxford Survey of Childhood Cancers in the United Kingdom, in particular, has high statistical precision, concerns have been raised, most recently by Boice and Miller [B41], about the possibility of bias and confounding. Several of these points, for example, the apparent disparity between the findings of case-control and cohort studies and the similarity of the relative risks for leukaemia and other cancers, have been considered by Doll and Wakeford [D17]. With respect to these specific points, Doll and Wakeford cited problems with some of the cohort obstetric x-ray studies, and noted that the cells that give rise to most childhood cancers other than leukaemia persist and are capable of dividing for only a short time, if at all, after birth [D17]. The doses received in the studies of obstetric x rays are somewhat uncertain, but the mean values are likely to have been 10–20 mGy. It is notable that studies of childhood leukaemia following another type of obstetric examination, namely ultrasound, have not shown elevated risks; for example, a recent national case-control study in Sweden using prospectively assembled data on prenatal exposure to ultrasound reported relative risks close to 1 [N16]. The other main source of information on leukaemia following *in utero* irradiation comes from atomic bomb survivors exposed *in utero*. Delongchamp et al. [D14] have reported some evidence of elevated leukaemia mortality in this group relative to controls in the period from October 1950 to May

1992, although based on only two deaths. No additional leukaemia cases were reported in an earlier analysis of cancer incidence [Y1]. In contrast to survivors exposed in childhood, there was no increasing trend in leukaemia risk with dose among the *in utero*-exposed survivors, owing to the absence of deaths at high doses [D14]. Indeed there were no leukaemia deaths at ages less than 15 years among those exposed *in utero*. However, the low statistical precision associated with the small numbers in this group should be noted. Overall, the available evidence points to an elevated leukaemia risk from *in utero* irradiation, although there is uncertainty over its magnitude.

287. Some studies of childhood leukaemia in relation to paternal preconception irradiation were also mentioned in the UNSCEAR 1994 Report [U2]. Although a case-control study in West Cumbria in the United Kingdom [G7] suggested an association between paternal preconception irradiation and leukaemia in the offspring of workers at the Sellafield plant, this finding was specific to workers in the village of Seascale near Sellafield and was not seen among the offspring of other Sellafield workers with similar preconception doses [H6]. Furthermore, the paternal preconception irradiation result was not replicated in subsequent studies of the children of radiation workers in Scotland [K2] or Canada [M16], and no leukaemia excess has been observed among offspring of the atomic bomb survivors [Y2]. A large study found an elevated risk of leukaemia in the children of nearly 120,000 male radiation workers in the United Kingdom compared with other children (relative risk = 1.83; 95% CI: 1.11–3.04); however, no association was found between leukaemia risk and levels of paternal preconception irradiation [D24]. In a study based on a cohort of nearly 40,000 children of male nuclear industry employees in the United Kingdom, which included workers in the just-mentioned study [D24], the incidence of cancer was found to be similar to national rates [R29]. In this instance, the only suggestion of an elevated risk was based on three cases with total preconception doses of at least 100 mSv [R29], two of which had already been reported in the study in West Cumbria [G7]. In reviews of this topic, Little et al. [L18] and Doll et al. [D10] concluded that the inconsistency not only with the other epidemiological data but also with experimental data makes it highly unlikely that the association observed at Seascale represents a causal relationship.

2. Internal low-LET exposures

288. A study of leukaemia incidence among nearly 47,000 patients in Sweden given ^{131}I for thyroid cancer, hyperthyroidism, or diagnostic purposes [H12], mostly in adulthood, was considered in detail in the UNSCEAR 1994 Report [U2] (see Table 21). Although there was no evidence of an association between bone marrow dose and leukaemia in this study, this may reflect a lack of statistical power associated with the generally low doses (mean 14 mGy). Ron et al. [R14] studied leukaemia mortality among hyperthyroidism patients, mostly from the United States, in relation to estimated bone marrow dose from ^{131}I therapy. There was no evidence of a trend in risk with dose, either for leukaemia excluding CLL (see Table 21) or CLL alone, although the generally low doses (mean of 42 mGy) limited the precision of this analysis [R14]. Statistical precision was even more of a concern in a study of thyroid cancer patients in France [D18], for which, even though the mean bone marrow dose was similar in magnitude (34 mGy), the cohort of 1,771 patients was much smaller than in the aforementioned studies. Although no leukaemias were observed in the French study, the number expected from national rates was only 1.28 [D18].

289. The European Childhood Leukaemia-Lymphoma Incidence Study (ECLIS), set up to monitor trends in rates following the Chernobyl accident, has examined data up to the end of 1991 from 36 cancer registries in 23 countries, including Belarus and parts of the Russian Federation [P12]. This is a geographical correlation study, in which doses and risks have been assessed for geographical areas rather than on an individual basis. As pointed out earlier, this approach may give rise to methodological problems and is not suitable for deriving risk estimates, although it does permit a general description of disease rates. The latest report from ECLIS found an overall increase in age-standardized rates of childhood leukaemias during 1980–1986, which continued at about the same rate during 1987–1991 [P12]. No correlation was found with the geographical distribution of effective dose due to fallout from the accident, based on values published in the UNSCEAR 1988 Report [U4]. In view of the very low bone marrow doses received in most of the areas studied (generally less than 1 mSv), this finding is not surprising. Indeed, to have any hope of detecting very small elevated risks, large studies such as this are required. In contrast, smaller studies often give variable results. For example, Petridou et al. [P15] reported an elevated risk of infant leukaemia in Greece among those *in utero* at the time of or soon after the Chernobyl accident. However, not only was this finding based on a subgroup analysis involving only 12 cases diagnosed in the first year of life, but it is inconsistent with the results of obstetric x-ray studies [U2]. Other small studies, such as those in Finland [A6], Sweden [H22], and Romania [D26], have not shown an association between childhood leukaemia and Chernobyl fallout. In Germany, Michaelis et al. [M30] reported an increased risk of infant leukaemia among those *in utero* at or soon after the time of the accident relative to those born at other times. However, this increase was, if anything, highest in those regions with the lowest levels of contamination, and the authors concluded that *in utero* exposure was not a cause of the elevated risk [M30, S53]. A study in Belarus [I22] has shown that the relative risk for infant leukaemia, while it is greater than 1, is not elevated to a statistically significant extent and is lower than the corresponding values from the studies in Germany [M30] and Greece [P15]. The issue of infant leukaemia following the Chernobyl accident is being examined further using the much larger ECLIS database [P25].

290. While much of the dose to those in western Europe from the Chernobyl accident arose from external exposures, internal exposures may have been more important closer to Chernobyl. Ivanov et al. [I5] reported similar rates of acute

leukaemia among children in areas of Belarus with varying levels of radionuclide contamination. Furthermore, in an analysis of aggregated data from contaminated areas of Belarus, the Russian Federation, and Ukraine, Prisyazhniuk et al. [P16] showed that while age-adjusted leukaemia rates rose from 1980 to 1994, this trend appeared to be similar for the periods before and after the Chernobyl accident; also, rates were similar in areas with different levels of contamination.

291. There has been interest in recent years in reports of cancer clusters in the vicinity of nuclear installations. Many of these reports were considered in the UNSCEAR 1994 report [U2] (see also [M34]). In the United Kingdom, excesses of childhood leukaemia have been reported around some nuclear sites, in particular, the Sellafield [C28] and Dounreay [C29] reprocessing plants. However, environmental assessments suggest that these findings are unlikely to be attributable to radioactive release from the sites. Indeed, while exposures associated with these sites often comprise a mixture of external and internal low-LET and internal high-LET exposures, they have been assessed to be generally less in total than exposures from natural radiation [C28, C29]. Elsewhere, studies in, for example, the United States [J1], Canada [M35], France [H40], western Germany [K25], and Japan [I15], have tended not to show excesses of cancer around nuclear installations, specifically of childhood cancer and/or leukaemia in some instances. Some exceptions have been reported; for example, Wing et al [W14] cited an excess of leukaemia around the Three Mile Island nuclear power plant in the United States. However, as indicated earlier in relation to lung cancer, Hatch et al. [H37, H38] interpreted their original analysis of these data as not providing convincing evidence of an association with the very low doses resulting from radiation emissions from the plant.

292. It should be borne in mind that inferences from studies around nuclear installations are limited by their geographical nature, the very small doses involved, and, as around some of the United Kingdom sites, for example, the relatively small numbers of cases. There are also difficulties in interpretation with the differing analyses performed; for example, with respect to age (0–4, 0–14, or 0–24 years), diagnostic category (leukaemia, leukaemia and NHL, all cancers), time period, and proximity to the installation. When many different analyses are performed, it would not be surprising to obtain a statistically significant finding, i.e. one that would arise 1 in 20 times by chance alone. The unavailability of data can also present a problem; for example, the ascertainment of childhood leukaemias may be incomplete owing to a lack of national incidence data [H40], or small-area data may not be available, e.g. as in parts of the United States studied by Jablon et al. [J1]. Some of these problems can be addressed through case-control or cohort studies, which collect data at the individual level. As mentioned earlier, the case-control approach has been valuable in addressing the issue of paternal preconception irradiation [D24]. However, difficulties can still arise in this type of study. For example, Pobel and Viel [P7] suggested an association between childhood leukaemia and the use of beaches around the La Hague reprocessing plant in France. However, this result was dependent on a small number of cases, relied on the recall of habits stretching back several decades, and involved multiple comparisons [C30, L38]. Furthermore, no such association was found around the Sellafield plant in the United Kingdom [G7].

3. Internal high-LET exposures

293. It has been suggested that uptake of radon by fat cells in the bone marrow might lead to irradiation of the haematopoietic stem cells [R10], and there have been some indications from geographical correlation studies, based on large-area data, of an association between radon exposure in dwellings and leukaemia [H14]. However, this suggestion has not been replicated in geographical studies using small-area data and more refined analyses [M13, R6]. More weight might be given to a large case-control study in the United States by Lubin et al. [L34] that collected data on an individual rather than a geographical basis (see Table 4 for details). No evidence was found of an association between acute lymphoblastic leukaemia in childhood and individual assessments of indoor radon exposure. In particular, for time-weighted average radon concentrations in excess of 148 Bq m^{-3}, the relative risk compared with concentrations of less than 37 Bq m^{-3} was 1.02 (95% CI: 0.5–2.0) based on matched case-control pairs [L34]. A study of childhood acute myeloid leukaemia in the United States [S52] and smaller studies of childhood cancers in Germany [K38] and of acute myeloid leukaemia in Italy [F7], all of which involved measurements of radon in homes, also did not show associations with leukaemia risks overall.

294. To test for any association between radon and the risk of cancers other than lung cancer in a study with individual dosimetry, Darby et al. [D8] performed a collaborative analysis of data from 11 cohorts of underground miners. Further details of the component cohorts are given in Table 4, and Table 21 contains some results for leukaemia. The combined cohort was very large (over 64,000 men) with over 1 million person-years of follow-up. There was an excess in mortality from leukaemia of all types relative to national or regional rates within 10 years of first employment (SMR = 1.93; 95% CI: 1.19–2.95, based on 21 deaths). However, restricting the analysis to the period when the 8th and 9th revisions of the International Classifications of Diseases were in operation, so that leukaemia subtypes could be distinguished, there was no evidence of an elevated level of leukaemia other than CLL (SMR = 1.28; 95% CI: 0.51–2.64, based on seven deaths). The leukaemia subtype with the highest SMR was acute myeloid leukaemia (SMR = 2.42; 95% CI: 0.51–2.64), although based on only three deaths. Perhaps of greater interest than SMRs were analyses in relation to cumulative radon exposure which, although based on small numbers, showed no trend in the risk of all leukaemia, leukaemia excluding CLL, or AML. More than 10 years after first employment, there was no indication of an elevated SMR, either for all leukaemias or specific subtypes. The possibly elevated SMR in the earlier period may well be due to chance, since agents encountered in mines, such as diesel

fumes and arsenic, are thought not to be leukaemogens, and the levels of gamma radiation in mines, although not always known, are likely to be too low to explain this result [D8]. The study therefore provides evidence that high concentrations of radon in air do not cause a material risk of leukaemia mortality.

295. An elevated level of leukaemia, in particular, myeloid leukaemia, was reported in studies of thorotrast patients in Germany [V8], Denmark [A4, A5], Portugal [D31], and Japan [M14]. Results from these studies are summarized in Table 21. Andersson et al. [A4] showed that the risk of AML and myelodysplastic syndrome increased in relation to cumulative dose, having taken account not only of the amount injected but also the time since injection. There was also a suggestion of a cell-killing effect at high doses, although this was not statistically significant. Based on a mean bone marrow dose of 1.3 Gy (high-LET), Andersson et al. derived a risk estimate for these diseases of 1.7 10^{-2} Gy^{-1}. While this suggests that the RBE of alpha radiation relative to low-LET radiation may be lower than the value of 20 recommended by ICRP [I1], it should be noted that the latter value was chosen to apply at low doses, rather than that at the high doses in this study. Furthermore, there are uncertainties in the risk estimate derived by Andersson et al. [A4] owing to the relatively small number of cases and imprecision in the estimation of individual doses. Hunacek and Kathren [H33] compared published risk coefficients with values determined from dose rates based on post-mortem radiochemical analysis of tissues from a thorotrast patient. Using results from thorotrast studies in Germany, Japan, and Portugal (but not Denmark), they obtained a leukaemia risk coefficient of 3.2 10^{-2} Gy^{-1} [H33], which is somewhat higher than that calculated by Andersson et al. [A4]. However, the former value is likely to be incorrect, owing to an error in calculating bone marrow dose rates based on data for the total skeleton. Furthermore, new dose calculations indicate that the bone marrow dose had been previously underestimated and that the risk per unit dose had been overestimated [I25].

296. There is some evidence for an excess of leukaemia among patients injected with ^{224}Ra [N4, W20], with one of these studies [W20] indicating an excess more than 30 years after the first injection of ^{224}Ra. However, inferences are restricted by the generally small number of cases and the absence of dose-response analyses. Among radium dial workers in the United States, the number of leukaemias observed was close to that expected in the general population [S7]. Although it has been suggested that the cases among pre-1930 dial painters arose early [S54], the small numbers in both this analysis and an analysis by bone marrow dose [S7] limit the interpretability of these data.

297. No leukaemias have been observed in the offspring of Danish thorotrast patients [A13]. Although this study was based on a small cohort, its statistical power was enhanced by the high doses to the testes from alpha radiation (mean dose = 0.94 Sv).

4. Summary

298. There is a substantial amount of information on the risks of leukaemia from radiation exposure. This reflects the high relative increase in risk compared with other cancer types and the temporal pattern in risk, with many of the excess leukaemias occurring within about the first two decades following exposure, particularly among those irradiated at young ages. There are some differences between the Life Span Study of atomic bomb survivors and some large studies of medically exposed groups in estimates of both the magnitude of the radiation risk and the shape of the dose response for external low-LET exposure. These findings may reflect differences between studies in the uniformity of exposure to the bone marrow and in the degree of fractionation and protraction of exposure, as well as differences in the pattern of risk between leukaemia subtypes. There is clear evidence of non-linearity in the dose response for leukaemia, which has a slope that decreases at lower doses.

299. A large international study of radiation workers suggested an elevated leukaemia risk, although the results were compatible with a range of values. Case-control studies of prenatal x rays indicate an increased risk of leukaemia in childhood due to *in utero* irradiation, although the absence of a dose-related increase in the sparse corresponding data for atomic bomb survivors adds uncertainty to the magnitude of the risk. Epidemiological evidence does not suggest that irradiation prior to conception gives rise to a material risk of childhood leukaemia.

300. The data available on internal exposures to low-LET radiation do not indicate elevated risks of leukaemia; this may well reflect the low statistical precision associated with generally small doses. There is no convincing evidence of an increased risk of leukaemia due to environmental exposures associated with the Chernobyl accident, although investigations are continuing. Excesses of childhood leukaemia have been reported around some nuclear installations in the United Kingdom, but generally not in other countries; these excesses are based on small numbers of cases and have not been explained on the basis of radioactive releases from the installations. Dose-related increases in leukaemia risk have been seen among patients with large exposures to high-LET radiation arising from injections of thorotrast, a diagnostic x-ray contrast medium. There is less evidence for elevated risks among patients injected with ^{224}Ra and little or no evidence for increased risks among radium dial workers or from studies with individual assessments of radon exposure, either in mines or in homes.

IV. LIFETIME RISK FOR TOTAL CANCER

301. In Chapter III the focus was on risks for specific cancer sites. The aim in this Chapter is to develop risk estimates for total cancer, in line with previous assessments of the Committee, most recently in the UNSCEAR 1994 Report [U2]. Many of the issues associated with producing such estimates were discussed in Chapters I and II. However, some of them are summarized here, together with points that are germane to total cancer risks.

302. The estimation of total cancer risks is in some ways easier than the estimation of risks for specific cancer sites. The most notable difference is the larger number of cancers available from epidemiological studies of all cancers. This means that the statistical precision of estimates based on such data should be greater than the precision for specific cancers. On the other hand, heterogeneity in risks between cancer types may counterbalance this. Indeed, "cancer" is a multitude of different diseases with different aetiologies.

303. As an example of an analysis based on a collection of cancer types, Figure IV shows estimates of the ERR per Sv for various types of solid cancer in survivors of the atomic bombings based on the most recent mortality data [P9]. These values have been adjusted for age at exposure and gender. Pierce et al. [P9] noted that the variation in the ERR per Sv between cancer sites is not statistically significant. However, they cautioned that this should not be taken as substantial evidence that the ERR per Sv is the same for all sites, given the differences in aetiology for different cancer types. Furthermore, the ERR is only one scale of representation, and the EAR per Sv should also be considered. However, because the baseline rates vary for different types of solid cancer, the EAR per Sv is likely to vary much more widely between cancer types than the ERR per Sv.

304. The increased statistical precision associated with an analysis of all solid cancers assists in the development of risk models. In particular, it may be possible to detect variations in risk with factors such as age, time, and gender that are not apparent in data for specific cancer sites. For example, Figure V summarizes models fitted to data on mortality from all solid cancers for the Japanese atomic bomb survivors [P9]. This indicates variations in the ERR per Sv and EAR per Sv with gender, age at exposure, and attained age that may not be evident in analyses for specific cancers. However, it should be recognized that such models might be affected by differences between cancer types in the pattern of risk. On the other hand, as previously mentioned in Section I.E, analyses conducted separately for various cancer sites may yield differences in trends in risk with, for example, age and/or time, simply as a consequence of chance variations. One possibility, suggested by Pierce and Preston [P6], is to analyse data for various cancer sites, or groupings thereof, in parallel. This may allow the development of models for which the level of the relative risk, for example, differs between cancer types but under which the variation with factors such as age and time is the same across cancer types.

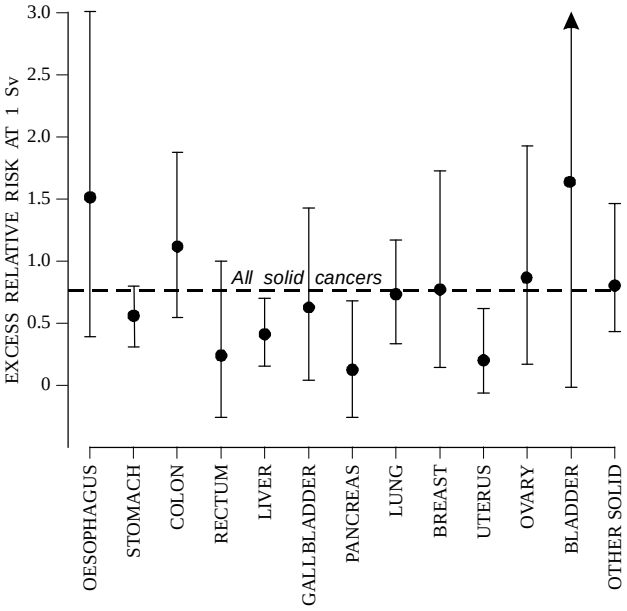

Figure IV. Excess relative risk (and 90% CI) for mortality from specific solid cancers and all solid cancers together (horizontal line) in survivors of the atomic bombings, standardized for females exposed at age 30 years [P9].

305. Related to the above considerations is the issue of whether one or more data sets should be used to estimate total cancer risks. Artefactual differences might arise if different data sets are used for different cancer types. However, this should be balanced against the quantity of data for a particular cancer type that is available from a given study. Indeed, some studies, such as case-control studies, have focused on only one or a few cancer sites and therefore cannot be used by themselves to estimate total cancer risks.

A. EXPRESSIONS OF LIFETIME RISK

306. There is some confusion in discussions and presentations of lifetime risks associated with radiation exposure. To simplify matters, the following discussion is restricted to mortality, and it is assumed that there are two causes of death: "cancer" and "non-cancer". However, the discussion can be generalized to deal with incident cases and multiple causes, any number of which may be affected by exposure.

307. The obvious definition of a lifetime risk is simply the difference between the proportion of people dying of cancer in an exposed population and the corresponding proportion in a similar population with no radiation exposure. This difference is called the excess lifetime risk (ELR). Formal mathematical expressions for the ELR and related quantities are given by Thomas et al. [T18].

308. While the ELR is of some value, it provides an incomplete summary of the effect of exposure on a population. This can be seen most clearly by considering death from any cause as the outcome of interest. In this case the ELR must be zero, since all people will eventually die of something, even if radiation changes the risk of death. However, the ELR is also misleading for cause-specific mortality. If exposure has the same relative impact on death rates for all causes, then cause-specific ELR estimates will be zero. In contrast, suppose that radiation increases the risk of death for cancer by some fraction but also increases the risk of death from non-cancer causes by a smaller amount. In this instance, the ELR for cancer deaths will be positive, while that for non-cancer deaths will be negative, even though radiation exposure increased non-cancer death rates.

309. One way to address problems with the ELR is to consider how exposed and unexposed populations differ with respect to the expected age at death for all causes or for specific causes of death. However, average life expectancies (or more comprehensive summaries of the distribution of ages at death) are difficult to interpret without a clear understanding of the general pattern of death rates in a population. In particular, what might be considered fairly large increases in death rates are associated with rather small changes in life expectancy. For example, based on death rates in the United States for 1985, a 50% increase in all-cause mortality for 20-years old would reduce their life expectancies by about three years. As another illustration of the problem with changes in life expectancy, consider a situation in which an exposure reduces life expectancy from 75 to 25 years for 1% of the population, for example, as a consequence of leukaemia following an exposure of 1 Gy. In this instance, the average life expectancy for the population would be reduced by 6 months. In general, changes in life expectancy are not a particularly useful summary of the exposure effects. To be useful, loss of life expectancy (LLE) should be related to some measure of the number of people whose life expectancy was affected by the exposure.

310. A useful alternative to the ELR can be developed by considering the (cause-specific) death rate defined by the difference in death rates for exposed and unexposed populations as an additional cause of death that has been introduced into a population. Technically this difference is not a rate function, since it would assume a negative value if exposure had a protective effect. However, by treating the difference as a rate, one can compute the fraction of deaths attributable to this "new" cause of death or the probability that an individual will die from a cancer associated with the exposure. This quantity has been described in [U2, T18] as the risk of exposure-induced death (REID). In contrast to the ELR, the REID is positive if exposure increases death rates and negative if exposure decreases death rates. Furthermore, cause-specific values of the REID are zero for any cause for which the rates are not affected by exposure.

311. The values called excess deaths in recent analyses of the atomic bomb survivor data (e.g. [P9]) are closely related to the REID. In particular, the Life Span Study excess deaths are the sum of REID estimates over the follow-up period, having allowed for gender, age at exposure, and dose, with population background rates determined by the experience of the cohort. The REID estimates presented later in this Chapter are computed using background rates from populations other than the Life Span Study, and they estimate the number of excess deaths for lifetime follow-up after exposure.

312. As in the UNSCEAR 1994 Report [U2] and recent Life Span Study reports, the quantity LLE divided by the REID, which can be thought of as the change in life expectancy per attributable case, provides a helpful summary of the impact of exposure on life expectancy. In the example given earlier, in which 1% of the population is affected, the change in life expectancy per attributable case is 50 years (i.e. 0.5 years/ 0.01), which is in line with expectations.

313. Mortality computations are, in principle, relatively straightforward; further details were given in the UNSCEAR 1994 Report [U2]. Gender-specific, age-dependent baseline total- and cause-specific death rates for the populations of interest are used to define the baseline survival probability function. For a given age at exposure, gender-specific excess rates for causes affected by radiation are added to the appropriate cause-specific baseline rates to give the cause-specific and total rates for the (hypothetical) exposed population. Conditional on age at exposure, these adjusted total rates define the age-specific survival probability in the exposed population. The risk measures of interest, namely, the ELR, REID and LLE, can be computed from these conditional survival probabilities and cause-specific disease rates.

314. For lifetime incidence computations, the gender- and age-specific survival probabilities for the unexposed populations are replaced by cancer-free survival probabilities. These functions are computed from gender- and age-specific rate functions defined as the sum of the total non-cancer death rate and the total cancer incidence rate. The total non-cancer death rate is defined as the difference between the total death rate and the total cancer death rate.

B. METHODS AND ASSUMPTIONS OF CALCULATIONS

315. The results presented here are derived from cause-specific attributable risks and the loss of life expectancy per attributable case in five populations: China, Japan, Puerto Rico, the United States, and the United Kingdom. Lifetime mortality risks are computed for the following cancers: oesophagus, stomach, colon, lung, liver, female breast, bladder, other solid cancers, and leukaemia, as well as all other (non-cancer) causes. For incidence, radiation effects on the risk of thyroid cancer are also considered. In the computations presented here, it is assumed that all organs receive the same dose. If exposure is limited to a single organ,

risks for that organ would be only slightly larger than the organ-specific risks discussed below. Even in a whole-body exposure it will be the case that different organs receive different doses; however, the differences in dose-specific risks between those from the joint computa-tion and those from a computation based on the actual doses to each organ will not be large. For example, in a situation in which the breast receives a dose of 1 Gy and the stomach a dose of 0.8 Gy, estimates of the breast cancer risk following a whole-body 1 Gy exposure and of the stomach cancer risk following a 0.8 Gy whole-body exposure will be good approximations to the actual organ-specific risks.

316. Risk estimates for mortality are also given for Chinese and Puerto Rican populations. These estimates make use of life-table and death-rate information given by Land and Sinclair [L12]. In these instances, the computations were carried out in terms of three "causes": non-cancer deaths, non-leukaemia cancer deaths, and leukaemia deaths.

317. Primary results are given for uniform whole-body exposures of 0.1 and 1 Gy for men and women exposed at 10, 30, or 50 years of age. These results depend on the following factors, each of which are discussed briefly below:

(a) the exposed population for which risk estimates are developed, and the models used to describe the excess risks in this population;
(b) the models used to describe risks at low doses;
(c) the method used to extend the excess risk models beyond the period of observation for the population from which these models were developed;
(d) the cause-specific mortality (or incidence) rates and the age structure of the populations to which the rates are applied;
(e) the methods used to transport excess risks based on models for one population to another population; and
(f) the method used to allow for fractionation or dose-rate effects.

1. Risk models

318. As in the UNSCEAR 1994 Report [U2], the risk estimates derived in this Section are based on recent data on the experience of the atomic bomb survivors. The data from Life Span Study Report 12 [P9], which covers the period from 1950 through 1990, were used for the estimation of cause-specific mortality risks for solid cancers. Solid cancer incidence risk estimates are based on linking the Life Span Study survivor cohort and the Hiroshima and Nagasaki tumour registry data [M2] for 1958 through 1987 [T1]. The cause-specific solid cancer mortality and incidence rate models used here were developed specifically for these computations. The method used to estimate risks at low doses is discussed in detail below.

319. Radiation effects are often described by models for cause-specific death rates or hazard functions. The hazard at age a is defined formally in terms of the ratio of the probability of dying from the cause in a short interval (a, a+l) to the length of the interval (l), given that one is alive at a. The hazard function in the absence of radiation exposure will be called the baseline hazard. It is reasonable to allow the baseline hazard, denoted as $h_0(a,s,p)$, to depend on gender (s) and calendar time period (p) in addition to age. One way to describe the effect of a radiation exposure is to consider the difference between the hazard function in the exposed population and the baseline hazard for this population. This difference is the excess absolute risk (EAR). The ratio of the EAR to the baseline hazard is the excess relative risk (ERR).

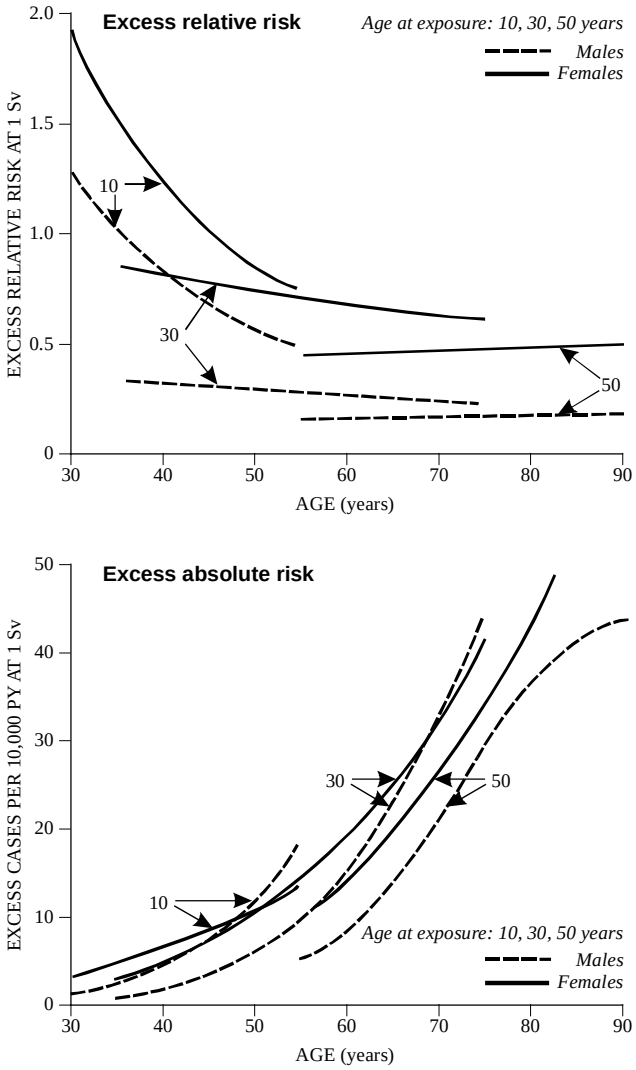

Figure V. ERR and EAR for solid cancer mortality among survivors of the atomic bombings in Japan [P9]. The lines show the patterns of risk in the data.

320. The leukaemia EAR model developed by Preston et al. [P4] was used to describe the effect of radiation on leukaemia risks in both the mortality and incidence computations. To allow for excess leukaemia risks during the first few years after exposure (about which the Life Span Study data provide no direct evidence), it is assumed that excess rates for the first five years are half of those seen five years after exposure.

321. Two types of ERR models were developed for solid cancers. These models are similar to those considered by Pierce et al. [P9] (see Figure V). In the first model, the

ERR depends on gender and age at exposure. For this age-at-exposure model, the cause-specific hazard rate has the form

$$h_d^{LSS}(a,s,e,\cdot) = h_0^{LSS}(\cdot)[1 + \beta\,\theta_s\,d\exp(\gamma e)]$$

322. In the model presented here, the baseline hazard, i.e. the hazard in the absence of radiation exposure, denoted here by $h_0(a,s,p)$, depends on age (a), gender (s), and calendar period (p). The dose-response slope is allowed to depend on gender and, for non-gender-specific cancers, is described in terms of the product of the slope for males (β_M) times a gender ratio parameter ($\theta_{F:M}$). Unless there was evidence of a significant lack of fit, the gender ratio and age-at-exposure (e) effects were assumed to be equal to those for all solid cancers as a whole. Lack of fit was defined as a deviance change [M38] of more than 4 for a single parameter or more than 6 for both parameters.

323. Under the second solid cancer risk model, the ERR depends on gender and attained age (i.e. age at death or cancer incidence, denoted by a) but not on age at exposure. For this attained-age model, the cause-specific hazard rate has the form

$$h_d^{LSS}(a,s,e,\cdot) = h_0^{LSS}(\cdot)[1 + \beta\,\theta_s\,d\,a^k]$$

in which the temporal variation in the ERR is modelled as a power function of attained age. As with the age-at-exposure model, the gender ratio and attained-age effects were taken to be equal to those for all solid cancers as a group unless there was evidence of a significant lack of fit.

324. The site-specific solid cancer ERR parameters for the mortality and incidence models are summarized in Table 31. For each site of interest and each model, the Table presents the gender-specific ERR per Gy estimates, together with the gender ratio (female:male) and the age-at-exposure and attained-age effects. The age-at-exposure effect is given as the percentage change in risk associated with a 10-year increase in age at exposure. The attained-age effect is the power of age. For the age-at-exposure model, the gender-specific estimates of ERR per Gy are for a person exposed at age 30 years. For the attained-age model, they are the ERR per Gy estimates for a person at attained age 50 years.

2. Low-dose response

325. The issue of cancer risks at low doses is discussed in detail in Annex G, *"Biological effects at low radiation doses"*. Among the points covered there are the minimum doses at which statistically significant elevated risks have been detected in epidemiological studies. As mentioned earlier in this Annex, the minimum doses for detectable effects depend on the statistical precision of the relevant study and can also be influenced by any potential bias in the study. While statistically powerful studies can allow effects to be detected at lower doses than small studies, there will be some small doses at which it will not be possible to detect an elevated risk. It is difficult to specify values at which no study will be able to identify an effect, given that, for example, further follow-up of groups such as the Japanese atomic bomb survivors will continue to increase in statistical power and so aid the future investigation of low-dose risks. However, the results cited in Annex G, *"Biological effects at low radiation doses"*, give some idea about minimum doses at which elevated risks can be seen at present.

326. Pierce et al. [P9] reported a statistically significant increasing trend in mortality risks in the 0–50 mSv range for all solid cancers combined among the Japanese atomic bomb survivors, based on follow-up to 1990. However, they also noted that the interpretation of this finding is not straightforward, since it reflects an increasing risk per unit dose in the low dose range not seen for cancer incidence in the survivors [T1]. Observed cancer death rates are increased by about 5% for survivors with doses in the 20–50 mSv range, which is larger than the roughly 2% increase predicted at these doses by linear models fitted to the full dose range. Pierce et al. [P9] suggested that this difference might be due to differential misclassification of cause of death, i.e. a slight bias towards recording cancer rather than other causes on the death certificate for atomic bomb survivors who are known to have been relatively close to the hypocentre. This illustrates how potential biases, while small in absolute terms, can affect the interpretation of low-dose risks. Dose-response relationships for the atomic bomb survivors are discussed further below.

327. Several authors [C35, L40] have raised questions on the statistical support for the low-dose findings in [P9]. However, as indicated by Pierce et al. [P28, P36], the statistical result at low doses is quite robust, although as noted earlier, the relatively small effects in this dose range mean that small biases could distort the inferences about the low-dose response function.

328. Annex G, *"Biological effects at low radiation doses"*, refers to some other studies that provide information on minimum doses for detectable effects. It should be noted that it may be easier to detect elevated risks for particular types of cancer or in specific age-at-exposure groups for which, owing to low background rates, small absolute increases in rates may lead to large relative risks. For example, in a combined analysis of data from seven studies of thyroid cancer after external radiation exposure, Ron et al. [R4] found that a linear dose response provided a good fit to the data on childhood exposure, not only at high doses but also down to 0.1 Gy (low-LET). Annex J, *"Exposures and effects of the Chernobyl accident"*, also reviews studies of childhood cancer following irradiation *in utero* (see also Sections III.K and III.P of this Annex). The Oxford Study of Childhood Cancers shows elevated risks of childhood cancer following prenatal x-ray exposures with a mean dose of 10–20 mGy [D17]; however, concerns have been raised [M31] about the interpretation of this result and the consistency with the findings for the *in-utero*-exposed atomic bomb survivors [D14].

329. Analyses of data across a range of doses usually provide a statistically more powerful approach to considering risks at low doses than focussing on results for specific dose categories. Indeed, the latter approach may yield chance findings owing to multiple significance testing. The mortality risks for all solid cancers combined and for leukaemia among the Japanese atomic bomb survivors, over a wide range of doses, were illustrated in Figure XVIII of Annex G, "*Biological effects at low radiation doses*". Dose-response analyses of data on cancer incidence [P4, T1] and mortality [P9] for the atomic bomb survivors have recently been conducted by Little and Muirhead [L41, L42] and by Hoel and Li [H45] (see also Annex G). It should be noted that in contrast to Hoel and Li [H45], Little and Muirhead [L41, L42] took account of random errors in dose estimates. These analyses showed that for solid cancers, either individually or combined, the atomic bomb survivor data are consistent with a linear dose response and that incorporating a threshold into the dose-response model does not significantly improve the fit [L41, L42]. The only exception may be non-melanoma skin cancer incidence, for which there is some evidence of a threshold at about 1 Sv [L41]. A further analysis of the atomic bomb data by Little and Muirhead [L50] also took account of possible systematic errors in neutron dose estimates for survivors in Hiroshima. This analysis showed little evidence of upward curvature in the dose response for the incidence of all solid tumours combined over the range 0–4 Gy (low-LET); there was more suggestion of upward curvature over the range 0–2 Gy (low-LET), although this was not significant at the 5% level [L50]. For leukaemia, as has been noted previously [P4, P9], a linear-quadratic dose-response model (such that the risk per unit dose is smaller at low than at high doses) provides a significantly better fit than a linear model. However, there is some evidence from the leukaemia incidence data that incorporating a threshold (estimated to be 0.12 Sv; 95% CI: 0.01–0.28) provides a better fit than the linear-quadratic model alone (two-sided p=0.04) [L41]. On the other hand, there is less evidence for such a threshold based on the corresponding mortality data (two-sided p=0.16) [L42]. Since the estimates of relative risk at low dose are similar for the leukaemia incidence and mortality data, Little and Muirhead [L42] suggested that the difference in findings may be due to the finer division of dose groups in the publicly available mortality data than in the corresponding incidence data.

330. In view of the above, the calculations given below are based on linear dose-response models for solid cancers and on a linear-quadratic model for leukaemia. The form of the risk models was described in the preceding Section.

3. Projection methods

331. Generally speaking, the age-at-exposure and attained-age models describe the Life Span Study data equally well. However, as will be seen below, these models lead to different projections of risk beyond the current follow-up period for survivors exposed as children. For people exposed to the atomic bombings after age 50, little projection is needed since their follow-up is close to complete. In Figure V, it can be seen that for this group the ERR basically is constant over time. For most sites, the age-at-exposure model assumes that ERRs for those exposed as children will remain at their current relatively high values throughout life; in contrast, the attained-age model assumes that ERRs will decline as the survivors get older. Thus, the two models correspond to different methods for projecting risks beyond the current follow-up.

332. In the UNSCEAR 1994 Report [U2], only age-at-exposure models were used, and various ad hoc (i.e. non-model-based) projection methods were used. One of those methods (constant ERR) is equivalent to the use of the age-at-exposure model, while the second method (constant ERR over the current follow-up, with risks declining in the future) is similar to the use of the attained-age model.

4. Populations and mortality rates

333. In Table 32, mortality and incidence estimates are given for five populations: China, Puerto Rico, Japan, the United Kingdom, and the United States. Cause-specific mortality rates for Japan, the United States, and the United Kingdom are based on 1985 national statistics in the three countries. Mortality rates for China and Puerto Rico are taken from Land and Sinclair [L12]. Data on cancer incidence rates were obtained from the current (7th) edition of Cancer Incidence in Five Continents [P5]. For the United States, data for the combined SEER registries were used. Japanese rates were computed as the unweighted average of rates for the Hiroshima, Nagasaki, and Osaka tumour registries. Rates from the Shanghai Cancer Registry were used for China.

334. Population age distributions were used to compute the population risks shown in Tables 33–37. The 1985 age distributions were used for Japan, the United States, and the United Kingdom. Estimates for China and Puerto Rico were based on the summary life-tables given by Land and Sinclair [L12].

5. Transport of risks between populations

335. For each risk model, two methods were used to transport site-specific solid cancer risks estimated for a Japanese population to populations of China, Puerto Rico, the United States or the United Kingdom. These methods will be called relative risk transport and absolute risk transport.

336. For the relative risk transport, the cause-specific hazard rate in the target population, T, was computed as the product of the baseline hazard in the target population and the (age-at-exposure or attained-age) ERR for the Japanese population, J:

$$h_{di}^{T}(a,s,e) = h_{0i}^{T}(a,s)\,[1 + ERR^{J}(d,s,a,e)]$$

337. For the absolute risk transport, the cause-specific hazard rate in the target population was computed as the

sum of the target-population baseline hazard and the EAR for the Japanese population:

$$h_{di}^{T}(a,s,e) = h_{0i}^{T}(a,s) + EAR^{J}(d,s,a,e)$$

Here the EAR function for the Japanese population was computed as the product of the appropriate ERR function for the model of interest (age-at-exposure or attained-age) and the corresponding Japanese baseline rate, namely

$$EAR^{J}(d,s,a,e) = h_{0i}^{J}(a,s)\, ERR^{J}(d,s,a,e)$$

For leukaemia, EARs were estimated directly in the survivors, and all transport was done using absolute rates.

6. Fractionation and dose-rate effects

338. Experimental and epidemiological information on cancer risks from fractionated or low-dose-rate exposure, relative to acute or high-dose-rate exposure, was reviewed in the UNSCEAR 1993 Report [U3] and is also considered in Annex G, "*Biological effects at low radiation doses*". The UNSCEAR 1993 Report indicated that risks associated with low-dose or low-dose-rate exposures may be less than those from acute high doses by a factor of as much as 3. The Committee has not examined all new studies since 1993 to assess potential changes in the range of values. However, some recent information on this topic is provided in this Annex, for example, from the comparison of results from the acutely exposed Japanese atomic bomb survivors and from tuberculosis patients with fractionated x-ray exposures from fluoroscopies. For lung cancer, there is no indication of an elevated risk in the Canadian [H7] and United States (Massachusetts) [D4] fluoroscopy studies, unlike in the atomic bomb survivors [P9, T1]. However, the severity of tuberculosis may have affected the findings for lung cancer in these patients. For breast cancer, it has been suggested, based on comparison of the fluoroscopy and atomic bomb survivor findings, that fractionation may not affect risks [L39], although a different interpretation has been put on this finding [B33].

339. Further information on low-dose-rate occupational and environmental exposures has also become available in recent years and is summarized both in this Annex and in Annex G, "*Biological effects at low radiation doses*". While it has been possible in some instances to find some evidence of an elevated risk (e.g. for leukaemia among nuclear industry workers [C11]), such studies do not currently have sufficient statistical power to allow those risks to be estimated with great precision. Furthermore, risk estimation based, for example, on groups in the former Soviet Union is sometimes complicated by exposures to both low- and high-LET radiation. Further investigation, including longer follow-up and more detailed analyses, may improve the estimation of risks from fractionated and low-dose-rate exposure. For the time being, however, the values for a reduction factor of less than 3 that were suggested in the UNSCEAR 1993 Report seem to be reasonable, notwithstanding the possibility of differences between some cancer types.

340. For leukaemia, the linear-quadratic dose-response model implies a reduction factor of 2 when extrapolating from acute high doses to low doses or low dose rates. It would, therefore, not be necessary to apply another reduction factor to the leukaemia results given for a dose of 0.1 Sv if the exposure was fractionated or protracted rather than acute. However, the results at 1 Sv for solid cancers could, tentatively, be reduced by a factor of 2 for fractionated or protracted exposures.

C. LIFETIME RISK ESTIMATES

341. The principal results of the calculation of lifetime risks are given in Table 33 for an acute whole-body dose of 1 Sv or 0.1 Sv. This Table presents solid cancer results for the two projection models (age-at-exposure and attained-age dependence of the ERR) and two risk transport models (ERR and EAR transport) for the five populations. As noted above, leukaemia risks always were based on an EAR model. The transport method makes little difference because non-CLL leukaemia rates are similar in the different populations; consequently, results are presented only for the EAR transport model.

342. For comparison, the estimates at 1 Sv for a Japanese population that were derived in the UNSCEAR 1994 Report [U2] are included in Table 33. The UNSCEAR 1994 estimates for the REID (10.9% averaged over gender) were based on an age-at-exposure model applied to Japanese rates and are generally comparable to the current estimates for solid cancers (11.2% averaged over gender). The 1994 leukaemia estimate of 1.1% averaged over gender is slightly higher than the current estimate of 0.9%. This difference arises because of slight differences in the leukaemia risk model and because, for the current computations, leukaemia was included as another "site" in a joint analysis of the impact of a whole-body exposure, while in 1994 leukaemia was considered separately from other causes (i.e. as if only the bone marrow had been exposed). The difference reflects the impact of increased hazards for the competing risks of radiation-associated solid cancers.

343. Although the solid cancer REID estimates are based on a linear dose-response model, the REID estimate for a dose of 0.1 Sv is slightly more than 10% of the estimate for a dose of 1 Sv. For example, considering solid cancer mortality in United States males using an attained age model and relative risk transport, the REID estimates for 1 and 0.1 Sv are 6.2% and 0.7%, respectively. This non-linearity reflects the effect of competing risks at lower doses vs. at higher doses. However, for these models, the REID estimates for solid cancers at lower doses are approximately linear in dose.

344. The use of the attained-age model leads to smaller lifetime risks for solid cancers than the corresponding age-at-exposure model. The reason for this can be seen in Table 34, which is based on a Japanese population. The persistence of high relative risks under the age-at-exposure model leads to large lifetime risks for those exposed as

children. For solid cancer mortality following exposure at age 10 years, the values of REID are 14% for men and 20% for women, while the corresponding gender-specific incidence risks are 31% and 37%, respectively. The attained-age model, which describes the current Life Span Study data as well as the age-at-exposure model, allows the relative risks for those exposed as children to decrease as they reach the ages of high cancer mortality or incidence. As a result, the estimated gender-specific solid cancer mortality and incidence risks following exposure at age 10 years are about half the values predicted by the age-at-exposure model. The population average lifetime risk estimates for the attained-age model are about 70% of those for the age-at-exposure model.

345. Some other measures of radiation detriment, based on mortality in a male Japanese population, are given in Table 35. As expected, the excess lifetime risk ELR is similar to the REID (i.e. the percentage of radiation-associated deaths) for leukaemia, but the former is less than the latter for all solid cancers. Furthermore, the excess lifetime risk is negative for non-cancer causes, since the sum of this measure over all causes must equal zero. The loss of life expectancy per attributable solid cancer death is similar under the attained-age and age-at-exposure projection models.

346. As indicated in Table 33, values of REID for solid cancer mortality in men are generally comparable for the Japanese, United Kingdom, and United States populations: about 9% with the age-at-exposure model and 6% with the attained-age model following a dose of 1 Sv. However, lifetime attributable risks for men in the Chinese and Puerto Rican populations are about 30% lower than those in Japan, the United Kingdom, and the United States. There is greater variability in female rates, but the same general pattern is seen in the magnitude of the risk estimates, with values of REID for Japan, the United Kingdom, and the United States being considerably greater than those for China and Puerto Rico. These differences reflect almost entirely differences in the lifetime probability of cancer mortality in these populations, as presented in Table 32, which in turn reflect the population-to-population variability in baseline rates.

347. Estimates of REID for women are consistently greater than those for men, largely reflecting gender differences in life expectancy and the contribution of breast cancer. REID estimates for cancer mortality in women exhibit greater sensitivity to both the risk projection model and the transport method than do those for men. This difference is primarily due to variations in breast cancer mortality between these populations.

348. Estimates of REID for cancer incidence are slightly lower for Japanese men (19% using the age-at-exposure model and 13% for the attained-age model) than for United States men (15% and 11% for the age-at-exposure and attained-age models, respectively), while estimates for men in the United Kingdom are somewhat higher (26% and 22%, respectively). These differences generally reflect differences in the baseline rates. Since lifetime baseline cancer incidence risks for China and Puerto Rico are more similar to those in Japan, the United Kingdom and the United States than are the corresponding mortality risks, the differences in incidence estimates of REID between these two countries and Japan, the United Kingdom, and the United States are not as marked as they are for mortality. REID estimates associated with relative risk transport tend to be larger for Western women than for Japanese women. This difference is due almost entirely to the higher breast cancer incidence and mortality in the United States and United Kingdom populations than in the Japanese population.

349. Tables 36 and 37 give detailed breakdowns by cancer type of estimates of REID risks for mortality and incidence, respectively, based on one of the above models, namely the attained-age projection model. When relative risk and absolute risk transport are compared for the populations of the United States and the United Kingdom, the main effect of using the latter rather than the former transport method is to reduce the REID estimates for women. This is due principally to reductions in the excess associated with breast and lung cancer, whose background rates are lower for Japanese women than for Western women. With this reduction, the differences in REID for the populations considered are less marked than under the relative risk transport.

350. Since the UNSCEAR 1994 Report [U2], further work has been undertaken to assess uncertainties in cancer risk estimates. In particular, NCRP report 126 [N17] assessed the uncertainty in the total fatal cancer risk for the United States population from external low-LET irradiation at low doses and low dose rates; it took account of the following factors:

(a) statistical uncertainties in the estimation of a risk factor, based on data for the Japanese atomic bomb survivors;
(b) possible bias due to over- or under-reporting of cancer deaths in the atomic bomb survivors;
(c) the effect of both random and systematic errors in dose estimates for the atomic bomb survivors;
(d) uncertainty in the method of transferring risks from Japan to the United States;
(e) uncertainty associated with the projection of risks over time, from the period of follow-up to a complete lifetime;
(f) uncertainty in the DDREF; and
(g) a subjective assessment of any remaining unspecified uncertainties.

351. Uncertainties associated with each of these factors were propagated using a Monte Carlo approach [N17]. For a United States populations of all ages and both genders, the mean value for the total cancer risk at low doses and low dose rates was estimated as $4.0\ 10^{-2}$ per Sv, with a 90% confidence interval of $1.2–8.8\ 10^{-2}$ per Sv. The shape of the total uncertainty distribution was skewed towards higher values, as a consequence of which the median value ($3.4\ 10^{-2}$ per Sv) was smaller than the mean. A sensitivity

analysis demonstrated that the main contributors to the total uncertainty were the DDREF (about 38% of the total), unspecified uncertainties (about 29%), and the transfer to the United States population (about 19%).

352. In a separate exercise supported by the United States Nuclear Regulatory Commission and the European Commission, uncertainties in cancer risk estimates were elicited from a series of experts [L27]. Using a formal analysis, the uncertainties provided by these experts were combined to obtain an overall distribution of uncertainty that took account of differences between the various subjective assessments. Table 38 shows the estimates of REID elicited for an acute dose of 1 Gy (low-LET) to a hypothetical European Union/United States population of all ages and both genders, together with the associated 90% confidence interval. For all cancers combined, the limits of the confidence interval range about a factor of three higher and lower around the median of 10.2%. This represents a slightly wider interval than that arising from the NCRP analysis [N17]. For specific cancer types, the uncertainty intervals in the European Union/United States analysis are wider, in relative terms, than the interval for all cancers combined, sometimes ranging from several order of magnitudes lower than the median value up to about an order of magnitude higher [L27]. However, these ranges encompassed previous estimates of risk.

CONCLUSIONS

353. Since the Committee's assessment of the risks of radiation-induced cancer in the UNSCEAR 1994 Report [U2], more information has become available from epidemiological studies of radiation-exposed groups. Some of this information relates to populations exposed to acute doses of external low-LET radiation. For example, mortality data have been updated to the end of 1990 for 86,572 survivors of the atomic bombings at Hiroshima and Nagasaki. As of December 1990, 56% of the survivors were still alive, and it was estimated that 421 excess cancers deaths had occurred; 334 from solid cancer and 87 from leukaemia. Both this study and further follow-up of patients who received medical radiation exposure have provided additional data on cancer risks at long times following irradiation, particularly for those exposed at young ages. However, there are still uncertainties in the projection of risks from the current follow-up periods until the end of life, given that most of the people who were irradiated at young ages are still alive.

354. The increased statistical precision associated with the longer follow-up and the resulting larger number of cancers in the above studies has also assisted in the examination of dose-response relationships, particularly at lower doses. For example, the most recent data for the Japanese atomic bomb survivors are largely consistent with linear or linear-quadratic dose trends over a wide range of doses. However, analyses restricted solely to low doses are complicated by the limitations of statistical precision, the potential for misleading findings owing to any small, undetected biases, and the effects of performing multiple tests of statistical significance when attempting to establish a minimum dose at which elevated risks can be detected. Longer follow-up of large groups such as the atomic bomb survivors will provide more information at low doses. However, epidemiology alone will not be able to resolve the issue of whether there are dose thresholds in risk. In particular, the inability to detect increases at very low doses using epidemiological methods does not mean that the underlying cancer risks are not elevated.

355. New findings have also been published from analyses of fractionated or chronic low-dose exposure to low-LET radiation, although the statistical precision of these studies is low in comparison with high-dose-rate results from the atomic bomb survivors. Analyses of data for nuclear workers indicate that the risk of leukaemia increases with increasing dose, whereas no dose response has been established for solid cancers. A comparison of the atomic bomb survivors with patients who received fractionated x-ray exposures in the course of treatment for tuberculosis suggests that dose fractionation may not reduce the risk of breast cancer, although this interpretation has been questioned in view of the potential effects of radiation quality. It is difficult to arrive at a definitive conclusion on the effects of dose rate on cancer risks, since the relevant epidemiological data are sparse and the effects may differ among cancer types. For example, no elevated risk of lung cancer was observed in tuberculosis patients who received fractionated exposures, whereas a statistically significant elevated risk was found in the atomic bomb survivors; however, the severity of tuberculosis may have affected the results for these patients.

356. Information on the effects of internal exposure, from both low- and high-LET radiation, has increased since the time of the UNSCEAR 1994 Report [U2]. In particular, the early reports of an elevation in thyroid cancer incidence in parts of the former Soviet Union contaminated as a result of the Chernobyl accident have been confirmed and suggest a link with radioactive iodine exposure during childhood. Nevertheless, risk estimation associated with these findings is still complicated by difficulties in dose estimation and in quantifying the effect of screening for the disease. This topic is considered in further detail in Annex J, *"Exposures and effects of the Chernobyl accident"*. Other studies in the former Soviet Union have provided further information relevant to internal exposures; for example, on lung, bone and liver cancers among workers at the Mayak plant and, to a lesser extent, on cancers among the population living near the Techa River, in both instances

in the southern Urals. However, the different sources of radiation exposure (both external and internal) and, in the case of the Techa River studies, the potential effects of migration, affect the quantification of risks. Results from several case-control studies of lung cancer and indoor radon have been published in recent years that, in combination, are consistent with extrapolations from data on radon-exposed miners, although the statistical uncertainties in the findings from the indoor studies are still too large to determine a reliable risk estimate.

357. Particular attention has been paid in this Annex to risks for specific cancer sites. Again, the information that has become available in recent years has helped in the examination of risks. However, there are still problems in characterizing risks for some cancer sites, owing to the low statistical precision associated with relatively small numbers of estimated excess cases. This can limit, for example, the ability to estimate trends in risk in relation to factors such as age at exposure, time since exposure, and gender. Furthermore, data are sometimes lacking or have not been published in a format that is detailed enough to allow an assessment of how risks vary among populations. An exception is breast cancer, where a comparison of data on the Japanese atomic bomb survivors and women with medical exposures in North America points to an absolute transfer of risks between populations. For some other sites, such as the stomach, there are indications that a multiplicative transfer between populations would be appropriate, although the evidence is generally not strong. There are some cancer sites for which there is little evidence for an association with radiation (e.g. non-Hodgkin's lymphoma, Hodgkin's disease, and multiple myeloma). While the risk evaluations for lymphomas are affected by the small numbers of cases in several studies, these results should be contrasted with the clear relation found in many populations between radiation and the risk of leukaemia (excluding CLL), which is also a rare disease.

358. The results presented in Tables 33–37 illustrate the sensitivity of lifetime risk estimates to variations in background rates. These findings suggest that this variability can lead to differences that are comparable to the variations associated with the transport method or method of risk projection. Issues of uncertainty in lifetime risk estimates are discussed in more detail in NCRP report 126 [N17]. The variability in these projections highlights the difficulty of choosing a single value to represent the lifetime risk of radiation-induced cancer. Furthermore, uncertainties in estimates of risk for specific types of cancer are generally greater than for all cancers combined.

359. Despite these difficulties, risk estimates are of considerable value for use in characterizing the impact of a radiation exposure on a population. Using the same approach taken in the UNSCEAR 1994 Report [U2], namely an age-at-exposure model applied to a Japanese population of all ages, the lifetime risk of exposure-induced death from all solid cancers combined following an acute dose of 1 Sv is estimated to be about 9% for men, 13% for women and 11% averaged over genders. The calculations in this Annex show that these values can vary among different populations and with different risk models. Overall, however, the risk estimates are consistent with the value of 10.9% for an acute dose of 1 Sv cited in the UNSCEAR1994 Report [U2]. The uncertainties in the above estimates may be of the order of a factor of 2, higher or lower. The estimates could be reduced by 50% for chronic exposures, again with an uncertainty factor of 2, higher or lower. Using the attained-age model, the estimated lifetime risks of exposure-induced death are about 70% of those based on the age-at-exposure model. Total solid cancer incidence risks can be taken as being roughly twice those for mortality. Lifetime solid cancer risk estimates for those exposed as children might be twice the estimates for a population exposed at all ages. However, continued follow-up of existing irradiated cohorts will be important in determining lifetime risks. The experience of the Japanese atomic bomb survivors is consistent with a linear dose-response for the risk of all solid cancers combined; therefore, as a first approximation, linear extrapolation of the estimates at 1 Sv acute dose can be used for estimating solid cancer risks at lower doses. For specific types of solid cancer, the risks estimated in this Annex are broadly similar to those presented in the UNSCEAR 1994 Report [U2].

360. The computations in this Annex suggest that lifetime risks for leukaemia are relatively invariant to the population used, both because an absolute risk transport model was used and because baseline rates of leukaemia, other than CLL, are less variable among populations than are baseline rates of solid cancers. For either gender, the lifetime risk of exposure-induced leukaemia mortality can be taken as 1% following an acute dose of 1 Sv. This is similar to the value of 1.1% at 1 Sv cited in the UNSCEAR 1994 Report [U2]. Based on a linear-quadratic dose-response model, decreasing the dose tenfold, from 1 Sv to 0.1 Sv, would be expected to reduce the lifetime risk estimate by a fraction of 20. Thus, the lifetime risk of exposure-induced death for leukaemia can be estimated as 0.05%, for either gender, following an acute dose of 0.1 Sv. No further reduction for chronic exposures is necessary. The uncertainty in the leukaemia risk estimate may be on the order of a factor of 2, higher or lower.

Table 1
Examples of high and low cancer rates in various populations [a] [b]
[P5]

Site of cancer	*Sex*	*High cancer incidence*		*Low cancer incidence*	
		Population	*Rate*	*Population*	*Rate*
Nasopharynx	Males	Hong Kong Singapore (Chinese) United States, San Francisco (Chinese)	24.3 18.5 11.6	Canada, Nova Scotia United States, New Mexico (Non-Hispanic white) Ireland, Southern	0.1 0.2 0.2
	Females	Hong Kong Singapore (Chinese) Canada, Northwest Territories	9.5 7.3 5.1	United Kingdom, south-western Finland Norway	0.1 0.1 0.1
Oesophagus	Males	United States, Connecticut (black) Hong Kong France, Haut Rhin	20.1 14.2 14.2	Israel (non-Jews) Italy, Sicily (Ragusa Province) Thailand, Chiang Mai	0.5 1.0 2.3
	Females	India, Bombay China, Tianjin United Kingdom, Scotland, West	8.3 6.2 5.2	United States, New Mexico (American Indian) Spain, Tarragona Israel (non-Jews)	0.2 0.2 0.2
Stomach	Males	Japan, Yamagata China, Shanghai Italy, Romagna	95.5 46.5 39.3	United States, Atlanta (white) Israel (non-Jews) Thailand, Chiang Mai	5.2 6.8 7.5
	Females	Japan, Yamagata Italy, Romagna China, Shanghai	40.1 22.8 21.0	United States, Iowa Israel (non-Jews) Canada, Saskatchewan	2.2 3.2 3.7
Colon	Males	United States, Detroit (black) United States, Hawaii (Japanese) Japan, Hiroshima	35.0 34.4 31.6	India, Madras Thailand, Chiang Mai Peru, Trujillo	1.8 4.2 4.4
	Females	New Zealand (non-Maori) Canada, Newfoundland United States, Detroit (black)	29.6 28.1 27.9	India, Madras Thailand, Chiang Mai Singapore (Indian)	1.3 3.7 4.7
Liver	Males	Japan, Osaka China, Shanghai United States, Los Angeles (Korean)	46.7 28.2 23.9	Canada, Prince Edward Island Netherlands, Eindhoven United Kingdom, south-western	0.7 1.3 1.6
	Females	Japan, Osaka China, Shanghai Thailand, Chiang Mai	11.5 9.8 9.7	Australia, Tasmania Canada, Prince Edward Island India, Madras	0.3 0.3 0.5
Lung and bronchus	Males	United States, New Orleans (black) New Zealand (Maori) Canada, Northwest Territories	110.8 99.7 90.3	United States, New Mexico (American Indian) Peru, Trujillo India, Madras	10.3 11.9 12.6
	Females	New Zealand (Maori) Canada, Northwest Territories United States, San Francisco (black)	72.9 65.6 44.3	India, Madras Spain, Zaragoza Malta	2.4 2.7 3.4
Melanoma of skin	Males	Australia, New South Wales New Zealand (non-Maori) United States, Hawaii (white)	33.1 25.0 19.5	Japan, Osaka China, Shanghai India, Bombay	0.2 0.3 0.4
	Females	New Zealand (non-Maori) Australia, New South Wales Austria, Tyrol	29.8 25.7 15.6	Japan, Osaka China, Shanghai India, Bombay	0.2 0.3 0.3
Breast	Females	United States, Los Angeles (Non-Hisp white) United States, Hawaii (white) Israel (Jews born in Israel)	103.7 96.5 90.5	Thailand, Chiang Mai Israel (non-Jews) United States, Los Angeles (Korean)	14.6 21.3 21.4
Cervix	Females	Peru, Trujillo India, Madras Colombia, Cali	53.5 38.9 34.4	Israel (non-Jews) China, Shanghai Finland	3.0 3.3 3.6

Table 1 (continued)

Site of cancer	*Sex*	*High cancer incidence*		*Low cancer incidence*	
		Population	*Rate*	*Population*	*Rate*
Prostate	Males	United States, Atlanta (black) United States, Hawaii (white) Canada, British Columbia	142.3 108.2 84.9	China, Tianjin India, Madras Thailand, Chiang Mai	1.9 3.6 4.1
Bladder	Males	Italy, Trieste Spain, Mallorca Switzerland, Geneva	38.7 36.4 32.5	United States, New Mexico (American Indian) United States, Hawaii (Hawaiian) Canada, British Columbia	2.6 3.9 11.3
	Females	Italy, Trieste Denmark United Kingdom, Scotland, West	9.4 7.7 7.5	United States, New Mexico (American Indian) France, Isere United States, Hawaii (Filipino)	0.6 2.6 2.7
Brain, central nervous system	Males	Italy, Trieste Iceland United States, Hawaii (white)	9.5 9.4 8.7	Singapore (Malay) Japan, Yamagata Thailand, Chiang Mai	1.6 1.8 2.0
	Females	Italy, Trieste Poland, Warsaw city United States, Atlanta (white)	8.7 5.9 5.8	United States, Los Angeles (Chinese) India, Madras Japan, Yamagata	1.1 1.1 1.7
Thyroid	Males	Iceland United States, Hawaii (Filipino) United States, Los Angeles (Filipino)	6.1 5.1 4.0	United Kingdom, Wessex Estonia Denmark	0.7 0.7 0.8
	Females	United States, Hawaii (Filipino) United States, Los Angeles (Filipino) Italy, Ferrara	25.5 11.2 11.1	India, Madras United Kingdom, Yorkshire Netherlands, Eindhoven	1.6 1.7 1.9
Non-Hodgkin's lymphoma	Males	United States, San Francisco (non-Hisp white) Italy, Romagna United States, Hawaii (white)	25.0 15.5 15.1	India, Madras Thailand, Chiang Mai Singapore (Indian)	3.7 3.8 3.9
	Females	Italy, Ferrara Israel (Jews born in Israel) United States, San Francisco (Hispanic white)	11.5 11.1 11.0	India, Madras China, Shanghai Estonia	2.0 2.5 2.5
Hodgkin's disease	Males	United States, San Francisco (non-Hisp white) Italy, Veneto Israel (Jews born in Israel)	4.3 4.0 3.2	China, Tianjin Japan, Miyagi Singapore (Chinese)	0.3 0.4 0.5
	Females	United States, Connecticut (white) Italy, Veneto Israel (Jews born in America or Europe)	3.6 3.5 3.1	Japan, Osaka China, Shanghai Hong Kong	0.2 0.3 0.3
Multiple myeloma	Males	United States, Los Angeles (black) New Zealand (Maori) Australian Capital Territory	9.5 5.7 5.4	Thailand, Chiang Mai China, Tianjin United States, Los Angeles (Japanese)	0.4 0.4 0.5
	Females	United States, Detroit (black) New Zealand (Maori) United States, Hawaii (Hawaiian)	6.4 5.8 4.2	Thailand, Chiang Mai China, Tianjin India, Madras	0.3 0.3 0.4
Leukaemia	Males	Italy, Trieste Australia, South Australia United States, Detroit (white)	15.0 13.3 12.7	India, Madras Singapore (Indian) Japan, Yamagata	3.0 3.0 4.4
	Females	Italy, Trieste Australia, South Australia United States, San Francisco (Filipino)	9.0 8.9 8.4	United States, Central Louisiana (black) India, Madras Japan, Miyagi	1.6 2.0 3.3

a Numbers given are age-standardized (world) annual incidence per 100,000 population.

b Registries for which IARC [P5] indicated problems in ascertainment have not been included in this Table. However, some of the differences in rates may be due in part to variations in the level of ascertainment and to random variation.

Table 2
Cohort and case-control epidemiological studies of the effects of exposures to low-LET radiation

Study	*Type of study*	*Population studied*		*Follow-up (years)*	*Total person years* [a]	*Type of exposure*	*Type of dosimetry*	*Cancers studied* [b]
		Characteristics	*National origin*					
EXTERNAL HIGH-DOSE-RATE EXPOSURES								
Exposure to atomic bombings								
Life Span Study [P9]	Mortality	50 113 exposed persons [c] 36 459 unexposed persons 55.5% females Age: 0–>90 (28.4) [d]	Japan	5–45	2 812 863 (32.5)	Gamma and neutron radiation from nuclear explosions	Individual estimates derived from detailed shielding histories	Leukaemia*, tongue, pharynx, oesophagus*, stomach*, colon*, rectum, liver*, gallbladder, pancreas, nose, larynx, lung*, bone, skin, female breast*, cervix uteri and uterus, ovary*, prostate, bladder, kidney, brain, other central nervous system, lymphoma, myeloma*
Life Span Study [P4, T1]	Incidence	37 270 exposed persons [e] 42 702 unexposed persons 55.5% females Age: 0–>90 (26.8)	Japan	13–42 [f]	1 950 567 [g] (24.4)	Gamma and neutron radiation from nuclear explosions	Individual estimates derived from detailed shielding histories	Leukaemia*, non-Hodgkin's lymphoma*, myeloma, oral cavity, salivary gland*, oesophagus, stomach*, colon*, rectum, liver*, gallbladder, pancreas, lung*, female breast*, non-melanoma skin*, uterus, ovary*, prostate, bladder*, central nervous system, thyroid*
Survivors of atomic bombings (*in utero*) [D14, Y1]	Mortality/ Incidence	1 078 exposed persons [h] 2 211 unexposed persons 50.7% females Exposure: *in utero*	Japan	5–47	n.a. [i]	Maternal exposure to gamma and neutron radiation at high dose rate	Mother's estimated uterus dose	Leukaemia, all solid cancers
Treatment of malignant disease								
Cervical cancer cohort [B11]	Incidence	82 616 exposed women 99 424 unexposed women Age: <30–>70 (26.8)	Canada, Denmark, Finland, Norway, Slovenia, Sweden, United Kingdom, United States	1–>30	1 278 950 (7.0)	Radiotherapy, including external beam and intra-cavity application and experimental reconstruction	Data on typical range of estimates for specific organs and phantom measurements	Oral cavity, salivary gland, oesophagus*, stomach, small intestine*, colon, rectum*, liver, gallbladder, pancreas*, lung*, breast, uterus, other genital*, kidney, bladder, melanoma, other skin, brain, thyroid, bone, connective tissue, leukaemia (non-CLL)*, myeloma, lymphoma
Lung cancer following breast cancer [I7]	Case-control 61 cases 120 controls from a cohort of 27 106 women	38 exposed women 143 unexposed women Age: 35–72 (50)	United States	10–46 (18 years per case)	n.a.	Radiotherapy	Individual doses from therapy records and experimental measurements	Lung cancer

Table 2 (continued)

Study	*Type of study*	*Population studied*		*Follow-up (years)*	*Total person years* [a]	*Type of exposure*	*Type of dosimetry*	*Cancers studied* [b]
		Characteristics	*National origin*					
Cervical cancer case-control [B1, B12, B50]	Case-control 4 188 cases 6 880 controls	10 286 exposed women 782 unexposed women Age: <30–>70 (26.8)	Austria, Canada, Czech Republic, Denmark, Finland, France, Germany, Iceland, Italy, Norway, Slovenia, Sweden, United Kingdom, United States	0–>30 (7.0 years per case)	n.a.	Radiotherapy, including external beam and intra-cavity application and experimental reconstruction	Individual doses from therapy records	Stomach*, pancreas, small intestine, colon, rectum*, breast, uterine corpus*, vagina*, ovary, vulva, bladder*, bone, connective tissue, leukaemia (non-CLL)*, myeloma, lymphoma, thyroid
Contralateral breast cancer, United States [B10]	Case-control 655 cases 1 189 controls from a cohort of 41 109 women	449 exposed women 1 395 unexposed women Age: <45–>60 (51)	United States	7–55 (~13 years per case)	n.a.	Radiotherapy	Individual doses from therapy records and experimental measurements	Contralateral breast among women less than 45 years old at exposure*, contralateral breast in older women
Contralateral breast cancer, Denmark [S20]	Case-control 529 cases 529 controls from a cohort of 56 540 women	157 exposed women 901 unexposed women Age: <45–>60 (51)	Denmark	12–47 (~16 years per case)	n.a.	Radiotherapy	Individual doses from therapy records and experimental measurements	Contralateral breast
Soft tissue sarcoma following breast cancer [K35]	Case-control 107 cases 321controls from a cohort of 122 991 women	310 exposed women 86 unexposed women 32 women with unknown exposure status Age: 29–86 (59)	Sweden	1–35 (10 years per case)	n.a.	Radiotherapy	Total absorbed energy from radiotherapy, and location of sarcoma in relation to the treatment region	Soft tissue sarcoma
Leukaemia following breast cancer [C9]	Case-control 90 cases 264 controls from a cohort of 82 700 women	110 exposed women 244 unexposed women Age: <50–>70 (61)	United States	<12 (~5 years per case)	n.a.	Adjuvant radiotherapy	Individual doses from therapy records and experimental measurements	Acute non-lymphocytic leukaemia and myelodysplastic syndrome*, chronic myelogenous leukaemia, acute lymphocytic leukaemia
Leukaemia following cancer of the uterine corpus [C10]	Case-control 218 cases 775 controls from a cohort of 110 000 women	612 exposed women 351 unexposed women 30 women with unknown exposure status Age: <55–>75 (62)	Canada, Denmark, Finland, Norway, United States	1–50	n.a.	Radiotherapy	Individual doses from therapy records and experimental measurements	Leukaemia*
Lung cancer following Hodgkin's disease (international) [K9]	Case-control 98 cases 259 controls	303 exposed persons 54 unexposed persons 15% female	Canada, Denmark, Finland, France, Norway, Slovenia, United Kingdom	1–>10	n.a.	Radiotherapy	Individual doses from therapy records and experimental measurements	Lung cancer

Table 2 (continued)

Study	*Type of study*	*Population studied*		*Follow-up (years)*	*Total person years* [a]	*Type of exposure*	*Type of dosimetry*	*Cancers studied* [b]
		Characteristics	*National origin*					
Lung cancer following Hodgkin's disease (Netherlands) [V2]	Case-control 30 cases 82 controls from a cohort of 1 939 patients	101 exposed persons 11 unexposed persons 4% female Age: <45–>55 (49.4)	Netherlands	1–23	n.a.	Radiotherapy	Individual doses from therapy records and experimental measurements	Lung cancer*
Breast cancer following Hodgkin's disease [H2]	Incidence/ Mortality	855 exposed women 30 unexposed women Age: 4–81 (28)	United States	0–29	8 832 (10)	Radiotherapy	Individual doses from therapy records	Breast cancer*
Leukaemia following Hodgkin's disease (international) [K40]	Case-control 163 cases 455 controls from a cohort of 29 552 patients	36% exposed 35% females Age: (40)	Canada, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Slovenia, United Kingdom	1–>10	n.a.	Radiotherapy	Individual doses from therapy records and experimental measurements	Leukaemia (non-CLL)
Leukaemia following non-Hodgkin's lymphoma (international) [T6]	Case-control 35 cases 140 controls from a cohort of 11 386 women	123 exposed persons 52 unexposed persons Age: <50–70	Canada, Netherlands, Sweden, United States	2–25 (7.6 years per case)	n.a.	Radiotherapy	Individual doses from therapy records and experimental measurements	Leukaemia
Leukaemia following non-Hodgkin's lymphoma (United States) [T15]	Incidence	61 exposed persons 50% females Age: 18–70 (49.5)	United States	2–22	590 (9.7)	Total body irradiation	Individual doses from therapy records and experimental measurements	Acute non-lymphocytic leukaemia*, all solid cancers
Childhood cancers (international) [T5, T7, T17]	Case-control 23 thyroid cancers / 89 controls 25 leukaemia / 90 controls 64 bone cancers/ 209 controls from a cohort of 9 170 members	112 exposed persons 388 unexposed persons 45% females Age: 0–18 (7)	Canada, France, Netherlands, Italy, United Kingdom, United States	5–48	50 609 (5.5)	Adjuvant radiotherapy	Individual doses from therapy records and experimental measurements	Thyroid*, leukaemia, bone sarcoma*

Table 2 (continued)

Study	*Type of study*	*Population studied*		*Follow-up (years)*	*Total person years* [a]	*Type of exposure*	*Type of dosimetry*	*Cancers studied* [b]
		Characteristics	*National origin*					
Childhood cancers (France/U.K.) [D19, D33]	Incidence	3 109 exposed persons 1 291 unexposed persons 45% females Age: 0–16 (7)	France, United Kingdom	3–48	66 000 (15)	External radiotherapy	Individual doses from therapy records and experimental measurements	All solid cancers combined*, breast*, bone*, soft tissue sarcoma*, thyroid*, brain*
Bone cancer after childhood cancer (United Kingdom) [H44]	Case-control, 59 cases 220 controls, largely within a 13 175-member cohort	208 exposed persons 71 unexposed persons Age: 0–14	United Kingdom	3–>20	n.a.	External radiotherapy	Individual doses from therapy records and experimental measurements	Bone cancer
Leukaemia after childhood cancer (UK) [H11]	Case-control 26 cases 96 controls	88 exposed persons 34 unexposed persons Age: 0–14	United Kingdom	1–43	n.a.	External radiotherapy	Individual doses from therapy records and experimental measurements	Leukaemia
Retinoblastoma [W11]	Incidence	962 exposed persons 642 unexposed persons 47% females Age: 0–17	United States	1–>60	n.a. (Median 20)	External radiotherapy	Individual doses from therapy records and experimental measurements	Soft tissue sarcoma*, bone and soft tissue sarcoma*, all other cancers
Thyroid cancer following childhood cancer [D20]	Incidence	2 827 exposed persons	France, United Kingdom	3–29	n.a.	External radiotherapy	Individual doses from therapy records and experimental measurements	Thyroid cancer*
Childhood Hodgkin's disease [B16]	Incidence	1 380 persons 8% unexposed 35% female Age: 1–16 (median 11)	Canada, France, Italy, United Kingdom, United States	0–37 (median 11.4)	15 660 (11.3)	Radiotherapy	Individual doses from therapy records and experimental measurements	Leukaemia*, non-Hodgkin's lymphoma*, breast*, thyroid*, other solid cancers*
Treatment of benign disease								
Childhood skin haemangioma: Stockholm [K23, L13, L16, L17, L24, L46]	Incidence/ Mortality	14 351 exposed persons [j] 67% females Age: 0–1.5 (0.5)	Sweden	1–67	406 355 (39)	Radiotherapy	Individual organ doses from therapy records and phantom measurements	Thyroid*, breast*, leukaemia, all other sites
Childhood skin haemangioma: Gothenburg [K22, K23, L15, L46]	Incidence	11 914 exposed persons 88% aged <1 year	Sweden	0-69	370 517 (31.1)	Radiotherapy	Individual organ doses from therapy records and phantom measurements	Thyroid*, other endocrine glands*, central nervous system*, all other sites

Table 2 (continued)

Study	*Type of study*	*Population studied*		*Follow-up (years)*	*Total person years* [a]	*Type of exposure*	*Type of dosimetry*	*Cancers studied* [b]
		Characteristics	*National origin*					
Benign lesions in locomotor system [D12, J2]	Incidence/ Mortality	20 024 exposed persons 49% females Age: <20–>70 (53)	Sweden	Up to 38	Incidence: 493 400 (24.6) Mortality: 392 900 (19.6)	X-ray therapy	Individual red bone marrow doses from therapy records and phantoms	Leukaemia*, non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma
Ankylosing spondylitis [W1, W2] [k]	Mortality	13 914 exposed persons 16.5% females Age: <20–>60	United Kingdom	1–57	245 413 (17.6)	X-ray therapy	Individual doses for leukaemia cases and a 1 in 15 sample of the population	Leukaemia*, other neoplasms* (except colon)
Israel tinea capitis [R5, R9, R16, R17]	Incidence/ Mortality	10 834 exposed persons 16 226 unexposed persons 50% females Age: <1–15 (7.1)	Israel	26–38	686 210 (25.3)	X-ray induced epilation	Individual doses from phantom measurements based on institution and age	Incidence: thyroid*, skin*, brain*, salivary gland*, breast Mortality: head and neck*, leukaemia*
New York tinea capitis [S27, S30]	Incidence	2 226 exposed persons 1 387 unexposed persons 16.1% females Age: <1–19 (7.7)	United States	20–39	98 881 (25.4)	X-ray induced epilation	Representative doses based on standard treatment	Thyroid*, skin*, brain, leukaemia, salivary gland
New York acute post-partum mastitis [S15, S30]	Incidence	571 exposed women 993 unexposed women Age: 14–>40 (27.8)	United States	20–35	38 784 (25.1)	X-ray therapy	Individual doses from therapy records	Breast*
Rochester thymic irradiation [H10, H31, S30]	Incidence	2 652 exposed persons 4 823 unexposed persons 42% females Age: 0–1	United States	23–>50	220 777 (29.5)	X-ray therapy	Individual doses from therapy records	Thyroid*, breast*, skin
Tonsil irradiation [S21, S28, S30]	Incidence	2 634 exposed persons [l] 40.7% females Age: 0–15 (4.3)	United States	0–50	88 101 (33)	X-ray therapy	Individual doses from therapy records and phantom measurements	Skin*, thyroid*, benign parathyroid*, salivary gland*, neural tumours*
Tonsil, thymus or acne irradiation [D5]	Incidence	416 exposed persons Age:(7.1)	United States	n.a.	11 000 (26.4)	Radiotherapy	Individual doses from therapy records	Thyroid*
Swedish benign breast disease [M8, M20, M28]	Incidence	1 216 exposed women 1 874 unexposed women Age: 10–>85	Sweden	5–60	56 900 (18)	X-ray therapy	Individual doses from therapy records and phantom measurements	Breast*, all other sites

Table 2 (continued)

Study	*Type of study*	*Population studied*		*Follow-up (years)*	*Total person years* [a]	*Type of exposure*	*Type of dosimetry*	*Cancers studied* [b]
		Characteristics	*National origin*					
Metropathia haemorrhagica [D7]	Mortality	2 067 exposed women Age: 35–60	United Kingdom	5–>30	53 144	X-ray therapy	Individual doses from therapy records and phantom measurements	Pelvic sites*, leukaemia* multiple myeloma*, lymphoma, all other sites [m]
Benign gynaecological disease [I6, I16]	Mortality	4 153 exposed women Age: 13–88 (46.6)	United States	0–60	109 910 (26.5)	Intrauterine ^{226}Ra	Individual doses from therapy records and phantom measurements	Leukaemia*, other haematolymphopoietic cancers, uterus*, bladder*, rectum*, other genital*, colon, bone (in pelvis), liver and gallbladder, stomach, kidney, pancreas*
Lymphoid hyperplasia screening [P8]	Incidence/ Prevalence	1 195 exposed persons 1 063 unexposed persons 40% females Age: 0–17 (6.9)	United States	12–44	66 000 (29)	X-ray therapy	Individual doses from therapy records and phantom measurements	Thyroid nodular disease*
Peptic ulcer [G6]	Mortality	1 831 exposed persons 1 778 unexposed persons 21.2% females Age: <35–>55 (49)	United States	20–51	77 757 (21.5)	X-ray therapy	Individual doses from therapy records and experimental measurements	Stomach*, colon, pancreas*, lung*, leukaemia*,female breast, oesophagus, rectum, liver, larynx, bone and connective tissue, bladder, prostate, kidney, brain, thyroid, non-Hodgkin's lymphoma, Hodgkin's disease, myeloma
Diagnostic examinations								
Massachusetts TB fluoroscopy [B3, S30]	Incidence	2 367 exposed women 2 427 unexposed women Age: 12–50 (26)	United States	0–>50	54 609 (11.4)	Multiple x-ray chest fluoroscopies	Individual exposures from medical records and doses from phantom measurements and computer simulations	Breast*, skin
Massachusetts TB fluoroscopy [D4]	Mortality	6 285 exposed persons 7 100 unexposed persons 49% females Age: 12–50 (26)	United States	0–>50	331 206 (24.7)	Multiple x-ray chest fluoroscopies	Individual exposures from medical records and doses from phantom measurements and computer simulations	Breast*, oesophagus*, lung, leukaemia
Canadian TB fluoroscopy [H7, H20]	Mortality	25 007 exposed persons 39 165 unexposed persons 50% females Age: <20–>35 (28)	Canada	0–57	1 608 491 (25.1)	Multiple x-ray chest fluoroscopies	Individual exposures from medical records and doses from phantom measurements	Lung, breast*
Diagnostic x rays (US health plans) [B39]	Case-control 565 leukaemia 318 NHL 208 multiple myeloma 1 390 controls	2 203 exposed persons 278 unexposed persons 39% females Age: 15–>50	United States	n.a.	n.a.	Diagnostic x rays	Average dose based on number and type of procedures and estimated doses from published literature	Leukaemia, non-Hodgkin's lymphoma, multiple myeloma

Table 2 (continued)

Study	*Type of study*	*Population studied*		*Follow-up (years)*	*Total person years* [a]	*Type of exposure*	*Type of dosimetry*	*Cancers studied* [b]
		Characteristics	*National origin*					
Medical and dental x rays (Los Angeles) [P35]	Case-control 408 cases 408 controls	62% females	United States	2–64	n.a.	Medical and dental diagnostic x rays	Average dose based on number and type of procedures and estimated doses from published literature	Parotid gland*
Diagnostic x rays (Los Angeles) [P10]	Case-control 130 cases 130 controls	39% females	United States	3–20	n.a.	Diagnostic x rays	Average dose based on number and type of procedures and estimated doses from published literature	Chronic myeloid leukaemia*
Diagnostic x rays (Sweden) [I9]	Case-control 484 cases 484 controls	736 exposed persons 232 unexposed persons 77% females Age: <20–>60	Sweden	5–>50	n.a.	Diagnostic x rays	Average dose based on number and type of procedures and estimated doses from published literature	Thyroid
Scoliosis [D34]	Mortality	4 822 exposed women 644 unexposed women Age: <3–≥10 (10.6)	United States	3->60	218 976 (40.1)	Diagnostic x-rays	Average dose based on number of treatments and estimated doses from published literature	Breast*
EXTERNAL LOW-DOSE OR LOW-DOSE-RATE EXPOSURES								
Prenatal exposure								
Oxford Survey of Childhood Cancers [S1, B2, M29]	Case-control 14 491 cases 14 491 controls	3 797 exposed persons 25 185 unexposed persons 56 % females Exposure: *in utero*	United Kingdom	16 (max.)	n.a.	Maternal x rays during pregnancy	Number of exposures with a model for dose per exposure	Leukaemia*, all solid tumours*
NE USA childhood cancers [M9]	Case-control 1 342 cases 14 292 controls	1 506 exposed persons 14 130 unexposed persons 49.2 % females Exposure: *in utero*	United States	20 (max.)	n.a.	Maternal x rays during pregnancy	Number of exposures	Leukaemia*, solid tumours
Occupational exposure								
Nuclear workers in Japan [E3]	Mortality	114 900 men	Japan	Up to 5	533 168 (4.6)	Exposures in nuclear power plants, fuel processing, and research facilities	Recorded exposures to external radiation	Leukaemia, all other cancers

Table 2 (continued)

Study	*Type of study*	*Population studied*		*Follow-up (years)*	*Total person years* [a]	*Type of exposure*	*Type of dosimetry*	*Cancers studied* [b]
		Characteristics	*National origin*					
Nuclear workers in Canada, United Kingdom and United States [C11] [n]	Mortality	95 673 workers 15% females	Canada United Kingdom United States	Up to 43	2 124 526 (22.2)	Exposures in nuclear power plants, fuel processing, and research facilities	Recorded exposures to external radiation	Leukaemia, all other cancers
National Registry for Radiation Workers, U.K. [M46] [o]	Mortality	124 743 monitored workers 9% females	United Kingdom	Up to 47	2 063 300 (16.5)	Exposures in nuclear power plants, fuel cycle, defence, and weapons production	Recorded exposures to external radiation	Leukaemia, all other cancers
Sellafield [C19, D21] [p]	Mortality / Incidence	10 028 monitored workers 3 711 other workers 19% females	United Kingdom	Up to 40	260 000 [q] (26)	Fuel processing and reactor operation	Recorded exposures to external radiation	Leukaemia, all other cancers
UK Atomic Energy Authority [C19, F6] [p]	Mortality / Incidence	21 344 monitored workers 18 071other workers 8% females	United Kingdom	Up to 42	534 000 [q] (25)	Nuclear and reactor research and fuel processing	Recorded exposures to external radiation	Leukaemia, all other cancers
UK Atomic Weapons Establishment [C19, B24] [p]	Mortality	9 389 monitored workers 12 463 other workers 9% females	United Kingdom	Up to 37	216 000 [q] (23)	Weapons research	Recorded exposures to external radiation	Leukaemia, all other cancers
Chapelcross [B38, M50]	Mortality/ Incidence	2 209 monitored workers 419 other workers 14% females	United Kingdom	Up to 41	63 967 (24.3)	Reactor operation	Recorded exposures to external radiation	Buccal cavity and pharynx, prostate, all cancers combined
National Dose Registry of Canada [A21] [r]	Mortality	206 620 monitored workers 49% females	Canada	Up to 47	2 861 093 (13.8)	Dental, medical, industrial and nuclear power	Recorded exposures to external radiation	Leukaemia, all other cancers
Atomic Energy of Canada Ltd. [C11, G16] [s]	Mortality	11 355 monitored workers 24% females	Canada	Up to 30	198 210 (17.5)	Nuclear and reactor research and related technologies	Recorded exposures to external radiation	Leukaemia, all other cancers
Hanford [G12, G17] [t]	Mortality	32 643 monitored workers 24% females	United States	Up to 43	633 511 (19.4)	Exposures in nuclear fuel cycle and research	Recorded exposures to external radiation	Leukaemia, all other cancers
Oak Ridge: X-10 and Y-12 plants [F5]	Mortality	28 347 men	United States (white)	Up to 40	n.a.	Exposures in nuclear fuel cycle and research	Recorded exposures to external radiation	Leukaemia, all other cancers

Table 2 (continued)

Study	*Type of study*	*Population studied*		*Follow-up (years)*	*Total person years* [a]	*Type of exposure*	*Type of dosimetry*	*Cancers studied* [b]
		Characteristics	*National origin*					
Rocky Flats [G12, W12]	Mortality	5 952 men	United States (white)	Up to 32	81 237 (13.6)	Exposures in nuclear fuel cycle and research	Recorded exposures to external radiation	Leukaemia, all other cancers
Portsmouth Naval Shipyard [R12]	Mortality	Males 8 960 monitored workers 15 585 other workers	United States (white)	Up to 26	n.a.	Work on overhauling and building nuclear submarines	Recorded exposures to external radiation	Leukaemia, all lymphatic and haemato-poietic neoplasms, all cancers combined
Rocketdyne / Atomics International [R27]	Mortality	4 563 monitored workers 6% females	United States	Up to 45	118 749 (26)	Exposures at a nuclear research and production facility	Recorded exposures to external radiation	Leukaemia, all other cancers
Mound facility [W21]	Mortality	Males 3 229 monitored workers 953 other workers	United States (white)	Up to 33	78 600 (18.8)	Exposures at a nuclear research and production facility	Recorded exposures to external radiation	Leukaemia, all other cancers
Chernobyl clean-up workers: Russian Fed. (cohort) [I13, I21] [u]	Incidence	114 504 male workers Age: <2--≥61	Russian Federation	0–9	797 781 (7.0)	Emergency and recovery work in the vicinity of Chernobyl	Assessed external radiation dose	Digestive*, respiratory, thyroid, all solid tumours combined, leukaemia*
Chernobyl clean-up workers: Russian Fed. (Leukaemia case-control) [I14]	Case-control 34 cases 136 controls from a cohort of 155 680 men	Males 87.3% with doses above 0.05 Sv Age: <20–>55	Russian Federation	2–7	n.a.	Emergency and recovery work in the vicinity of Chernobyl	Assessed external radiation dose	Leukaemia
Chernobyl clean-up workers: Estonia [I10, R20, T13]	Mortality Incidence	4 742 men Age: <30–>60	Estonia	0–7	30 643 (6.5)	Emergency and recovery work in the vicinity of Chernobyl	Recorded radiation doses	Thyroid, all other sites
Mayak workers [K10, K11, K32, K34]	Mortality	15 601 persons monitored for external radiation 3 229 other workers 25% females [v]	Russian Federation	0–46	211 427 (31.8) [w]	Exposures in nuclear fuel cycle and research	Recorded exposures to external radiation	Lung, leukaemia*
Mayak workers: stomach cancer study [Z1]	Case-control 157 cases 346 controls	40 persons with external doses above 3 Gy 463 with lower doses 10% females	Russian Federation	Up to 37	n.a.	Exposures in nuclear fuel cycle and research	Recorded exposures to external radiation and measurements of plutonium	Stomach*

Table 2 (continued)

Study	*Type of study*	*Population studied*		*Follow-up (years)*	*Total person years* [a]	*Type of exposure*	*Type of dosimetry*	*Cancers studied* [b]
		Characteristics	*National origin*					
Japanese radiological technologists [A25]	Mortality	9 179 radiological technologists (2 300 with recorded doses)	Japan	Up to 28	n.a.	Radiology	Recorded exposures to external radiation	All cancers combined*, oesophagus, stomach, colorectal, lung
Danish radio-therapy staff [A15]	Incidence	4 151 persons Age: <20–≥50	Denmark	Up to 32	49 553 (11.9)	Work in radio-therapy departments	Recorded exposures to external radiation	Leukaemia, prostate*, all other cancers
Natural radiation								
Yangjiang [A11, S35, T12, T25, T26, Z2 [x]]	Mortality	89 694 persons in high-background area 35 385 persons in control area 50% females All ages	China	Up to 17	1 698 350 (13.6)	Continuous background radiation	Individual estimates, both direct (TLD measurements) and indirect (environmental measurements and occupancy patterns)	Leukaemia, all other sites
Central Italy [F7]	Case-control 44 cases 211 controls	Males Age at diagnosis: 35–80 (68) 76% with gamma dose rate above 300 nGy h^{-1}	Italy	10	n.a.	Gamma radiation Radon	Measurements in last dwelling occupied and characteristics of dwellings	Acute myeloid leukaemia
INTERNAL LOW-DOSE-RATE EXPOSURES								
Medical exposures								
Diagnostic ^{131}I [H4, H12, H27] [y]	Incidence	34 104 exposed persons 80% females Age: 1–75 (43)	Sweden	5–39	653 093 (19.1)	Diagnostic ^{131}I	Individual values of activity administered; organ dose estimates for thyroid	Thyroid, leukaemia, all other sites
Swedish ^{131}I hyperthyroidism [H23, H24] [z]	Incidence/ Mortality	10 522 exposed persons 82% females Age: 13–70	Sweden	1–26	139 018 (13.6)	Treatment of hyperthyroidism	Average administered activity (multiple treatments)	Stomach*, kidney*, brain*, all other sites [aa]
United States thyrotoxicosis patients [D22, R14, S36] [bb]	Incidence/ Mortality	23 020 exposed persons 12 573 unexposed persons 79% females Age: <10–80	United States	0–45	738 831 (20.8)	Treatment of hyperthyroidism	Individual values of activity administered; organ-dose estimates	Buccal cavity, oesophagus, stomach, colorectal, liver, pancreas, larynx, lung*, breast*, uterus, ovary, prostate, bladder, kidney*, brain and other central nervous system tumours, thyroid*, lymphoma, myeloma, leukaemia

Table 2 (continued)

Study	*Type of study*	*Population studied*		*Follow-up (years)*	*Total person years* [a]	*Type of exposure*	*Type of dosimetry*	*Cancers studied* [b]
		Characteristics	*National origin*					
Iodine-131 hyperthyroidism, United Kingdom [F8]	Incidence/ Mortality	7 417 exposed persons 83% females Age: ≤49–≥70 (57)	United Kingdom	1–≥20	72 073 (9.7)	Treatment of hyper-thyroidism	Individual values of activity administered	Thyroid*, bladder, uterine, small bowel*, all other sites
Swedish ^{131}I thyroid cancer [H26]	Incidence	834 exposed persons 1 121 unexposed persons 75% females Age: 5–75 (48)	Sweden	2–34	25 830 (13.2)	Treatment of thyroid cancer	Individual values of activity administered	Leukaemia, salivary glands*, kidney*, all other sites
French therapeutic ^{131}I [D18]	Incidence	846 persons with therapeutic exposures 501 persons with diagnostic exposures 274 unexposed persons 79 % females Age: 5–89 (40)	France	2–37	14 615 (10)	Diagnostic and therapeutic ^{131}I exposures for thyroid cancer patients	Individual values of activity administered and organ dose estimates	Colon, leukaemia, all other sites
Environmental exposures								
Techa River population [K5, K27]	Mortality	26 485 exposed persons 58% females Age: 0–96 (29)	Russian Federation (ethnic Russians and Tartars/ Bashkirs)	Up to 39	n.a.	Internal and external exposures to radioactive waste discharged by nuclear weapons production plant	Dose reconstruction based on environmental measurements of gamma dose rate and whole-body counting	Leukaemia*, lymphoma, stomach, liver, lung, breast, bone, all other sites
Chernobyl-related exposure in Belarus [A26]	Case-control 107 cases 214 controls	52% females Age: 0–16	Belarus	Up to 6	n.a.	Internal exposure to radioactive iodine in areas contaminated by the Chernobyl accident	^{131}I dose estimated from ground deposition of ^{137}Cs and ^{131}I, contemporary thyroid radiation measurements, and from questionnaires and interviews	Thyroid*
Marshall Islands fallout [H35, R21]	Prevalence	2 273 exposed persons 55% females Age: 5–>60	Marshall Islands	29–31	n.a.	Short-lived radionuclides from nuclear explosion	Estimated average dose; distance was also used as a surrogate	Thyroid
Utah ^{131}I fallout: thyroid disease [K36]	Prevalence	2 473 persons	United States	12–17 and 32–33 [cc]	n.a.	Fallout from nuclear weapons tests	Based on residence histories and fallout deposition records	Thyroid

Table 2 (continued)

Study	*Type of study*	*Population studied*		*Follow-up (years)*	*Total person years* [a]	*Type of exposure*	*Type of dosimetry*	*Cancers studied* [b]
		Characteristics	*National origin*					
Utah ^{131}I fallout [S37]	Case-control	92 persons with bone-marrow doses of 6 mGy or more 6 415 persons with lower doses	United States	Up to 30	n.a.	Fallout from nuclear weapons tests	Based on residence histories and fallout deposition records	Leukaemia
Occupational exposures								
UK Atomic Energy Authority: prostate cancer study [R26]	Case-control 136 cases 404 controls	Males Age at diagnosis: <65–>75 14% of subjects with documented internal exposure	United Kingdom	n.a.	n.a.	Exposures in nuclear fuel cycle and research	Urine measurements and whole-body monitoring	Prostate*

a Mean per person in parentheses.
b An asterisk denotes sites for which statistically significant excesses are reported in the exposed group (cohort studies) or for which a higher proportion of the cases were exposed to radiation (case-control studies).
c Exposed to more than 0.005 Sv weighted colon dose.
d Age at exposure, mean in parentheses.
e Exposed to more than 0.01 Sv weighted colon dose.
f 5–42 years for leukaemia and lymphomas [P4].
g Based on the follow-up for solid cancer [T1].
h Figures quoted are for the mortality study [D14]. Exposure denotes doses above 0.01 Sv.
i Not available.
j Figures quoted in [L16].
k Figures quoted are for the leukaemia study [W2].
l Figures quoted in [S21].
m Significance tests based on 5-year survivors (2 years for leukaemia).
n Includes workers in studies [B24, C19, D21, F6, G12, G16, G17, W12, W23].
o Includes workers in studies [B24, B38, C19, D21, F6].
p Figures quoted are from [C19].
q Values for monitored workers only.
r Includes workers in study [G16].
s Figures quoted are from [C11].
t Figures quoted are from [G12].
u Figures quoted are from [I21].
v Figures quoted are from [K32].
w Figures are for males employed before 1959 [K34].
x Figures quoted are from [T25, T26].
y Figures quoted are for the thyroid cancer study [H4].
z Figures quoted are for the incidence study [H23].
aa Significance tests based on 10-year survivors.
bb Figures quoted are from [R14].
cc Periods of thyroid examinations, relative to the peak fallout in 1953 [K36].

Table 3
Strengths and limitations of major cohort and case-control epidemiological studies of carcinogenic effects of exposures to low-LET radiation

Study	*Strengths*	*Limitations*
EXTERNAL HIGH-DOSE-RATE EXPOSURES		
Exposures to atomic bombings		
Life Span Study [P4, P9, T1]	Large population of all ages and both sexes not selected because of disease or occupation Wide range of doses Comprehensive individual dosimetry Survivors followed prospectively for up to 45 years Complete mortality ascertainment Cancer incidence ascertainment	Acute, high-dose-rate exposure that provides no direct information on effects of gradual low-dose-rate exposures Restriction to 5-year survivors for mortality (13 years for incidence) Possible contribution of neutrons somewhat uncertain Possible effects of thermal or mechanical injury and conditions following the bombings uncertain
Survivors of atomic bombings (*in utero*) [D14, Y1]	Not selected for exposure Reasonably accurate estimate of dose Mortality follow-up relatively complete Follow-up into adulthood	Small numbers of exposed individuals and cases Incidence determination may not be complete Mechanical and thermal effects may have influenced results
Treatment of malignant disease		
Cervical cancer cohort [B11, B12, B50]	Large-scale incidence study based on tumour registry records Long-term follow-up Relatively complete ascertainment of cancers Non-exposed comparison patients	Very large doses to some organs result in cell killing and tissue damage Potential misclassification of metastatic disease for some organs Potential misclassification of exposure No individual dosimetry Characteristics of patients with cervical cancer differ from general population
Cervical cancer case-control [B1]	Comprehensive individual dosimetry for many organs Dose-response analyses Other strengths as above [B11]	As above [B11], except problems with individual dosimetry and comparison with general population now removed Small number of non-exposed cases Partial-body and partial-organ dosimetry complex
Lung cancer following breast cancer [I7]	Individual estimates of radiation dose to different segments of the lungs Large number of non-irradiated patients Most patients did not receive chemotherapy Substantial proportion of patients with over 20 years of follow-up	Small number of lung cancers Lack of data on individual smoking habits Potential inaccuracies in partial-body dosimetry
Contralateral breast cancer [B10, S20]	Large numbers of incident cases within population-based tumour registries Individual radiation dosimetry Wide range of doses	Limited number of young women Possibility of over matching, resulting in some concordance of exposure between cases and controls Possible misclassification of metastases or recurrence
Soft-tissue sarcoma following breast cancer [K35]	Incident cases identified from a population-based tumour registry	Analyses based on estimates of energy imparted from radiotherapy (i.e. product of the mass of the patient and the absorbed dose), rather than organ dose
Leukaemia following breast cancer [C9]	Comprehensive individual dosimetry for bone-marrow compartments Comprehensive ascertainment of treatment information to separate chemotherapy risk Dose-response analyses	Very large high-dose partial-body exposure to chest wall, probably resulting in cell-killing
Leukaemia following cancer or the uterine corpus [C10]	Large number of incident cases with population-based cancer registries Comprehensive individual dosimetry for bone-marrow compartments Attempt to adjust for chemotherapy Large non-irradiated comparison group Dose-response analyses covering doses below 1.5 Gy as well as above 10 Gy	Effects of cell-killing at high doses Potential inaccuracies in partial-body dosimetry
Lung cancer following Hodgkin's disease (international) [K9]	Individual estimates of radiation dose to the affected lung Some data on individual smoking habits Detailed information on chemotherapy Relatively large number of cases	Smoking data limited, and reported more fully for cases than for controls Follow-up period generally less than 10 years

Table 3 (continued)

Study	*Strengths*	*Limitations*
Lung cancer following Hodgkin's disease (Netherlands) [V2]	Individual estimates of radiation dose to the area of the lung where the tumour developed Individual data on smoking habits Extensive data on doses from chemotherapy	Small number of cases Limited follow-up (median 10 years) Few females
Breast cancer following Hodgkin's disease [H2]	Individual assessment of doses Analysis by age at exposure	Small number of cases Limited follow-up Mostly very high doses (>40 Gy)
Leukaemia following Hodgkin's disease (international) [K40]	Individual radiation dosimetry Detailed information on chemotherapy	Follow-up period generally less than 10 years
Leukaemia following non-Hodgkin's lymphoma (international) [T6]	Comprehensive individual dosimetry for bone marrow compartments Detailed information on chemotherapy	Small number of cases No dose-response analysis, other than separation into two groups
Leukaemia following non-Hodgkin's lymphoma (United States) [T15]	Individual dosimetry for bone marrow Detailed information on chemotherapy	Very small cohort; few cases No comparison group of unexposed patients
Childhood cancers (international) [T5, T7, T17]	Comprehensive individual dosimetry to estimate organ doses Attempt to adjust for drug exposure Dose-response analyses	Only high-dose exposures Potential for some overmatching since hospital-based Complete dosimetry not always available
Childhood cancers (France/United Kingdom) [D19, D33]	Incidence follow-up Doses from radiotherapy and chemotherapy estimated	Individual dose estimates generally not used in analyses Lack of external comparison group Small numbers for specific types of cancers
Bone cancer and leukaemia after childhood cancer (United Kingdom) [H44, H11]	Incidence follow-up Individual dosimetry Information available on chemotherapy	Most of the findings concern doses of 5–10 Gy or more
Retinoblastoma [W11]	Long-term incidence follow-up Individual dose estimates for bone and soft sarcoma sites Wide range of doses	Little information on chemotherapy Most of the findings concern doses of 5 Gy or more
Thyroid cancer following childhood cancers [D20]	Incidence follow-up Individual organ dose estimates Wide range of thyroid doses	Lack of external comparison group
Childhood Hodgkin's disease [B16]	Cohort of persons exposed at young ages to high radiation doses Individual dosimetry Information available on chemotherapy doses	Small numbers of cases No formal modelling of dose-response or of chemotherapy effects
Treatment of benign disease		
Childhood skin haemangioma [K23, L13, L15, L16, L17, L24, L46]	Long-term and complete follow-up Comprehensive individual dosimetry for many organs Incidence ascertained Protracted exposure to radium plaques	Relatively small numbers of specific cancers
Benign lesions in locomotor system [D12, J2]	Long-term and complete follow-up Individual dose estimates Incidence and mortality ascertained	Uncertainties in computing individual doses to sites, based upon a sample of records
Ankylosing spondylitis [W1, W2]	Large number of exposed patients Long-term and complete mortality follow-up Detailed dosimetry for leukaemia cases and sample of cohort Small non-exposed group evaluated for general reassurance that leukaemia risk was unrelated to underlying disease	Comparisons with general population Underlying disease related to colon cancer and possibly other conditions Individual dose estimates available only for leukaemia cases and a 1 in 15 sample of the population
Israel tinea capitis [R5, R9, R16, R17]	Large number of exposed patients Two control groups Ascertainment of cancer from hospital records and tumour registry Individual dosimetry for many organs	Dosimetry for some sites (e.g. thyroid) uncertain, owing to possible patient movement or uncertainty in tumour location Limited dose range

Table 3 (continued)

Study	*Strengths*	*Limitations*
New York tinea capitis [S27, S30]	Relatively good dose ascertainment for skin and other cancers	Small number of cancers No recent follow-up information Few females
New York post-partum mastitis [S15, S30]	Individual estimates of breast dose from medical records Breast cancer incidence ascertained Dose-response analyses	All exposed women were parous, but comparison women were not (380 non-exposed and sisters of both exposed and non-exposed) Inflamed and lactating breast might modify radiation effect
Rochester thymic irradiation [H10]	Individual dosimetry for thyroid and some other sites Sibling control group Long follow-up Fractionation effects could be evaluated Dose-response analyses	Radiation treatment fields for newborns varied, and dosimetry uncertain for some sites Adjustment in analysis for sibship size uncertain Questionnaire follow-up may have resulted in under-ascertainment of cases
Tonsil irradiation [S21, S28, S30]	Individual dosimetry for thyroid and some other sites Long follow-up Large numbers of cases for certain sites Dose-responses analyses	Effect of screening on ascertainment of thyroid cancer and nodules No unexposed control group
Tonsil, thymus or acne irradiation [D5]	Long period between exposure and examination Prospective as well as retrospective follow-up	Possible screening effect Small cohort No unexposed control group
Swedish benign breast disease [M8, M20, M28]	Incidence study with long-term follow-up Individual dosimetry for many organs Fractionated exposure Unexposed control group	Lack of data on potential confounders Small numbers for most cancer types, other than breast
Benign gynaecological disease [D7, I6, I16]	Large number of exposed women Non-exposed women with benign gynaecological disease Very long mortality follow-up Individual dosimetry Protracted exposures to radium implants (10-24 hours) Dose-response analyses	Uncertainty in proportion of active bone-marrow exposed Small numbers of specific types of cancer Misclassification on certain cancers on death certificates (e.g. pancreas)
Lymphoid hyperplasia screening [P8]	Individual dosimetry Comparison of questionnaire and clinical examination results Comparison group treated by surgery for the same condition	Apparent bias in questionnaire data, owing to self-selection of subjects Clinical examinations provide data on prevalence rather than incidence Study of thyroid nodules; cancer cases not confirmed
Peptic ulcer [G6]	Individual dosimetry Non-exposed patients with peptic ulcer Exceptionally long follow-up (50 years) Some risk factor information available in records	Standardized radiotherapy precluded dose-response analyses Non-homogeneous dose distribution within organs, such that simple averaging may be misleading Metastatic spread on stomach cancer probably misclassified as liver and pancreatic cancer on death certificates Possible selection of somewhat unfit patients for radiotherapy rather than surgery
Diagnostic examinations		
Massachusetts TB fluoroscopy [B3, D4, S30]	Incidence study with long-term follow-up (50 years) Individual dosimetry based on patient records and measurements Non-exposed TB patients Fractionated exposures occurred over many years Dose-response analyses	Uncertainty in dose estimates related to fluoroscopic exposure time and patient orientation Questionnaire response probably under-ascertained cancers Debilitating effect of TB may have modified radiation effect for some sites, e.g. lung
Diagnostic x rays (US health plans) [B39]	Information on diagnostic x rays abstracted from medical records Surveillance bias unlikely, since cases and controls were at equal risk for having x-ray procedures recorded and malignancy diagnosed	Potential for ascertainment bias, e.g. through early diagnosis of a malignancy Analyses based on number of x-ray procedures rather than actual doses
Canadian TB fluoroscopy [H7, H20]	Large number of patients Non-exposed TB comparison group Individual dosimetry for lung and female breast Fractionated exposures occurred over many years Dose-response analyses	Mortality limits comparisons with breast cancer incidence series, e.g. time response Uncertainties in dosimetry limit precise quantification of risk Different dose responses for female breast cancer between one sanatorium and the rest of Canada may indicate errors in dosimetry, differential ascertainment, or differences in biological response

Table 3 (continued)

Study	*Strengths*	*Limitations*
Diagnostic medical and dental x rays (Los Angeles) [P10, P35]	Dosimetry attempted based on number and type of examinations	No available records of x rays Potential for recall bias in dose assessment Doses likely to have been underestimated
Diagnostic x rays (Sweden) [I9]	Information on diagnostic x rays over many years abstracted from medical records	Analyses based on number and type of x-ray procedures rather than actual doses
Scoliosis [D34]	Adolescence possibly a vulnerable age for exposure Dosimetry undertaken based on number of films and breast exposure Dose-response analysis	Comparison with general population potentially misleading, since scoliosis associated with several breast cancer risk factors (e.g. nulliparity) Dose estimates may be subject to bias as well as random error
EXTERNAL LOW-DOSE OR LOW-DOSE-RATE EXPOSURES		
Prenatal exposures		
Oxford Survey of Childhood Cancers [S1, B2, M29]	Very large numbers Comprehensive evaluation of potential confounding Early concerns over response bias and selection bias resolved	Uncertainty in fetal dose from obstetric x-ray examinations Similar relative risks for leukaemia and other cancers may point to possible residual confounding
North-eastern United States childhood cancers [M9]	Large numbers Reliance on obstetric records	Uncertainty in fetal dose
Occupational exposures		
Nuclear workers	Often large numbers Personal dosimetry Low-dose fractionated exposures Could provide useful information in future	Low doses make clear demonstration of radiation effect difficult Possibly confounding influence of chemical and other toxic exposures in workplace Healthy worker effect Mortality follow-up Lifestyle factors (e.g. smoking histories) generally not available
Chernobyl clean-up workers	Often large numbers Low-dose fractionated exposures Could provide useful information in future	Difficulties in assessing individual exposures Possible differences in cancer ascertainment relative to the general population Short period of follow-up so far
Mayak workers [K10, K11, K32, K34, Z1]	Wide range of exposures Individual measurements of external gamma dose and plutonium body burden Individual information on potential confounders in stomach cancer study	Possible uncertainties in assessment of exposures Further details of ascertainment of stomach cancer cases and controls desirable
Medical workers	Often large numbers Low-dose fractionated exposures over long periods	General lack of information on individual doses precludes usefulness to date
Natural radiation		
Yangjiang [T12, A11, Z2, S35, T25, T26]	Large cohorts in high background and control areas Stable population Extensive dosimetry for region Assessment of potential confounders	Mortality follow-up Small numbers for some cancer types Low doses
Central Italy [F7]	Individual measurements of domestic gamma radiation and radon	Small number of cases Mortality data only Measurements only in last home Low doses
INTERNAL LOW-DOSE-RATE EXPOSURES		
Medical exposures		
Swedish ^{131}I thyroid cancer [H23, H24]	Large numbers Nearly complete incidence ascertainment Administered activities of ^{131}I known	Comparison with general population Dose-response not based on organ doses High-dose cell-killing probably reduced possible thyroid effect Patients selected for treatment

Table 3 (continued)

Study	*Strengths*	*Limitations*
Diagnostic ^{131}I [H4, H12, H27]	Large numbers Unbiased and nearly complete ascertainment of cancers through linkage with cancer registry Administered activities of ^{131}I known for each patient Organ doses to the thyroid computed with some precision Dose-response analyses for thyroid cancer and leukaemia, based on wide range of doses Low-dose-rate exposure	Comparison with general population only, except for thyroid cancer and leukaemia Reason for some examinations related to high detection of thyroid cancers, i.e. suspicion of thyroid tumour was often correct Doses to organs other than thyroid very low Population under surveillance
United States thyrotoxicosis patients [D22, R14, S36]	Large numbers of patients treated with ^{131}I Large non-exposed comparison groups Comprehensive follow-up effort Administered activities of ^{131}I known	Individual doses computed only for certain organs Mortality follow-up Few patients irradiated at young ages Possibility of selection bias by treatment
Swedish ^{131}I thyroid cancer [H26]	Incidence follow-up Administered activities of ^{131}I known Unexposed group	Individual doses not computed Small numbers for specific cancer types Few patients irradiated at young ages Possibility of selection bias by treatment
French therapeutic ^{131}I [D18]	Incidence follow-up Administered activities of ^{131}I known Exclusion of patients who received external radiotherapy Unexposed group	Individual doses not computed Small numbers for specific cancer types Few patients irradiated at young ages Possibility of selection bias by treatment
Environmental exposures		
Techa River population [K5, K27]	Large numbers with relatively long follow-up Wide range of estimated doses Unselected population; attempted use of local population rates for comparison Possible to examine ethnic differences in cancer risk Potential for future	Dosimetry difficult and not individual Mixture of internal and external exposures complicates dosimetry Follow-up and cancer ascertainment uncertain Contribution of chemical exposures not evaluated
Chernobyl-related exposure [A26]	Large numbers exposed Wide range of thyroid doses within the states of the former Soviet Union	Mixture of radioiodines and availability of data make dose estimation difficult, particularly for individuals Possible differences in cancer ascertainment relative to the general population Fairly short period of follow-up so far
Marshall Islands fallout [H35, R21]	Population unselected for exposure Comprehensive long-term medical follow-up Individual dosimetry attempted	Mixture of radioiodines and gamma radiation preclude accurate dose estimation Surgery and hormonal therapy probably influenced subsequent occurrence of thyroid neoplasms Small numbers
Utah ^{131}I fallout: thyroid disease [K36]	Comprehensive dosimetry attempted Protracted exposures at low rate	Possible recall bias in consumption data used for risk estimation Possible under-ascertainment of disease in low-dose subjects Small number of thyroid cancers
Utah ^{131}I fallout [S37]	Comprehensive dosimetry attempted Large number of leukaemia deaths Protracted exposures at low rate	Uncertainty in estimating bone marrow doses Estimated cumulative doses lower than from natural background radiation
Occupational exposures		
UK Atomic Energy Authority: Prostate cancer study [R26]	Information abstracted for study subjects on socio-demographic factors, exposures to radionuclides, external doses and other substances in the workplace Cases and controls selected from an existing cohort	Exposure to some radionuclides tended to be simultaneous, making it difficult to study them individually

Table 4
Cohort and case-control epidemiological studies of the effects of exposures to high-LET radiation

Study	*Type of study*	*Population studied*		*Follow-up (years)*	*Total person-years* [a]	*Type of exposure*	*Type of dosimetry*	*Cancers studied* [b]
		Characteristics	*National origin*					
Treatment of benign disease								
^{224}Ra TB and ankylosing spondylitis patients [H8, N4, N14, S14]	Incidence	899 exposed persons 31% females 24% aged [c] ≤20 years	Germany	0–54	23 400 (28.8) [d]	Injection with ^{224}Ra	Internal dosimetric calculations based on amount injected	Bone*, breast*, connective tissue*, liver*, kidney*, thyroid*, ovary, leukaemia, pancreas, uterus, prostate, bladder*, stomach, colon, lung
^{224}Ra ankylosing spondylitis patients [W3, W20]	Incidence	1 577 exposed persons 1 462 unexposed persons	Germany	0–51	63 500 (20.8)	Injection with ^{224}Ra	Information on amount injected	Bone and connective tissue, leukaemia*, non-Hodgkin's lymphoma, Hodgkin's disease, stomach, liver, lung, urinary system, female breast
Diagnostic examinations								
German thorotrast patients [V1, V8]	Mortality	2 326 exposed persons 1 890 unexposed persons 26% females	Germany	3–>50	n.a. [e]	Injection with thorotrast	Hospital records of amounts injected; CT measurements of some patients; x-ray films	Liver*, extrahepatic bile ducts*, gallbladder, myeloid leukaemia*, pancreas*, myelodysplastic syndrome*, non-Hodgkin's lymphoma*, plasmacytoma, larynx, bone sarcoma, lung, mesothelioma*, Hodgkin's disease, lymphatic leukaemia, kidney, bladder, prostate, adrenal, brain, GI tract
Danish thorotrast patients [A4, A5] [f]	Incidence/ Mortality	800 exposed persons 1 236 unexposed persons 49% females 17% aged <20	Denmark	1–>50	49 883 (24.5)	Injection with thorotrast	Records of amount injected; dosimetric factors for dose to liver and bone marrow	Liver*, leukaemia*, brain and nervous system*, lung, breast, ovary, all other sites
Swedish thorotrast patients [M48]	Mortality	693 exposed persons 43% females Ages: 2–66 (35)	Sweden	6–60	10 077 (14.5)	Injection with thorotrast	Records of amount injected	All malignant neoplasms*, all benign neoplasms*
Portuguese thorotrast patients [D3, D31] [g]	Mortality	1 131 exposed persons 1 032 unexposed persons 39% females Age: 5–>65 (34 for exposed, 40 for unexposed)	Portugal	0–68	36 321 (16.8)	Injection with thorotrast	Hospital records of amount injected; dosimetric factors for alpha dose to liver	Liver*, gallbladder, lung, bone*, nervous system, leukaemia (excluding chronic lymphatic)*, unspecific sites, all neoplasms*

Table 4 (continued)

Study	*Type of study*	*Population studied*		*Follow-up (years)*	*Total person-years* [a]	*Type of exposure*	*Type of dosimetry*	*Cancers studied* [b]
		Characteristics	*National origin*					
Early Japanese thorotrast patients [M14, M47]	Mortality	262 exposed persons 1 630 unexposed persons Age: 20–39	Japan	18–68	n.a.	Injection with thorotrast	Amount injected	Liver*, lung, bone sarcoma, leukaemia*
Later Japanese thorotrast patients [K33, M14]	Mortality	150 exposed persons Age: 15–39	Japan	34–65	n.a.	Injection with thorotrast	Amount injected	Liver*, lung, leukaemia*
Occupational exposure: radium								
United States radium luminizers [C27, S12, S16, S54] [h]	Incidence/ Mortality	2 543 females	United States	0–71.5	119 020 (46.8)	Ingestion of ^{226}Ra and ^{228}Ra	Body burdens of about 1 500 women assessed by measurement of gamma rays and /or exhaled radon; used for calculation of systemic intake and skeletal dose	Bone sarcoma*, paranasal sinuses and mastoid air cells*, stomach, colon, rectum, liver, lung, breast*, pancreas, brain and other central nervous system tumours, leukaemia, multiple myeloma
United Kingdom radium luminizers [B13, B14]	Mortality	1 203 females	United Kingdom	47 (max.)	44 883	Work with radium	Some measurements of body burdens Assessments of external doses	Breast, leukaemia, osteosarcoma, all cancers combined
Occupational exposure: plutonium								
Mayak plutonium workers [G23, K10, K11, K32 K34, K42] [i]	Mortality	4 186 persons with measured plutonium body burdens (1 479 males employed before 1959) 14 644 other workers (5 174 males employed before 1959) 25% females [j]	Russian Federation	Up to 47	211 427 (31.8) [k]	Exposures to plutonium in nuclear fuel cycle and research	Measurement of plutonium in urine Recorded exposures to external radiation	Lung*, liver*, bone*
Mayak radiochemical plant workers: lung cancer study [T2]	Case-control 162 cases 338 controls	283 persons with Pu body burden > 0.75 kBq; 217 persons with lower body burdens 11% females	Russian Federation	42 (max.)	n.a.	Exposures to plutonium in nuclear fuel cycle and research	Measurement of plutonium in urine Recorded exposures to external radiation	Lung cancer*
Sellafield plutonium workers [O1]	Incidence/ Mortality	5 203 plutonium workers 4 609 of whom had plutonium dose assessed 5 179 other radiation workers 4 003 non-radiation workers 19% females	United Kingdom	Up to 46 for mortality; up to 40 for incidence	415 432 (29)	Exposures to plutonium in nuclear fuel cycle and research	Measurement of plutonium in urine Recorded exposures to external radiation	Stomach, colon, pancreas, lung, pleura, breast, prostate, bladder, brain and other central nervous system tumours, ill-defined and secondary, non-Hodgkin's lymphoma, leukaemia

Table 4 (continued)

Study	*Type of study*	*Population studied*		*Follow-up (years)*	*Total person-years* [a]	*Type of exposure*	*Type of dosimetry*	*Cancers studied* [b]
		Characteristics	*National origin*					
Rocky Flats workers [W12]	Mortality	5 413 males with external and/or plutonium exposures	United States	Up to 28	52 772 (9.7)	Exposures to plutonium in nuclear fuel cycle and research	Measurement of plutonium in urine Recorded exposures to external radiation	Oesophagus, stomach, colon, rectum, liver, pancreas, larynx, lung, skin, prostate, bladder, kidney, brain and other central nervous system tumours, non-Hodgkin's lymphoma, multiple myeloma, myeloid leukaemia
Los Alamos workers [W8]	Mortality	3 775 males with Pu body burden of 74 Bq or more 11 952 males with lower body burdens	United States	Up to 47	456 637 (29)	Exposures to plutonium in nuclear fuel cycle and research	Measurement of plutonium in urine Recorded exposures to external radiation	Oral, stomach, colon, rectum, pancreas, lung, bone, prostate, bladder, kidney, brain and other central nervous system tumours, all lymphatic/haematopoietic cancers
Occupational exposure: others (excluding radon in mines)								
Three United Kingdom industry workforces [C33]	Mortality	17 605 workers monitored for radionuclide exposure 23 156 other radiation workers 8% females	United Kingdom	Up to 43	1 020 000 (25)	Exposures in nuclear fuel cycle and research	Data on monitoring for plutonium, tritium, and other radionuclides	Lung, pleura, skin, uterus, prostate, multiple myeloma, leukaemia, other cancers
Oak Ridge, Y-12 workers [C32]	Mortality	Males 3 490 workers with internal exposure monitoring data 3 291 other workers Age at entry: 16–64	United States (white)	Up to 33	133 535 (19.7)	Exposures in nuclear fuel cycle and research	Urine measurements and whole-body monitoring of internally deposited uranium	Lung, brain and other central nervous system
Mound workers [W22]	Mortality	4 402 males	United States (white)	Up to 40	104 326 (23.7)	Exposures in nuclear fuel cycle and research	Measurement of polonium in urine	Oral, oesophagus, stomach, colon, rectum, liver, pancreas, lung, bone, skin, prostate, bladder, kidney, brain and other central nervous system tumours, thyroid, non-Hodgkin's lymphoma, Hodgkin's disease, leukaemia
Florida phosphate workers [C34]	Mortality	23 012 males Age at entry: (median 25)	United States	Up to 44	545 867 (23.7)	Exposures in mining and chemical processing of phosphate ores	Assessments of cumulative exposures to alpha and gamma radiation, based on job histories	Lung

Table 4 (continued)

Study	*Type of study*	*Population studied*		*Follow-up (years)*	*Total person-years* [a]	*Type of exposure*	*Type of dosimetry*	*Cancers studied* [b]
		Characteristics	*National origin*					
Fernald workers [D32, R25]	Mortality	4 014 males Age at entry: (30.4)	United States (white)	Up to 49	124 177 (30.9)	Exposures in nuclear fuel cycle and research	Measurement of uranium, thorium and radium compounds in urine, plus environmental area sampling Recorded exposures to external radiation	Lung, respiratory tract, upper gastrointestinal tract, lower gastrointestinal tract, bladder and kidney, haematopoietic and lymphopoietic neoplasms
Chinese iron and steel workers [L49]	Mortality	Males 5 985 exposed 2 849 unexposed	China	Up to 17	111 286 (12.6)	Exposure to thorium-containing dust in an iron and steel company	Assessment of lung doses from inhalation	Lung, leukaemia*
Occupational exposure: radon in mines								
Chinese tin miners [D8, L4, X1] [l]	Mortality	13 649 exposed males 3 494 unexposed males Age: <10–>30	China	0–>25	175 342 (10.2)	Radon in tin mines	Measurements of WL from 1972; reconstruction of earlier values	Lung cancer*, all other cancers
West Bohemia uranium miners [D8, L4, T3, T22] [l]	Mortality	4 284 exposed males Age: <25–>45	Czech Republic	0–>25	107 868 (25.2)	Radon in uranium mines	Measurements of radon progeny after 1967; radon measured since 1949, with equilibrium values based on ventilation	Lung cancer*, all other cancers
Colorado Plateau uranium miners [D8, L4, H17] [l]	Mortality	3 347 exposed males Age: <25–>45	United States	0–>25	82 435 (24.6)	Radon in uranium mines	Measurements of radon progeny during 1951–1968; few measurements earlier	Lung cancer*, all other cancers
Ontario uranium miners [D8, L4, K4] [l]	Mortality	21 346 exposed males Age: <25–>45	Canada	0–>15	380 718 (17.8)	Radon in uranium and gold mines	Measurements of WL in uranium mines from 1957; no measurements in gold mines before 1961, a few during the 1960s and 1970s and extensive measurements thereafter	Lung cancer*, all other cancers
Newfoundland fluorspar miners [D8, L4, M15] [l]	Mortality	1 751 exposed males 337 unexposed males Age: <20–>30	Canada	0–>15	48 742 (23.3)	Radon in fluorspar mines	WL estimated from work environment, architecture and ventilation before 1960. Systematic measurement programme stated in 1968	Lung cancer*, all other cancers

Table 4 (continued)

Study	*Type of study*	*Population studied*		*Follow-up (years)*	*Total person-years* [a]	*Type of exposure*	*Type of dosimetry*	*Cancers studied* [b]
		Characteristics	*National origin*					
Swedish iron miners [D8, L4, R8] [l]	Mortality	1 294 exposed males Age: <25–>30	Sweden	0–>25	33 293 (25.7)	Radon in iron mine	Radon measurements made during 1968–1975, with estimation of WL using characteristics of natural and mechanical ventilation	Lung cancer*, all other cancers
New Mexico uranium miners [D8, L4, S19] [l]	Mortality	3 457 exposed males 12 unexposed males Age: <30–>40	United States	0–>15	58 949 (17.0)	Radon in uranium mines	Extensive measurements; for individual miners since 1969	Lung cancer*, all other cancers
Beaverlodge uranium miners [D8, L4, H15, H18] [l]	Mortality	6 895 exposed males 1 591 unexposed males Age: <30–>45	Canada	0–>20	118 385 (14.0)	Radon in uranium mine	Measurements of radon progeny after 1967; radon measurements earlier, mainly for control purposes	Lung cancer*, all other cancers
Port Radium uranium miners [D8, L4, H16] [l]	Mortality	1 420 exposed males 683 unexposed males Age: <30–>45	Canada	0–>25	52 676 (25.2)	Radon in uranium mine	Measurements for 1945–1958; no exposures estimated before 1940	Lung cancer*, all other cancers
Radium Hill uranium miners [L4, W7] [l]	Mortality	1 457 exposed males 1 059 unexposed males Age: <35–>40	Australia	0–>25	51 850 (21.9)	Radon in uranium mine	Measurements of radon during 1954–1961, but not earlier	Lung cancer*
French uranium miners [D8, L4, T8] [l]	Mortality	1 769 exposed males 16 unexposed males Age: <30–>40	France	0–>25	44 043 (24.7)	Radon in uranium mines	Systematic monitoring after 1957; only a few measurements during 1947–1955	Lung cancer*, all other cancers
Cornish tin miners [D8, H13]	Mortality	2 535 males	United Kingdom	0–>25	66 900 (26.4)	Radon in tin mines	Monitoring of radon concentrations since 1967; no measurements in previous decades	Lung cancer*, all other cancers
Residential radon studies								
United States acute lymphoblastic leukaemia study [L34]	Case-control 505 cases 443 controls	48% females Age at diagnosis: 0–14 10% with time-weighted average radon concentrations above 148 Bq m^{-3}	United States	n.a.	n.a.	Radon in homes	Track-etch detector measurements in homes occupied by subjects	Acute lymphoblastic leukaemia
United States acute myeloid leukaemia study [S52]	Case-control 173 cases 254 controls	51% females Age at diagnosis: 0–17 Mean time-weighted average radon concentration 53 Bq m^{-3} (14% above 100 Bq m^{-3})	United States	n.a.	n.a.	Radon in homes	Track-etch detector measurements in homes occupied by subject at time of diagnosis	Acute myeloid leukaemia

Table 4 (continued)

Study	*Type of study*	*Population studied*		*Follow-up (years)*	*Total person-years* [a]	*Type of exposure*	*Type of dosimetry*	*Cancers studied* [b]
		Characteristics	*National origin*					
West German childhood cancer [K38]	Case control 82 leukaemia cases 82 solid tumour cases 209 controls	Age at diagnosis: 0–14 Mean time-weighted average radon concentration 27 Bq m^{-3}	Germany	n.a.	n.a.	Radon in homes	Track-etch detector measurements in homes occupied by subjects for at least one year	Leukaemia, solid tumours
Central Italy [F7]	Case-control 44 cases 211 controls	Males Age at diagnosis: 35–80 (68) 75% with radon concentration above 100 Bq m^{-3}	Italy	10	n.a.	Radon and gamma radiation in homes	Measurements in last dwelling occupied and characteristics of dwellings	Acute myeloid leukaemia
New Jersey [S50]	Case-control 433 cases 422 controls	Females Age at diagnosis: all (65% aged 58 or more) Mean time-weighted-average radon concentration 26 Bq m^{-3} (20% above 37 Bq m^{-3})	United States	n.a.	n.a.	Radon in homes	Track-etch detector measurements in homes occupied by subjects	Lung cancer
Shenyang [B37]	Case-control 308 cases 362 controls	Females Age at diagnosis: 30–69 Mean time-weighted-average radon concentration 118 Bq m^{-3}	China	n.a.	n.a.	Radon in homes	Track-etch detector measurements in homes occupied by subjects	Lung cancer
Stockholm [P32]	Case-control 210 cases 400 controls	Females Age at diagnosis: all Mean time-weighted-average radon concentration 128 Bq m^{-3}	Sweden	n.a.	n.a.	Radon in homes	Track-etch detector measurements in homes occupied by subjects	Lung cancer
Swedish nationwide [P33]	Case-control 1 281 cases 2 576 controls	47% females Age at diagnosis: 35–74 Mean time-weighted-average radon concentration 107 Bq m^{-3}	Sweden	n.a.	n.a.	Radon in homes	Track-etch detector measurements in homes occupied by subjects	Lung cancer
Winnipeg [L44]	Case-control 738 cases 738 controls	34% females Age at diagnosis: 35–80 Mean time-weighted-average radon concentration 107 Bq m^{-3}	Canada	n.a.	n.a.	Radon in homes	Track-etch detector measurements in homes occupied by subjects	Lung cancer

Table 4 (continued)

Study	*Type of study*	*Population studied*		*Follow-up (years)*	*Total person-years* [a]	*Type of exposure*	*Type of dosimetry*	*Cancers studied* [b]
		Characteristics	*National origin*					
Missouri-I [A22]	Case-control 538 cases 1 183 controls	Females Age at diagnosis: 30–84 Mean time-weighted-average radon concentration 67 Bq m^{-3}	United States	n.a.	n.a.	Radon in homes	Track-etch detector measurements in homes occupied by subjects	Lung cancer
Finland-I [R23]	Case-control 238 cases 434 controls	Males Age at diagnosis: all Mean time-weighted-average radon concentration 220 Bq m^{-3}	Finland	n.a.	n.a.	Radon in homes	Track-etch detector measurements in homes occupied by subjects	Lung cancer
Finland-II [A23]	Case-control 1 055 cases 1 544 controls (517 matched pairs)	97% males Age at diagnosis: all Mean time-weighted-average radon concentration 96 Bq m^{-3}	Finland	n.a.	n.a.	Radon in homes	Track-etch detector measurements in homes occupied by subjects	Lung cancer
West Germany [W17]	Case-control 1 449 cases 2 297 controls	18% females Age at diagnosis: <75 Mean radon concentration 49 Bq m^{-3} (cases) 50 Bq m^{-3} (controls); corresponding values of 67 Bq m^{-3} (cases) 60 Bq m^{-3} (controls) in radon-prone areas	Germany	n.a.	n.a.	Radon in homes	Track-etch detector measurements in homes occupied by subjects	Lung cancer
East Germany [W18]	Case-control 1 053 cases 1 667 controls	12% females Age at diagnosis: <75 Mean radon concentration 87 Bq m^{-3} (cases) 90 Bq m^{-3} (controls) in living room; corresponding values of 66 Bq m^{-3} (cases) 63 Bq m^{-3} (controls) in bedrooms in radon-prone areas	Germany	n.a.	n.a.	Radon in homes	Track-etch detector measurements in homes occupied by subjects	Lung cancer
Southwest England [D30]	Case-control 982 cases 3 185 controls	33% females Age at diagnosis: <75 Mean time-weighted-average radon concentration 58 Bq m^{-3} (cases) 56 Bq m^{-3} (controls)	United Kingdom	n.a.	n.a.	Radon in homes	Track-etch detector measurements in homes occupied by subjects	Lung cancer

Table 4 (continued)

Study	*Type of study*	*Population studied*		*Follow-up (years)*	*Total person-years* [a]	*Type of exposure*	*Type of dosimetry*	*Cancers studied* [b]
		Characteristics	*National origin*					
Missouri-II [A24]	Case-control 512 cases 553 controls	Females Age at diagnosis: <75 Mean time-weighted average radon concentration 64.6 Bq m^{-3} based on CR-39 surface measurements (58.5 Bq m^{-3} based on track-etch measurements)	United States	n.a.	n.a.	Radon in homes	Track-etch and CR-39 detector measurements in homes occupied by subjects	Lung cancer

a Mean per person in parentheses.
b An asterisk denotes sites for which statistically significant excesses are reported in the exposed group (cohort studies) or for which a higher proportion of the cases were exposed to radiation (case-control studies).
c Age at first exposure, mean in parentheses.
d Figures quoted are for 812 persons with complete information [N14].
e Not available.
f Figures quoted are from [A5], for persons eligible for the cancer incidence analysis.
g Figures quoted are for persons followed up to the end of 1996 [D31].
h Figures quoted are from [S12].
i Figures quoted are from [K10]. Preliminary results from a follow-up to the end of 1993 are given in [K11], but not to the same detail.
j Figures based on [K32, K34].
k Figures for males employed before 1959 [K34].
l Figures are from [L45].

Table 5
Strengths and limitations of major cohort and case-control epidemiological studies of carcinogenic effects of exposures to high-LET radiation

Study	*Strengths*	*Limitations*
Treatment for benign disease		
^{224}Ra patients	Large number of excess bone cancers Long-term follow-up Substantial proportion of patients treated in childhood or adolescence	Uncertainties in organ doses for individual patients Other aspects of treatment may be relevant (e.g. x rays) Comparison group constructed only recently for the Spiess study [S14]
Diagnostic examinations		
Thorotrast patients	Large number of excess cancers Long-term follow-up	Uncertainties in organ doses for individual patients Chemical attributes of thorotrast might influence risks
Occupational exposures		
Radium luminizers	Protracted exposures from ^{226}Ra Large numbers of excess cancers in United States study	Potential inaccuracies in estimating radium intakes Distribution of radium in bone may be non-uniform External irradiation may be relevant for breast cancers
Mayak workers	Wide range of exposures Individual measurements of plutonium body burden and external gamma dose Information on smoking and other potential confounders in the lung cancer case-control study	Possible uncertainties in assessment of exposures Further details of the ascertainment of subjects in the lung cancer case-control study [T2] would be desirable
United Kingdom and United States nuclear workers	Individual measurements of plutonium body burden or other internally deposited radionuclides, and external gamma dose	General lack of information on smoking and other potential non-radiation confounders Possible uncertainties in assessment of internal exposures
Florida phosphate workers [C34]	Relatively large number of person-years Assessment of exposures to other agents (e.g. silica and acid mists)	Not possible to obtain direct quantitative estimates of exposure levels Absence of data on smoking habits for lung cancer analysis
Chinese iron and steel workers [L49]	Assessments made of lung doses from inhalation of thorium Information available on smoking habits	Lung doses generally low Small number of deaths for specific cancer types
Radon-exposed underground miners	Large numbers Protracted exposures over several years Wide range of cumulative exposures Exposure-response analyses	Uncertainties in assessment of early exposures Possible modifying effect of other types of exposure (e.g. arsenic) Smoking histories limited or not available
Environmental exposures		
Residential radon	Large numbers in most studies Protracted exposures over many years Individual data on radon and smoking	Uncertainties in assessing exposures (measurement error, mobility between dwellings, structural changes to dwellings) Radon concentrations low for many subjects

Table 6
Risk estimates for cancer incidence and mortality from studies of radiation exposure: oesophageal cancer
The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this Table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.01 Sv or more for incidence and 0.005 Sv or more (weighted colon dose) for mortality

Study		*Observed cases*	*Expected cases*	*Mean dose (Sv)*	*Person-years*	*Average excess relative risk [a] at 1 Sv*	*Average excess absolute risk [a] (10^4 PYSv)$^{-1}$*
EXTERNAL LOW-LET EXPOSURES							
Incidence							
Life Span Study [T1]							
Sex	Male	68	66.2	0.23	297 452	0.12	0.26
	Female	16	11.2	0.22	491 130	1.95	0.44
Age at exposure	<20 years	8	8.2	0.23	297 452	−0.11	−0.03
	>20 years	76	69.2	0.22	491 130	0.45	0.63
All		84	77.4	0.23	788 582	0.37 (−0.45−1.31) [b]	0.36 (−0.44−1.28) [b]
Cervical cancer cohort [B11] [c]		12	11.0	0.35	178 243	0.26 (95% CI: −1.1−1.3) [b]	0.16 (95% CI: −0.6−1.3) [b]
Mortality							
Life Span Study [P9]							
Age at exposure							
Males	<20 years	13	15.9	0.21	376 371	- 0.87 (-2.44 -1.40)	- 0.37 (-1.04 -0.59)
	20-39 years	30	31.2	0.25	117 959	- 0.15 (-1.22 -1.20)	- 0.40 (-3.22 -3.18)
	>40 years	61	55.0	0.23	132 009	0.48 (-0.50 -1.64)	1.99 (-2.10 -6.82)
Females	<20 years	0	0.0	0.20	416 447	–	–
	20-39 years	14	10.2	0.19	358 988	1.94 (-0.88 -5.96)	0.55 (-0.25 -1.69)
	>40 years	19	12.9	0.17	201 931	2.78 (-0.20 -6.81)	1.77 (-0.13 -4.34)
Time since exposure							
Both sexes	5-10 years	13	12.9	0.22	261 996	0.05 (-1.87 -2.81)	0.02 (-0.92 -1.38)
	11-25 years	52	40.6	0.20	658 705	1.41 (0.02 -3.08)	0.87 (0.01 -1.90)
	26-40 years	51	49.2	0.20	533 369	0.18 (-0.97 -1.57)	0.17 (-0.89 -1.45)
	41-45 years	21	16.2	0.19	144 940	1.55 (-0.67 -4.52)	1.73 (-0.75 -5.04)
All		137	125.2	0.21	1 603 705	0.76 (0.02 -1.59) [b]	0.56 (0.02 -1.16) [b]
Ankylosing spondylitis [W1] [d]		74	38	5.55	287 095	0.17 (95% CI: 0.09−0.25) [e]	0.23 (95% CI: 0.1−0.3) [b]
Metropathia haemorrhagica [D7]		9	9.27	0.05	47 144	−0.58 (<−0.2−13.9) [b]	−0.94 (−7.0 −22.5) [b]
Massachusetts TB fluoroscopy [D4]		14	6.7	0.80	169 425	n.a. [f]	n.a.
Nuclear workers in Canada, United Kingdom, United States [C11]		104	n.a.	0.04	2 124 526	>0 [g]	n.a.
Nuclear workers in Japan [E3]		25	37.1	0.014	533 168	>0 [g]	n.a.
INTERNAL LOW-LET EXPOSURES							
Mortality							
United States thyrotoxicosis [R14]		25	25	n.a.	385 468	n.a. [h]	n.a.

a 90% CI in parentheses derived from published data for Life Span Study and using exact Poisson methods for the other studies.
b Estimates based on method described in the introduction to Chapter III.
c The values given are for 10-year survivors.
d The values given exclude the period within five years of first treatment.
e Dose-response analysis based on the number of treatment courses given.
f Not available.
g Based on a 10-year lag. Trend not statistically significant..
h No apparent trend with administered level of ^{131}I, although a significance test was not performed.

Table 7
Risk estimates for cancer incidence and mortality from studies of radiation exposure: stomach cancer
The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this Table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.01 Sv or more for incidence and 0.005 Sv or more (weighted colon dose) for mortality

Study		*Observed cases*	*Expected cases*	*Mean dose (Sv)*	*Person-years*	*Average excess relative risk [a] at 1 Sv*	*Average excess absolute risk [a] (10^4 PYSv)$^{-1}$*
EXTERNAL LOW-LET EXPOSURES							
Incidence							
Life Span Study [T1]							
Sex	Male	679	660.4	0.24	298 700	0.12	2.61
	Female	628	561.3	0.23	493 900	0.52	5.86
Age at exposure	<20 years	167	142.0	0.24	365 200	0.74	2.87
	>20 years	1 140	1 079.7	0.23	427 300	0.24	6.15
All		1 307	1 221.7	0.23	792 500	0.30 (0.2–0.5) [b]	4.68 (2.5–7.4) [b]
Cervical cancer case-control [B1] [c]		348	167.3	2	n.a.	0.54 (0.05–1.5)	1.23
Mayak workers [Z1]		20 [d]	n.a.	>3	n.a.	1.1 (95% CI: 0.01–3.4) [e]	n.a.
Swedish benign breast disease [M28]		14	15.6	0.66	26 493	1.3 (95% CI: 0–4.4)	n.a.
Stockholm skin haemangioma [L16]		5	~6	0.09	406 565	<0	<0
Mortality							
Life Span Study [P9]							
Age at exposure							
Males	<20 years	78	75.2	0.21	369 372	0.18 (–0.7–1.2)	0.37 (–1.4–2.5)
	20-39 years	193	188.2	0.21	116 442	0.12 (–0.4–0.7)	1.96 (–7.1–12.0)
	>40 years	536	527.0	0.21	129 183	0.08 (–0.3–0.4)	3.30 (–10.2–17.8)
Females	<20 years	63	51.6	0.21	414 045	1.05 (–0.1–2.4)	1.31 (–0.1–3.0)
	20-39 years	257	233.6	0.21	357 293	0.48 (–0.0–1.0)	3.12 (–0.3–6.8)
	>40 years	390	369.0	0.21	201 031	0.27 (–0.1–0.7)	4.97 (–2.6–13.0)
Time since exposure							
Both sexes	5-10 years	153	151.6	0.21	186 468	0.04 (–0.6–0.7)	0.35 (–4.7–6.0)
	11-25 years	610	581.0	0.21	725 251	0.24 (–0.1– [f])	1.90 (–0.7– [e])
	26-40 years	606	573.8	0.21	530 897	0.27 (–0.1–0.6)	2.89 (–0.6–6.6)
	41-45 years	148	137.7	0.21	144 740	0.36 (–0.3–1.1)	3.38 (–3.0–10.5)
All		1 517	1 444.1	0.21	1 587 355	0.24 (0.03–0.5) [b]	2.19 (0.30–4.1) [b]
Ankylosing spondylitis [W1] [g]		127	128	3.21	287 095	–0.004 (95% CI: –0.05-0.05) [h]	–0.02 (95% CI: –0.2-0.2)
Yangjiang background radiation [T25, T26]		70	77.8	n.a. [i]	1 246 340	–0.27(95% CI: –1.37-2.69) [j]	n.a.
Peptic ulcer [G6]		40	14.4 [k]	14.8	35 815	0.15	0.25
Metropathia haemorrhagica [D7] [l]		33	26.8	0.23	47 144	1.01 (<–0.2–2.8) [b]	5.72 (<–2.4–16) [b]
Benign gynaecological disease [I16] [m]		23	21.8	0.2	71 958	0.27 (–4.25–4.80) [n]	0.83 (<0–72.7) [b]
Nuclear workers in Canada, United Kingdom, United States [C11]		275	n.a.	0.04	2 124 526	<0 [o]	n.a.
Nuclear workers in Japan [E3]		149	177.2	0.014	533 168	<0 [o]	n.a.

Table 7 (continued)

Study	*Observed cases*	*Expected cases*	*Mean dose*	*Person-years*	*Average relative risk* [p]	
INTERNAL LOW-LET EXPOSURES						
Incidence						
Swedish hyperthyroid patients [H23]	58 [q]	43.6	0.25 Gy	n.a.	2.32 [r]	
Mortality						
United States thyrotoxicosis patients [R14]	82	78.0	0.178	385 468	>0 [s]	
INTERNAL HIGH-LET EXPOSURES						
Incidence						
^{224}Ra ankylosing spondylitis patients [W20]	18	12.2	n.a.	32 800	1.56 [t, u]	
^{224}Ra ankylosing spondylitis patients [N4]	13	~11	n.a.	25 000	~1.2	
Danish thorotrast patients [A5]	7	6.9	n.a.	19 365	1.82 (0.61–5.66) [t]	
Mortality						
German thorotrast patients [V3, V8]	30 [v]	n.a.	20.6 ml [w]	n.a.	0.6 [t]	

a 90% CI in parentheses derived from published data for Life Span Study and using exact Poisson methods for the other studies.
b Estimates based on method described in the introduction to Chapter III.
c Based on 5-year survivors. The observed and expected numbers are for both exposed and unexposed persons. The excess absolute risk estimate was computed using background incidence rates estimated using the cervical cancer cohort study [B11].
d Workers with external gamma dose in excess of 3 Gy.
e ERR among those with external gamma doses in excess of 3 Gy relative to those with lower doses.
f Calculation of upper confidence limit did not converge.
g The values given exclude the period within five years of first treatment.
h Dose-response analysis based on the number of treatment courses given.
i Mean annual effective dose = 6.4 mSv.
j Based on a 10-year latent period.
k Based on unirradiated patients.
l The values given exclude the period within five years of irradiation.
m The observed and expected number of cases are for 10-year survivors. The estimated number of expected cases incorporated an adjustment based on the Poisson regression model given in [I16].
n Wald-type CI.
o Based on a 10-year lag. Trend not statistically significant.
p 95% CI in parentheses.
q Restricted to the period 10 or more years after treatment.
r Relative risk at 1 Gy.
s No apparent trend with administered activity of ^{131}I , although a significance test was not performed.
t Relative to unexposed controls.
u In the control group, 16 stomach cancers were diagnosed, compared with 16.9 expected.
v Number quoted in an earlier follow-up [V3].
w Amount of thorotrast administered.

Table 8
Risk estimates for cancer incidence and mortality from studies of radiation exposure: colon cancer
The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this Table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.01 Sv or more for incidence and 0.005 Sv or more (weighted colon dose) for mortality

Study		*Observed cases*	*Expected cases*	*Mean dose (Sv)*	*Person-years*	*Average excess relative risk* [a] *at 1 Sv*	*Average excess absolute risk* [a] *(10^4 PYSv)$^{-1}$*
EXTERNAL LOW-LET EXPOSURES							
Incidence							
Life Span Study [T1]							
Sex	Male	109	90.7	0.23	297 500	0.87	2.66
	Female	114	103.0	0.22	491 100	0.48	1.01
Age at exposure	<20 years	32	28.0	0.23	363 300	0.62	0.48
	>20 years	191	165.7	0.22	425 300	0.70	2.71
All		223	193.7	0.23	788 600	0.67 (0.1–1.3) [b]	1.65 (0.7–3.0) [b]
Cervical cancer case-control [B1] [c]		409	409	24	n.a.	0.00 (–0.01–0.02)	0.01 (–0.09–0.18)
Stockholm skin haemangioma [L16]		12	~11	0.07	406 565	0.37 [d]	0.11
Mortality							
Life Span Study [P9]							
Age at exposure							
Males	<20 years	18	13.8	0.20	369 372	1.52 (–0.8–4.7)	0.57 (–0.3–1.7)
	20-39 years	25	22.7	0.20	116 442	0.51 (–1.2–2.7)	0.99 (–2.3–5.2)
	>40 years	45	42.7	0.20	129 183	0.27 (–1.0–1.8)	0.88 (–3.2–5.8)
Females	<20 years	9	5.6	0.20	414 045	2.96 (–0.8–8.9)	0.40 (–0.1–1.2)
	20-39 years	49	40.4	0.20	357 283	1.06 (–0.3–2.7)	1.20 (–0.3–3.0)
	>40 years	52	48.0	0.20	201 031	0.42 (–0.8–1.8)	1.00 (–1.8–4.4)
Time since exposure							
Both sexes	5-10 years	9	9.4	0.20	186 468	–0.22 (–2.5–3.3)	–0.11 (–1.3–1.7)
	11-25 years	41	37.7	0.20	725 251	0.44 (–0.9–2.1)	0.23 (–0.5–1.1)
	26-40 years	97	85.3	0.20	530 897	0.69 (–0.2–1.7)	1.10 (–0.4–2.8)
	41-45 years	51	41.9	0.20	144 740	1.08 (–0.2–2.7)	3.14 (–0.7–7.8)
All		198	173.2	0.20	1 587 355	0.71 (0.06–1.4) [b]	0.78 (0.07–1.6) [b]
Benign gynaecological disease [I16] [e]		75	46.6	1.3	71 958	0.51 (–0.8–5.61)	3.2 (–0.9–7.1) [b]
Metropathia haemorrhagica [D7] [f]		47	33	3.2	47 144	0.13 (95% CI: 0.01–0.26)	0.92 (95% CI: 0.1–1.8) [b]
Peptic ulcer [G6]		31	24.0 [g]	6	35 815	0.05 (95% CI: –0.05–0.22) [b]	0.33 [b]
Nuclear workers in Canada, United Kingdom, United States [C11]		343	n.a.	0.04	2 124 526	<0 [d, h]	n.a.
Nuclear workers in Japan [E3]		51	42.6	0.014	533 168	<0 [d, h]	n.a.

Study	*Observed cases*	*Expected cases*	*Mean dose*	*Person-years*	*Average relative risk* [i]	
INTERNAL LOW-LET EXPOSURES						
Mortality						
United States thyrotoxicosis patients [R14] [j]	282	255	0.108 [k]	385 468	n.a. [l]	

Table 8 (continued)

Study	*Observed cases*	*Expected cases*	*Mean dose*	*Person-years*	*Average relative risk* [i]	
INTERNAL HIGH-LET EXPOSURES						
Incidence						
Danish thorotrast patients [A5]	9	7.1	n.a.	19 365	1.28 (0.54–2.84) [m]	
Mortality						
German thorotrast patients [V3, V8]	10 [n]	n.a.	20.6 ml [o]	n.a.	~0.5 [m]	

a 90% CI in parentheses derived from published data for Life Span Study and using exact Poisson methods for the other studies.
b Estimates based on method described in the introduction to Chapter III.
c Based on 10-year survivors. The observed and expected numbers cover both exposed and unexposed persons. The excess absolute risk estimate was computed using background incidence rates, estimated using the cervical cancer cohort study [B11].
d Not statistically significantly different from zero.
e The observed and expected number of cases are for 10-year survivors. The estimated number of expected cases incorporated an adjustment based on the Poisson regression model given in [I16].
f The values given exclude the period within five years of irradiation.
g Based on unirradiated patients.
h Based on a 10-year lag.
i 95% CI in parentheses.
j Data for colorectal cancer [R14].
k Value for small intestine [R14].
l No apparent trend with administered activity of ^{131}I, although a significance test was not performed.
m Relative to unexposed controls.
n Number quoted in earlier follow-up [V3].
o Amount of thorotrast administered.

Table 9
Risk estimates for cancer incidence and mortality from studies of radiation exposure: liver cancer
The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this Table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.01 Sv or more for incidence and 0.005 Sv or more (weighted colon dose) for mortality

Study		*Observed cases*	*Expected cases*	*Mean dose (Sv)*	*Person-years*	*Average excess relative risk* [a] *at 1 Sv*	*Average excess absolute risk* [a] *(10^6 PYSv)$^{-1}$*
EXTERNAL LOW-LET EXPOSURES							
Incidence							
Life Span Study [T1] [b]							
Sex	Male	174	150.1	0.24	299 646	0.66	3.32
	Female	110	104.4	0.23	496 606	0.23	0.49
Age at exposure	<20 years	63	48.3	0.24	367 003	1.27	1.67
	>20 years	221	206.2	0.23	429 249	0.31	1.50
All		284	254.5	0.24	796 252	0.48 (0.04–0.96) [c]	1.55 (0.13–3.08) [c]
Cervical cancer cohort [B11] [d]		8	8.8	1.50	178 243	−0.06 (−0.37–0.4) [c]	−0.03 (−0.16–0.2) [c]
Swedish benign breast disease [M28]		12	11.3	0.66	26 493	0.09 (95% CI: <0–1.4)	n.a.
Mortality							
Life Span Study [P9] [e]							
Age at exposure							
Males	<20 years	67	60.2	0.20	371 456	0.57 (−0.50–1.82)	0.92 (−0.81–2.95)
	20-39 years	73	66.5	0.24	116 815	0.41 (−0.44–1.41)	2.34 (−2.52–8.01)
	>40 years	108	99.5	0.21	129 974	0.40 (−0.38–1.28)	3.06 (−2.90–9.82)
Females	<20 years	17	16.2	0.20	416 768	0.23 (−1.62–2.78)	0.09 (−0.63–1.08)
	20-39 years	65	58.1	0.20	359 129	0.60 (−0.50–1.89)	0.96 (−0.81–3.05)
	>40 years	102	97.0	0.17	202 013	0.29 (−0.65–1.37)	1.40 (−3.13–6.56)
Time since exposure							
Both sexes	5-10 years	42	38.9	0.22	186 468	0.36 (−0.82–1.80)	0.75 (−1.71–3.75)
	11-25 years	112	104.1	0.22	725 251	0.34 (−0.39–1.18)	0.49 (−0.56–1.69)
	26-40 years	178	162.8	0.22	530 897	0.42 (−0.17–1.08)	1.30 (−0.53–3.32)
	41-45 years	100	90.5	0.22	144 740	0.48 (−0.32–1.38)	2.97 (−2.01–8.65)
All		432	397.6	0.22	1 596 155	0.42 (0.04–0.83) [c]	1.08 (0.10–2.15) [c]
Ankylosing spondylitis [W1] [f]		11	13.6	2.13	287 095	−0.09 (−0.24–0.2) [c]	−0.04 (−0.11–0.1) [c]
Peptic ulcer [G6]		9	11.4 [g]	4.61	35 815	−0.05 (95% CI: −0.15–0.24) [c]	−0.15 [c]
Benign gynaecological disease [I16] [h]		9 [i]	16.6	0.21	71 958	−2.18 (−3.26–−0.3) [c]	−5.03 (−7.52–−0.7) [c]
Yangjiang background radiation [T25, T26]		171	213.8	n.a. [j]	1 246 340	−0.99 (95% CI: −1.60–0.10) [k]	n.a.
Nuclear workers in Canada United Kingdom, United States [C11]		33	n.a.	0.04	2 124 526	~0	n.a.
Nuclear workers in Japan [E3]		111	128.9	0.014	533 168	>0 [l]	n.a.

Study		*Observed cases*	*Expected cases*	*Mean dose*	*Person-years*	*Average relative risk* [m]	
INTERNAL LOW-LET EXPOSURES							
Mortality							
United States thyrotoxicosis patients [R14]		39	44.8	n.a.	385 468	n.a.	

Table 9 (continued)

Study	*Observed cases*	*Expected cases*	*Mean dose*	*Person-years*	*Average relative risk* [m]	
INTERNAL HIGH-LET EXPOSURES						
Incidence						
Danish thorotrast patients [A5]	84	0.7	3.9–6.1 Gy	n.a.	194.2 [n] (31.0–1 216)	
Mortality						
German thorotrast patients [V1, V8]	454	3.6	4.9 Gy	n.a.	25 Gy^{-1}	
Portuguese thorotrast patients [D3]	104	6.6	26 ml thorotrast	16 963	5.7 [n]	
Combined Japanese thorotrast patients [M14]	143	4	n.a.	10 685	n.a.	

a 90% in parentheses derived from published data for Life Span Study and using exact Poisson methods for the other studies.
b Based on histologically verified cases.
c Estimates based on method described in the introduction to Chapter III.
d Based on 10-year survivors.
e Includes deaths coded as primary liver cancer and liver cancer not specified as secondary.
f The values given exclude the period within five years of first treatment.
g Based on unirradiated patients.
h The estimated number of expected cases incorporated an adjustment based on the Poisson regression model given in [I16].
i Including gallbladder.
j Mean annual effective dose = 6.4 mSv.
k Based on a 10-year latent period.
l Based on a 10-year lag. Trend not statistically significant.
m 95% CI in parentheses.
n Per 10 ml injected dose.

Table 10
Risk estimates for cancer incidence and mortality from studies of radiation exposure: lung cancer
The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this Table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.01 Sv or more for incidence and 0.005 Sv or more (weighted colon dose) for mortality

Study	*Observed cases*	*Expected cases*	*Mean dose (Sv)*	*Person-years*	*Average excess relative risk [a] at 1 Sv*	*Average excess absolute risk [a] (10^4 PYSv)$^{-1}$*
EXTERNAL LOW-LET EXPOSURES						
Incidence						
Life Span Study [T1]						
Sex Male	245	224.7	0.25	302 000	0.36	2.67
Female	211	140.1	0.24	500 700	2.08	5.81
Age at exposure <20 years	30	26.2	0.25	370 000	0.57	0.41
>20 years	426	338.5	0.24	432 700	1.06	8.27
Time since exposure 5-19 years	85	67.8	0.24	288 566	1.04	2.45
20-29 years	146	116.3	0.24	317 535	1.05	3.85
30-42 years	225	186.4	0.24	314 545	0.85	5.05
All	456	364.7	0.25	802 700	1.00 (0.6–1.4) [b]	4.55 (2.4–6.0) [b]
Hodgkin's disease (international) [K9]	79	n.a.	2.2	n.a.	n.a. [c]	n.a.
Hodgkin's disease (Netherlands) [V2]	29	n.a.	7	n.a.	~1 (95% CI: <0– ~10)	n.a.
Breast cancer [I7]	17	n.a.	9.8 [d]	n.a.	0.08 (95% CI: –0.77–0.22) [e]	0.9
Swedish benign breast disease [M28]	10	11.2	0.75	26 493	0.38 (95% CI: <0–0.6)	n.a.
Stockholm skin haemangioma [L16]	11	~9	0.12	406 565	1.4	0.33
Mortality						
Life Span Study [P9]						
Age at exposure						
Males <20 years	30	28.4	0.23	369 372	0.24 (–1.0–1.9)	0.18 (–0.8–1.4)
20-39 years	97	90.8	0.23	116 442	0.30 (–0.5–1.2)	2.32 (–3.5–9.0)
>40 years	182	164.8	0.23	129 183	0.45 (–0.1–1.1)	5.80 (–1.5–1.1)
Females <20 years	18	16.6	0.23	414 045	0.37 (–1.3–2.6)	0.15 (–0.5–1.1)
20-39 years	125	115.3	0.23	357 283	0.37 (–0.3–1.1)	1.18 (–1.0–3.6)
>40 years	132	115.4	0.23	201 031	0.63 (–0.1–1.4)	3.60 (–0.4–8.0)
Time since exposure						
Both sexes 5-10 years	10	8.3	0.23	186 468	0.87 (–1.5–4.5)	0.39 (–0.7–2.0)
11-25 years	158	143.7	0.23	725 251	0.43 (–0.2–1.1)	0.86 (–0.3–2.2)
26-40 years	297	268.4	0.23	530 897	0.46 (0.01–0.9)	2.34 (0.07–4.8)
41-45 years	119	107.4	0.23	144 740	0.47 (–0.2–1.3)	3.50 (–1.7–9.4)
All	584	526.1	0.23	1 587 355	0.48 (0.16–0.8) [b]	1.59 (0.53–2.7) [b]
Ankylosing spondylitis [W1] [f]	563	469	2.54	287 095	0.05 (95% CI: (0.002–0.09) [g]	0.9 (95% CI: 0.0–1.4) [b]
Canadian TB fluoroscopy [H7] [h]	455	473.7	1.02	672 071	0.00 (95% CI: –0.06–0.07)	0.0 (95% CI: –0.4–0.4)
Peptic ulcer [G6]	99	58.2 [i]	1.79	35 815	0.39 (95% CI: 0.11–0.78) [b]	6.36 [b]
Massachusetts TB fluoroscopy [D4]	69	81.8	0.84	169 425	–0.19 (<–0.2–0.04) [b]	–0.90 (<–1.8–0.2) [b]
Yangjiang background radiation [T25, T26]	62	76.5	n.a. [j]	1 246 340	–0.68 (95% CI: –1.58–1.67) [k]	n.a.
Nuclear workers in Canada, United Kingdom, United States [C11]	1 238	n.a.	0.04	2 124 526	<0 [l]	n.a.

Table 10 (continued)

Study	*Observed cases*	*Expected cases*	*Mean dose (Sv)*	*Person-years*	*Average excess relative risk* [m] *at 1 Sv*	*Average excess absolute risk* [a] *(10^4 PYSv)$^{-1}$*
Nuclear workers in Japan [E3]	117	124.9	0.014	533 168	<0 [l]	n.a.
Mayak reactor workers (cohort study) [n] [K34]	47	56.23	1.02	67 097	−0.161 [l]	−11.7 [l]
Study	*Observed cases*	*Expected cases*	*Mean WLM*	*Person-years*	*Average ERR* [o] *at 100 WLM*	
INTERNAL HIGH-LET EXPOSURES (Occupational radon)						
Mortality						
Chinese tin miners [L4, X1] [p]	936	649	277.4	135 357	0.16 (0.1–0.2)	
West Bohemia uranium miners [L4, T22] [q]	702	137.7	219	106 983	0.64 (0.4–1.1)	
Colorado Plateau uranium miners [H17, L4] [o]	327	74	807.2	75 032	0.42 (0.3–0.7)	
Ontario uranium miners [K4, L4] [o]	282	221	30.8	319 701	0.89 (0.5–1.5)	
Newfoundland fluorspar miners [L4, M15] [r]	138	32.1	382.8	48 189	0.70 (0.44–1.14)	
Swedish iron miners [L4, R8] [o]	79	44.7	80.6	32 452	0.95 (0.1–4.1)	
New Mexico uranium miners [L4, S19] [o]	68	23.5	110.3	46 797	1.72 (0.6–6.7)	
Beaverlodge uranium miners [H15, H18, L4] [o]	56	15.4	81.3 [s]	68 040	3.25 (1.0–9.6) [t]	
Port Radium uranium miners [H16, L4] [o]	39	26.7	242.8	31 454	0.19 (0.1–0.6)	
Radium Hill uranium miners [L4, W7] [o]	32	23.1	7.6	25 549	5.06 (1.0–12.2)	
French uranium miners [L4, T8] [o]	45	36.1	68.7	39 487	0.36 (0.0–1.3)	
Cornish tin miners [D8, H13]	82	n.a.	65	66 900	0.045 [u]	
Study	*Observed cases*	*Expected cases*	*Mean concentration (Bq m^{-3})*	*Person-years*	*Average ERR* [k] *at 100 Bq m^{-3}*	
INTERNAL HIGH-LET EXPOSURES (Residental radon)						
Incidence						
Meta-analysis of eight case-control studies [L21]	4 263	n.a.	n.a.	n.a.	0.09 (0.0–0.2)	
West Germany [W17]						
Entire study region	1 449	n.a.	49 [v]	n.a.	−0.02 (−0.18-0.17)	
Radon-prone areas	365	n.a.	67 [o]	n.a.	0.13 (−0.12-0.46)	
East Germany [W18]	1 053	n.a.	87 [w]	n.a.	0.04 (−0.04-0.12)	
Southwest England [D30]	982	n.a.	58 [o]	n.a.	0.08 (−0.03-0.20)	
Missouri-II [A24]						
Based on track-etch measurements	247	n.a.	58.5	n.a.	0.06 (−0.1-0.6)	
Based on CR-39 surface measurements	372	n.a.	64.6	n.a.	0.65 (0.1-2.0)	

Table 10 (continued)

Study	*Observed cases*	*Expected cases*	*Mean dose*	*Person-years*	*Average relative risk* [n]	
INTERNAL HIGH-LET EXPOSURES (other than radon)						
Incidence						
Mayak radiochemical plant workers (case-control study) [T2]	60 [x]	n.a.	n.a.	n.a.	3.1 (1.8–5.1) [y]	
^{224}Ra ankylosing spondylitis patients [W20]	25	35.7	n.a.	32 800	1.20 [z]	
^{224}Ra ankylosing spondylitis patients [N4]	20	30	n.a.	25 500	0.67	
Danish thorotrast patients [A5]	21	10.9 [aa]	0.18 Gy [ab]	19 365	0.7 (0.3–1.7) [ac]	
Mortality						
Mayak workers (cohort study) [j]	105	42.18	6.56 Sv [ad]	31 693	0.321 Sv^{-1} (0.20–0.47)	
Sellafield plutonium workers [O1]	133	145.8	0.19 Sv	415 432	1.12 [ae]	
Japanese thorotrast patients, combined data [M14]	11	n.a.	17 ml [af]	10 685	2.0 (1.0–3.9)	
German thorotrast patients [V1]	53	n.a.	20.6 ml [ag]	n.a.	0.75 [ah]	
Portuguese thorotrast patients [D31]	10	n.a.	26.3 ml [af]	16 963	4.68 (0.24–92.1) [ai]	
Los Alamos workers [aj] [W8]	8	n.a.	n.a.	n.a.	1.78 (0.79–3.99) [ak]	

a 90% CI in parentheses derived from published data for Life Span Study and using exact Poisson methods for the other studies.
b Estimates based on method described in the introduction to Chapter III.
c Relative risks quoted in Section III.E.
d Average dose to both lungs for irradiated controls.
e Wald-type CI; likelihood-based lower confidence bound could not be identified.
f The values given exclude the period within five years of first treatment.
g Dose-response analysis based on the number of treatment courses given.
h The values given exclude the period within ten years of exposure and ages at risk less than 20 years.
i Based on unirradiated patients.
j Mean annual effective dose = 6.4 mSv.
k Based on a 10-year latent period.
l Trend not statistically significant.
m 90% CI in parentheses derived from published data for Life Span Study and using exact Poisson methods for the other studies.
n Results presented here for males only.
o 95% CI in parentheses.
p The values cited are from [L4], unless indicated otherwise, and except for the expected number of cases which has been calculated as $O/(1+100\,\alpha D)$, where O is the observed cases, α is the ERR at 100 WLM and D is the mean WLM.
q Values cited are based on data from [T22].
r Values cited are from [M15], and include non-exposed miners.
s Revised value for persons in nested case–control study [H18].
t Values based on case-control analysis with revised exposure estimates [H18].
u Coefficient based on time-weighted cumulative exposure.
v Value for cases.
w Value for cases, based on measurements in living room [W18].
x Workers with plutonium body burden above 5.55 kBq.
y Comparison group consists of workers with plutonium body burden below 5.55 kBq.
z Relative to unexposed controls, among whom 29 cases were observed, compared with 49.6 expected [W20].
aa Based on national rates [A5].
ab As given in [A12].
ac Relative to unexposed controls, with adjustment for sex, age at angiography, and calendar period.
ad Alpha dose to lung, based on a radiation weighting factor of 20 [K34].
ae Relative to other radiation workers at Sellafield; difference is not statistically significant [O1].
af Mean amount of thorotrast administered in the first series of Japanese patients [M47].
ag Amount of thorotrast administered.
ah Relative to unexposed controls.
ai Based on three deaths in the control group, and excluding the first five years after administration of thorotrast [D31].
aj Workers with plutonium body burden of 74 Bq or more.
ak Comparison group consists of workers with plutonium body burden below 74 Bq.

Table 11
Risk estimates for cancer incidence and mortality from studies of radiation exposure: malignancies of the bone and connective tissue
The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this Table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.01 Sv or more for incidence and 0.005 Sv or more (weighted colon dose) for mortality

Study	*Observed cases*	*Expected cases*	*Mean dose (Sv)*	*Person-years*	*Average excess relative risk* [a] *at 1 Sv*	*Average excess absolute risk* [a] *(10^4 PYSv)$^{-1}$*
EXTERNAL LOW-LET EXPOSURES						
Incidence						
Life Span Study [T1]						
Sex Male	9	6.4	0.23	297 500	1.78	0.38
Female	7	5.7	0.22	491 100	0.99	0.12
Age at exposure <20 years	4	1.1	0.23	363 300	11.0	0.34
>20 years	12	11.0	0.22	425 300	0.42	0.11
All	16	12.1	0.23	788 600	1.42 (<−0.2−4.5) [b]	0.22 (<−0.1−0.7) [b]
Retinoblastoma patients [W11] (bone and soft tissue sarcoma) [c]	81	16.9	0.0 [d]	n.a.	0.19 (95% CI: 0.14−0.32)	n.a.
Childhood radiotherapy, international [T17]	54	20.0	27.0	n.a.	0.06 (0.01−0.2) [b]	n.a.
Childhood cancer, United Kingdom (bone) [e] [H44]	49	18.8	10[d]	n.a.	0.16 (95% CI: 0.07−0.37)	n.a.
Cervical cancer case-control [B1] (connective tissue) [f]	46	70.8	7.0	n.a.	−0.05 (−0.11−0.13)	−0.01 (−0.03−0.03)
Cervical cancer case-control [B1] (bone) [f]	15	10.4	22	n.a.	0.02 (−0.03−0.21) [b]	n.a.
Mortality						
Life Span Study [R1]						
Sex Male	14	10.8	0.23	471 800	1.26	0.29
Female	10	8.5	0.23	731 300	0.81	0.09
Age at exposure <20 years	3	1.9	0.23	574 500	2.58	0.08
>20 years	21	17.4	0.22	628 600	0.92	0.26
All	24	19.3	0.23	1 203 100	1.07 (<−0.2−3.3) [b]	0.17 (<−0.1−0.5) [b]
Ankylosing spondylitis [W1] [g] (bone and connective and soft tissue)	19	6.3	4.54	287 095	0.44 [b]	0.097 [b]
Nuclear workers in Canada, United Kingdom, United States [C11] (bone)	11	n.a.	0.04	2 124 526	<0 [h]	n.a.
Nuclear workers in Canada, United Kingdom, United States [C11] (connective tissue)	19	n.a.	0.04	2 124 526	>0 [h]	n.a.

Study	*Observed cases*	*Expected cases*	*Mean dose*	*Person-years*	*Average relative risk* [i]	*Average excess absolute risk (10^4 PYSv)$^{-1}$*
INTERNAL HIGH-LET EXPOSURES						
Incidence						
^{224}Ra TB and ankylosing spondylitis patients (bone) [N14]	55	0.2	30.6 Gy	25 500	n.a.	n.a.
^{224}Ra ankylosing spondylitis patients (bone and connective tissue) [W20]	4	1.3	~6 Gy	32 800	4.3 [j]	n.a.

Table 11 (continued)

Study	*Observed cases*	*Expected cases*	*Mean dose*	*Person-years*	*Average relative risk* [i]	*Average excess absolute risk* $(10^4\ PYSv)^{-1}$
German thorotrast patients (bone sarcoma [V8]	4	n.a.	20.6 ml [k]	n.a.	~3.3 [l]	n.a.
Mortality						
United States radium luminizers [m] (bone) [C27, R35, S12, S16, S54, S56]	46	<1	8.6 Gy	35 819	n.a.	~13
Portuguese thorotrast patients (bone) [D31]	16	n.a.	26.3 ml [k]	16 963	7.08 (1.65–30.3) [n]	n.a.

a 90% CI in parentheses derived from published data for Life Span Study and using exact Poisson methods for the other studies.
b Estimates based on method described in the introduction to Chapter III.
c Results are for patients with bone or soft tissue sarcoma for whom dosimetry information was available.
d Mean dose for controls of bone cancer cases.
e Results are based on a case-control analysis of bone cancer.
f Based on one-year survivors. The observed and expected numbers cover both exposed and unexposed persons. The excess absolute risk for connective tissue was computed using baseline incidence data derived from the cohort study [B11].
g The values given exclude the period within five years of first treatment.
h Based on a 10-year lag. Trend not statistically significantly different from zero.
i 95% CI in parentheses.
j Relative to unexposed controls, among whom one case was observed compared with 1.4 expected [W20].
k Amount of thorotrast administered.
l Crude relative risk, based on one case in the control group. This relative risk is not significantly different from 1 ($p>0.05$) [V8].
m Based on pre-1930 workers with an average skeletal dose greater than zero [C27].
n Based on five deaths in the control group, and excluding the first five years after administration of thorotrast [D31].

Table 12
Risk estimates for cancer incidence and mortality from studies of radiation exposure: skin cancer
The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this Table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.01 Sv or more for incidence and 0.005 Sv or more (weighted colon dose) for mortality

Study		*Observed cases*	*Expected cases*	*Mean dose (Sv)*	*Person-years*	*Average excess relative risk [a] at 1 Sv*	*Average excess absolute risk [a] (10^4 PYSv)$^{-1}$*
EXTERNAL LOW-LET EXPOSURES							
Incidence							
Life Span Study [T1]							
Sex	Male	41	31.4	0.33	324 100	0.92	0.89
	Female	57	44.4	0.32	538 900	0.88	0.72
Age at exposure	<20 years	21	7.7	0.32	399 300	5.37	1.04
	>20 years	77	68.2	0.33	463 700	0.39	0.58
All		98	75.9	0.33	863 000	0.88 (0.4–1.9) [b]	0.78 (0.4–1.4) [b]
Childhood exposure							
Israel tinea capitis [R16]		42	10.0	6.8	265 070	0.47 (0.3–0.7) [b]	0.18 (0.1–0.25) [b]
New York tinea capitis (whites) [c] [S27, S30]		83	24.0	5.0	52 000 [d]	0.49 (0.37–0.63) [b]	2.5 (1.9–3.2) [b]
Rochester thymic irradiation [c] [H31, S30]		14	4.2	2.3	87 000 [d]	1.05 (0.50–1.9) [b]	0.50 (0.3–0.9) [b]
Tonsil irradiation [c] [S28, S30]		63	45.0	3.8	96 000 [d]	0.11 (0.03–0.19) [b]	0.50 (0.2–1.0) [b]
Adult exposure							
Cervical cancer cohort [B1]		88	100	10	342 786	–0.01 (–0.02–0.01) [b]	–0.02 (–0.06–0.03) [b]
Massachusetts TB fluoroscopy [c] [D16, S30]		80	75.3	9.6	122 000 [d]	0.01 (0–0.03) [b]	0.04 (0–0.2) [b]
New York mastitis [c] [S30]		14	10.7	2.6	14 000 [d]	0.12 (0–0.8) [b]	0.90 (0–2.8) [b]

a 90% CI in parentheses derived from published data for Life Span Study and using exact Poisson methods for the other studies.
b Estimates based on method described in the introduction to Chapter III.
c From data presented by Shore [S30].
d Person-years estimated from data presented by Shore [S30].

Table 13
Risk estimates for cancer incidence and mortality from studies of radiation exposure: female breast cancer
The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this Table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.01 Sv or more for incidence and 0.005 Sv or more (weighted colon dose) for mortality. For case-control studies, the observed number of cases covers both exposed and unexposed persons.

Study	*Observed cases*	*Expected cases*	*Mean dose (Sv)*	*Person-years*	*Average excess relative risk [a] at 1 Sv*	*Average excess absolute risk [a] (10^4 PYSv)$^{-1}$*
EXTERNAL LOW-LET EXPOSURES						
Incidence						
Life Span Study [T1]						
Age at exposure <20 years	122	62.8	0.28	202 600	3.32 (2.3–4.4)	10.3 (7.2–14)
>20 years	173	137.1	0.27	308 000	0.98 (0.4–1.6)	4.36 (1.8–7.2)
Time since exposure 5–19 years	49	36.9	0.28	161 400	1.19	2.72
20–29 years	87	63.5	0.27	175 800	1.34	4.86
30–42 years	159	99.5	0.27	173 400	2.21	12.68
All	295	199.9	0.27	510 600	1.74 (1.1–2.2) [b]	6.80 (4.9–8.7) [b]
Massachusetts TB fluoroscopy [B3]	142	107.6	0.79	54 600	0.40 (0.2–0.7) [b]	7.98 (3.6–13) [b]
New York acute post-partum mastitis [S15]	54	20.8	3.7	9 800	0.43 (0.3–0.6) [b]	9.14 (6.0–13) [b]
Swedish benign breast disease [M8, M20]	115	28.8	8.46	37 400	0.35 (0.3–0.4) [b]	2.72 (2.2–3.3) [b]
Cervical cancer case control [c] [B50]	953 [d]	1083.0	0.31	n.a.	–0.2 (<–0.2–0.3)	<–0.3 (<–0.3–0.2)
Without ovaries	91 [e]	82.6	0.31	n.a.	0.33 (<–0.2–5.8)	n.a.
Contralateral breast						
Denmark [S20]	529	508.7	2.51	n.a.	0.02 (<–0.1–0.2) [b]	n.a.
United States [B10]	655	550.4	2.82	n.a.	0.07 (<–0.1–0.2) [b]	n.a.
Rochester thymic irradiation [f] [H10]	22	7.8	0.76	38 200	2.39 (1.2–4.0) [b]	4.89 (2.4–8.1) [b]
Childhood skin haemangioma [f] [L46]	245	204	0.33	600 000	0.35 (95% CI: 0.18–0.59)	1.44 (95% CI: 0.78–2.28)
Hodgkin's disease (Stanford) [H2]	25	6.1	~44.0	100 057	0.07 (0.04–0.11) [b]	0.04 (0.03–0.07) [b]
Childhood Hodgkin's disease [f] [B16]	17	0.2	20	n.a.	n.a. [g]	n.a.
Mortality						
Life Span Study [P9]						
Age at exposure <20 years	52	29.1	0.25	414 045	3.16 (1.61–5.0)	2.22 (1.13–3.5)
20–39 years	57	50.0	0.25	357 283	0.56 (–0.4–1.7)	0.78 (–0.5–2.4)
>40 years	33	30.2	0.25	201 031	0.37 (–0.8–1.8)	0.55 (–1.2–2.8)
Time since exposure 5–10 years	16	22.3	0.25	108 719	–1.12 (–2.2–0.4)	–2.30 (–4.5–0.8)
11–25 years	47	40.9	0.25	442 174	0.60 (–0.4–1.19)	0.55 (–0.4–1.7)
26–40 years	54	36.5	0.25	330 501	1.19 (0.66–3.4)	2.11 (0.72–3.8)
41–45 years	25	13.5	0.25	90 964	3.43 (1.16–6.4)	5.07 (1.72–9.4)
All	142	107.6	0.25	972 358	1.28 (0.57–2.1) [b]	1.42 (0.63–2.3) [b]
Scoliosis patients [f] [D34]	70	35.7	0.11	184 508	5.4 (95% CI: 1.2–14.1)	12.9 (95% CI: 4.0–21.0)
Ankylosing spondylitis [W1] [h]	42	39.3	0.59	n.a.	0.08 (95% CI: –0.30–0.65) [i]	n.a.
Canadian TB fluoroscopy [H20]	349	237	0.89	411 706	0.90 (95% CI: 0.55–1.39) [j]	3.16 (95% CI: 1.97–4.78) [k]
Nuclear workers in Canada, United Kingdom, United States [C11]	84	n.a.	0.04	n.a.	>0 [l]	n.a.

Table 13 (continued)

Study	*Observed cases*	*Expected cases*	*Mean dose*	*Person-years*	*Average ERR at 1 Sv*	
INTERNAL HIGH-LET EXPOSURES						
Incidence						
^{224}Ra TB and ankylosing spondylitis patients [N4]	28	8	~0.1 Gy [m]	n.a.	0.9	

a 90% CI in parentheses derived from published data for Life Span Study and using exact Poisson methods for the other studies.
b Estimates based on method described in the introduction to Chapter III.
c Excess absolute risk among cervical cancer patients is computed using baseline incidence data derived from the cohort study [B11].
d Based on 5-year survivors.
e Based on 10-year survivors.
f Population exposed as children.
g Relative risks by dose group quoted in Section III.H.1.
h The values given exclude the period within five years of first treatment.
i Dose-response analysis based on the number of treatment courses given.
j Including a factor to allow for differences between Nova Scotia and other Canadian provinces. Values apply to exposure at age 15 years.
k Including a factor to allow for differences between Nova Scotia and other Canadian provinces. Values apply 20 years following exposure at age 15 years.
l Based on a 10-year lag. Trend not statistically significant.
m High-LET breast dose from radium-224.

Table 14
Risk estimates for cancer incidence and mortality from studies of radiation exposure: prostate cancer
The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this Table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.01 Sv or more for incidence and 0.005 Sv or more (weighted colon dose) for mortality

Study	*Observed cases*	*Expected cases*	*Mean dose (Sv)*	*Person-years*	*Average excess relative risk* [a] *at 1 Sv*	*Average excess absolute risk* [a] *$(10^4$ PYSv$)^{-1}$*
EXTERNAL LOW-LET EXPOSURES						
Incidence						
Life Span Study [T1]	95	92.01	0.21	297 500	0.14 (−0.6−1.0) [b]	0.44 (−1.8−3.0) [b]
Mortality						
Ankylosing spondylitis [W1] [c]	88	64.7	2.18	n.a.	0.14 (95% CI: 0.02−0.28) [d]	n.a.
Peptic ulcer [G6]	26	18.7 [e]	0.08	n.a.	4.9 (95% CI: −2.5−15.0) [b]	n.a.
Nuclear workers in Canada, United Kingdom, United States [C11]	256	n.a.	0.04	n.a.	<0 [f]	n.a.
Study	*Observed cases*	*Expected cases*	*Mean dose*	*Person-years*	*Average relative risk* [g]	
INTERNAL LOW-LET EXPOSURES						
Incidence						
UK Atomic Energy Authority workers: case-control study [R26]	28 [h]	n.a.	n.a.	n.a.	2.36 (1.26−4.43)	
Mortality						
United States thyrotoxicosis patients [R14]	36	52.7	<0.1	n.a.	n.a. [i]	
INTERNAL HIGH-LET EXPOSURES						
Incidence						
^{224}Ra TB and ankylosing spondylitis patients [N4]	16	~12	n.a.	n.a.	~1.3	
Mortality						
German thorotrast patients [V8]	21	n.a.	20.6 ml [j]	n.a.	~0.9 [k]	

a 90% CI in parentheses derived from published data for Life Span Study and using exact Poisson methods for the other studies.
b Estimates based on method described in the introduction to Chapter III.
c The values given exclude the period within five years of first treatment.
d Dose-response analysis based on the number of treatment courses given.
e Based on unirradiated patients.
f Based on a 10-year lag. One-sided p-value for increasing trend equals 0.953, based on a normal approximation.
g 95% CI in parentheses.
h Men who worked in environments potentially contaminated with ^{51}Cr, ^{59}Fe, ^{60}Co, ^{65}Zn or ^{3}H.
i No apparent trend with administered activity of ^{131}I, although a significance test was not performed.
j Amount of thorotrast administered.
k Relative to unexposed controls.

Table 15
Risk estimates for cancer incidence and mortality from studies of radiation exposure: cancer of the urinary bladder
The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this Table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.01 Sv or more for incidence and 0.005 Sv or more (weighted colon dose) for mortality

Study		*Observed cases*	*Expected cases*	*Mean dose (Sv)*	*Person-years*	*Average excess relative risk* [a] *at 1 Sv*	*Average excess absolute risk* [a] *$(10^4$ PYSv$)^{-1}$*
EXTERNAL LOW-LET EXPOSURES							
Incidence							
Life Span Study [T1]							
Sex	Male	76	70.3	0.23	297 500	0.35	0.84
	Female	39	27.9	0.22	491 200	1.80	1.02
Age at exposure	<20 years	12	10.3	0.23	363 300	0.71	0.20
	>20 years	103	87.8	0.22	425 300	0.79	1.62
All		115	98.1	0.23	788 600	0.76 (0.3–2.1) [b]	0.95 (0.3–2.1) [b]
Cervical cancer case-control [B1] [c]		273	65.8	45	n.a	0.07 (0.02–0.17)	0.12 (0.04–0.3)
Mortality							
Life Span Study [P9]							
Age at exposure							
Males	<20 years	6	3.4	0.20	371 260	3.83 (−1.19–12.50)	0.35 (−0.11–1.15)
	20–39 years	5	4.1	0.23	116 726	0.90 (−2.26–6.63)	0.32 (−0.80–2.35)
	>40 years	39	35.4	0.21	129 809	0.48 (−0.83–2.11)	1.32 (−2.27–5.75)
Females	<20 years	2	1.7	0.20	416 447	1.05 (−3.90–13.98)	0.04 (−0.15–0.55)
	20–39 years	7	8.1	0.19	358 988	−0.69 (−3.07–3.27)	−0.15 (−0.69–0.73)
	>40 years	23	19.5	0.17	201 931	1.04 (−1.14–3.91)	1.00 (−1.10–3.78)
Time since exposure							
Both sexes	5–10 years	4	5.0	0.20	258 146	−1.02 (−3.67–4.14)	−0.20 (−0.71–0.81)
	11–25 years	29	28.3	0.20	658 705	0.12 (−1.34–2.00)	0.05 (−0.58–0.86)
	26–40 years	35	26.1	0.20	533 369	1.75 (−0.04–3.98)	0.85 (−0.02–1.94)
	41–45 years	14	16.6	0.19	144 940	−0.82 (−2.55–1.65)	−0.94 (−2.92–1.89)
All		82	72.2	0.20	1 595 161	0.58 (−0.40–1.72) [b]	0.27 (−0.19–0.79) [b]
Benign gynaecological disease [I16] [d]		19	9.0	6.00	71 958	0.20 (0.08–0.35)	0.24 (0.1–0.4) [b]
Metropathia haemorrhagica [D7] [e]		20	6.7	5.20	47 144	0.40 (95% CI: 0.15–0.66)	0.55 (95% CI: 0.2–0.9) [b]
Ankylosing spondylitis [W1] [f]		71	46.1	2.18	287 095	0.24 (95% CI: 0.09–0.41) [g]	0.39 (95% CI: 0.19–0.54) [b]
Nuclear workers in Canada, United Kingdom, United States [C11]		104	n.a.	0.04	2 142 526	>0 [h]	n.a.

a 90% CI in parentheses derived from published data for Life Span Study and using exact Poisson methods for the other studies.
b Estimates based on method described in the introduction to Chapter III.
c Based on 10-year survivors. The observed and expected numbers cover both exposed and unexposed persons. The excess absolute risk estimate was computed using background incidence rates estimated using the cervical cancer cohort study [B11].
d The observed and expected number of cases are for 10-year survivors. The estimated number of expected cases incorporated an adjustment based upon the Poisson regression model given in [I16].
e The values given exclude the period within five years of irradiation.
f The values given exclude the period within five years of first treatment.
g Dose-response analysis based on the number of treatment courses given.
h Based on a 10-year lag. Trend not statistically significant.

Table 16
Risk estimates for cancer incidence and mortality from studies of radiation exposure: brain and central nervous system tumours
The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this Table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.01 Sv or more for incidence.

Study		*Observed cases*	*Expected cases*	*Mean dose (Sv)*	*Person-years*	*Average excess relative risk [a] at 1 Sv*	*Average excess absolute risk [a] (10^4 PYSv)$^{-1}$*
EXTERNAL LOW-LET EXPOSURES							
Incidence							
Life Span Study [T1]							
Sex	Male	20	21.7	0.27	307 100	−0.30	−0.21
	Female	51	45.3	0.26	509 300	0.48	0.43
Age at exposure	<20 years	20	15.7	0.26	376 100	1.05	0.44
	>20 years	51	51.4	0.26	440 200	−0.03	−0.03
	All	71	67.1	0.26	816 300	0.22 (<0−1.3) [b]	0.18 (<0−0.8) [b]
Israel tinea capitis [R17]		60	8.4	1.5	283 930	4.08 (3.1−5.2) [b]	1.2 (0.9−1.5) [b]
New York tinea capitis [A16]		8	1.4	1.4	48 115	3.4 (1.3−6.7) [b]	0.98 (0.4−1.9) [b]
Swedish pooled skin haemangioma [K23]		83	58.0	0.07	913 402	2.7 (95% CI: 1.0−5.6)	2.1 (95% CI: 0.3−4.4)
Mortality							
Pituitary adenoma (UK) [B22]		5	0.5	45	3 760	0.20 (0.07−0.45) [b]	0.27 (0.09−0.59) [b]
Nuclear workers in Canada, United Kingdom, United States[C11]		122	n.a.	0.04	2 142 526	<0 [c]	n.a.

a 90% CI in parentheses derived from published data for Life Span Study and using exact Poisson methods for the other studies.
b Estimates based on method described in the introduction to Chapter III.
c Based on a 10-year lag. Trend not statistically significant.

Table 17
Risk estimates for cancer incidence and mortality from studies of radiation exposure: thyroid cancer
The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this Table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.01 Sv or more for incidence

Study	*Observed cases*	*Expected cases*	*Mean dose (Sv)*	*Person-years*	*Average excess relative risk [a] at 1 Sv*	*Average excess absolute risk [a] (10^4 PYSv)$^{-1}$*
EXTERNAL LOW-LET EXPOSURES						
Incidence						
Life Span Study [T1]						
Sex Male	22	14.9	0.27	307 167	1.80	0.87
Female	110	79.4	0.26	510 388	1.49	2.32
Age at exposure 0–9 years	24	7.6	0.21	185 507	10.25	4.21
10–19 years	35	14.6	0.31	190 087	4.50	3.46
20–29 years	18	17.5	0.28	132 738	0.10	0.13
>30 years	55	54.5	0.25	309 224	0.04	0.06
All	132	94.3	0.26	817 600	1.5 (0.5–2.1) [b]	1.8 (0.8–2.5) [b]
Tuberculosis, adenitis screening [H3, S8]						
Age at exposure <20 years	6	0.0	8.20	950	36.5 (16–72) [b]	7.7 (3.3–15) [b]
>20 years	2	0.2	8.20	3 100	1.2 (0.1–3.7) [b]	0.7 (0.1–2.4) [b]
Cohort studies of children						
Life Span Study [T1] Age at exposure 0–19 years	59	22.2	0.26	375 600	6.3 (5.1–10.1) [b]	3.8 (2.7–5.4) [b]
Israeli tinea capitis [R9] [c]	43	10.7	0.1	274 180	34 (23–47) [b]	13 (9.0–18) [b]
New York tinea capitis [S8]	2	1.4 [d]	0.1	79 500	7.7(<0–60) [b]	1.3 (<0–10.3) [b]
Rochester thymic irradiation [e] [S18]	37	2.7	1.4	82 204	9.5 (6.9–12.7) [b]	3.0 (2.2–4.0) [b]
Childhood cancer [f] [T5]	23	0.4	12.5	50 609	4.5 (3.1–6.4) [b]	0.4 (0.2–0.5) [b]
Stockholm skin haemangioma [L13]	17	7.5	0.26	406 355	4.9 (95% CI: 1.3–10.2)	0.9 ((95% CI: 0.2–1.9)
Gothenburg skin haemangioma [L15]	15	8	0.12	370 517	7.5 (95% CI: 0.4–18.1)	1.6 (95% CI: 0.09–3.9)
Screening studies of children						
Lymphoid hyperplasia screening [e, g] [P8, S8]	13	5.4 [b]	0.24	34 700	5.9 (1.8–11.8) [b]	9.1 (2.7–18.3) [b]
Thymus adenitis screening [M4, S8]	16	1.1 [b]	2.9	44 310	4.5 (2.7–7.0) [b]	1.2 (0.7–1.8) [b]
Michael Reese, tonsils [h] [S21]	309	110.4	0.6	88 101	3.0 (2.6–3.5) [b]	37.6 (32–43) [b]
Tonsils/thymus/acne screening [D5, S8]	11	0.2 [b]	4.5	6 800	12.0 (6.6–20) [b]	3.5 (2.0–5.9) [b]
Pooled analysis of five studies of children						
Life Span Study Israeli tinea capitis Rochester thymic irradiation Lymphoid hyperplasia screening Michael Reese tonsil [R4]	436	n.a.	n.a.	n.a.	7.7 (95% CI: 2.1–28.7)	4.4 (95% CI: 1.9–10.1)
Studies of adults						
Cervical cancer case-control [d] [B1]	43	18.8	0.11	n.a.	12.3 (<0–76) [b]	6.9 (<0–39.2) [b]
Cervical cancer cohort [d, i] [B11]	16	12.5	0.11	342 786	2.5 (<0–6.8) [b]	0.9 (<0–2.5) [b]
Stanford thyroid [H9]	6	0.4	45	17 700	0.3 (0.1–0.7) [b]	0.07 (0.03–0.1) [b]

Table 17 (continued)

Study	*Observed cases*	*Expected cases*	*Mean dose*	*Person-years*	*Average relative risk*	
INTERNAL LOW-LET EXPOSURES						
Incidence						
Diagnostic ^{131}I [H4]	67	49.7	1.1	653 093	n.a. [j]	

a 90% CI in parentheses derived from published data for Life Span Study and using exact Poisson methods for the other studies.
b Estimates based on method described in the introduction to Chapter III.
c Doses to the thyroid in this study may be much more uncertain than doses to organs directly in the x-ray beam.
d Expected number of cases computed using excess relative risk estimates given in [S8].
e Known dose. PY and expected number of cases estimated from data given in [S8].
f Based on cohort members with 15 or more years of follow-up and population-expected rates.
g This was a study of nodular disease, and cancer cases were not confirmed.
h Study includes no unexposed controls; estimates of the number of expected cases were computed using the fitted excess relative risk reported in [S21]. Results are based on the new dosimetry described in [S21]. The large excess absolute risk in this study illustrates the impact of screening on thyroid cancer risk estimates. As described in [S21], a special thyroid screening programme in this cohort was initiated in 1974. This screening led to a large increase in the number of incident cases detected among both cases and controls. The paper describes an analysis in which allowance was made for the effect of screening. The screening-adjusted excess absolute risk was estimated as 1.7 (10^{-4} PYGy)$^{-1}$.
i Excludes cases diagnosed during first 10 years of follow-up.
j Trend not statistically significant (see Table 28).

Table 18
Risk estimates for cancer incidence and mortality from studies of radiation exposure: non-Hodgkin's lymphoma
The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this Table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.01 Sv or more for incidence.

Study	*Observed cases*	*Expected cases*	*Mean dose (Sv)* [a]	*Person-years*	*Average excess relative risk* [b] *at 1 Sv*	*Average excess absolute risk* [b] *(10^4 PYSv)$^{-1}$*
EXTERNAL LOW-LET EXPOSURES						
Incidence						
Life Span Study [P4]						
Sex Male	41	33.2	0.26	412 400	0.91	0.73
Female	35	38.3	0.25	664 500	−0.34	−0.20
Age at exposure <20 years	17	15.8	0.26	478 100	0.30	0.10
>20 years	59	55.7	0.25	598 800	0.24	0.22
All	76	71.5	0.25	1 076 900	0.25 (<0.2−1.1) [c]	0.17(<−0.3−0.8) [c]
Cervical cancer case-control [d] [B1]	94	37.5	7.10	n.a.	0.21 (−0.03−0.93) [c]	n.a.
Benign lesions in the locomotor system [D12]	81	80.3	0.39	392 900	0.02 [c]	0.05 [c]
Mortality						
Benign lesions in the locomotor system [D12]	50	56.9	0.39	439 400	−0.31 [c]	−0.40 [c]
Ankylosing spondylitis [W1] [e]	37	21.3	4.38	287 095	0.17 [c]	0.77 [c]
Benign gynaecological disease [I6]	40	42.5	1.19	246 821	−0.05 (<-0.2−0.2) [c]	−0.08 (<-0.3−0.3) [c]
Massachusetts TB fluoroscopy [D4]	13 [f]	13.1	0.09	157 578	−0.05 (<−0.2−6.5) [c]	−0.04 (<-0.2−5.4) [c]
Peptic ulcer [G6]	12	6.4 [g]	1.55	35 815	0.57 (95% CI: −0.19−2.6) [c]	1.01 [c]
Nuclear workers in Canada, United Kingdom and United States [C11]	135	n.a.	0.04	2 142 526	<0 [h]	n.a.

Study	*Observed cases*	*Expected cases*	*Mean dose (Sv)*	*Person-years*	*Average excess relative risk at 1 Sv*	
INTERNAL LOW-LET EXPOSURES						
Incidence						
Diagnostic ^{131}I [H27]	95	78.5	0.00019 [i]	527 056	n.a.	
Swedish ^{131}I hyperthyroid [H23]	22	32.4	0.06	139 018	n.a.	
Mortality						
United States thyrotoxicosis [j] [R14]	74	n.a.	0.042	735 255	0.6 [h]	

Study	*Observed cases*	*Expected cases*	*Mean dose*	*Person-years*	*Average relative risk* [k]	
INTERNAL HIGH-LET EXPOSURES						
Incidence						
Danish Thorotrast patients [A5]	2	1.6	n.a.	19 365	1.47 (0.19-8.87) [l]	

Table 18 (continued)

Study	*Observed cases*	*Expected cases*	*Mean dose (Sv)*	*Person-years*	*Average excess relative risk at 1 Sv*	
^{224}Ra ankylosing spondylitis patients [W3]	2	0.9–1.8	n.a.	n.a.	~2 [m]	
Mortality						
German Thorotrast patients [V8]	15	n.a.	20.6 ml [n]	n.a.	~2.5 [o]	

a Mean dose to red bone marrow.
b 90% CI in parentheses derived from published data for Life Span Study and using exact Poisson methods for the other studies.
c Estimates based on method described in the introduction to Chapter III.
d Based on 5-year survivors. The observed and expected numbers cover both exposed and unexposed persons.
e The values given exclude the period within five years of first treatment. Mean dose to bone marrow taken from [W2].
f Includes deaths from multiple myeloma.
g Based on unirradiated patients.
h Not statistically significantly different from zero.
i Mean dose to bone marrow given in [H12].
j Some patients from the United Kingdom were included in this analysis [R14].
k 95% CI in parentheses.
l Risk relative to an unexposed control group, in which three cases were observed compared with 3.5 expected.
m Risk relative to an unexposed control group, in which one case was observed compared with 1.0–2.3 expected.
n Amount of thorotrast administered.
o Crude relative risk, based on five cases in an unexposed control group.

Table 19
Risk estimates for cancer incidence and mortality from studies of radiation exposure: Hodgkin's disease
The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this Table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.01 Sv or more for incidence.

Study	*Observed cases*	*Expected cases*	*Mean dose (Sv)* [a]	*Person-years*	*Average excess relative risk* [b] *at 1 Sv*	*Average excess absolute risk* [b] *(10^4 PYSv)$^{-1}$*
EXTERNAL LOW-LET EXPOSURES						
Incidence						
Life Span Study [P4]	10	9.02	0.23	1 076 500	0.43 (−1.6−3.5) [c]	0.04 (−0.1-0.3) [c]
Cervical cancer case-control [B1] [d]	14	n.a.	7.10	n.a.	n.a. [e]	n.a.
Benign lesions in the locomotor system [D12]	17	22.3	0.39	392 900	−0.61 [c]	−0.35 [c]
Mortality						
Benign lesions in the locomotor system [D12]	21	15.4	0.39	439 400	0.93 [c]	0.33 [c]
Ankylosing spondylitis [W1] [f]	13	7.9	4.38	287 095	0.15 [c]	0.04 [c]
Benign gyenaecological disease [I6]	10	6.6	1.19	246 821	0.43 [c]	0.12 [c]
Nuclear workers in Canada, United Kingdom, and United States [C11]	43	n.a.	0.04	2 142 526	>0 [g]	n.a.
Study	*Observed cases*	*Expected cases*	*Mean dose (Sv)*	*Person-years*	*Average excess relative risk at 1 Sv*	
INTERNAL LOW-LET EXPOSURES						
Incidence						
Diagnostic ^{131}I [H27]	27	20.0	0.00019 [h]	527 056	n.a.	
Swedish ^{131}I hyperthyroid [H23]	6	7.2	0.06	139 018	n.a.	
Mortality						
United States thyrotoxicosis [i] [R14]	12	n.a.	0.042	735 255	−1 [g]	
Study	*Observed cases*	*Expected cases*	*Mean dose*	*Person-years*	*Average relative risk* [j]	
INTERNAL HIGH-LET EXPOSURES						
Incidence						
Danish thorotrast patients [A5]	1	0.65	n.a.	19 365	1.6 (0.06−40.4) [k]	
^{224}Ra ankylosing spondylitis patients [W3]	1	0.8−1.1	n.a.	n.a.	n.a. [l]	
Mortality						
German thorotrast patients [V8]	2	n.a.	20.6 ml [m]	n.a.	~0.8 [n]	

a Mean dose to red bone marrow.
b 90% CI in parentheses derived from published data for Life Span Study and using exact Poisson methods for the other studies.
c Estimates based on method described in the introduction to Chapter III.
d Based on one-year survivors. The observed number of cases covers both exposed and unexposed persons.
e Unmatched relative risk of 0.63 (90% CI: 0.2-2.6), compared to those with <2 Sv.
f The values given exclude the period within five years of first treatment. Mean dose to bone marrow taken from [W2].
g Trend not statistically significant.
h Mean dose to bone marrow given in [H12].
i Some patients from the United Kingdom were included in this analysis [R14].
j 95% CI in parentheses.
k Risk relative to an unexposed control group, in which one case was observed compared with 1.04 expected.
l In an unexposed control group, no cases were observed compared with 0.8−1.1 expected.
m Amount of thorotrast administered.
n Crude relative risk, based on two cases in an unexposed control group.

Table 20
Risk estimates for cancer incidence and mortality from studies of radiation exposure: multiple myeloma
The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this Table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.01 Sv or more for incidence and 0.005 Sv or more (weighted colon dose) for mortality

Study	*Observed cases*	*Expected cases*	*Mean dose (Sv)* [a]	*Person-years*	*Average excess relative risk* [b] *at 1 Sv*	*Average excess absolute risk* [b] *(10^4 PYSv)$^{-1}$*
EXTERNAL LOW-LET EXPOSURES						
Incidence						
Life Span Study [P4]						
Sex Male	12	9.2	0.26	412 400	0.17	0.26
Female	18	19.3	0.25	664 500	−0.28	−0.08
Age at exposure <20 years	4	3.1	0.26	478 100	1.07	0.07
>20 years	26	25.4	0.25	598 800	0.09	0.04
All	30	28.6	0.25	1 076 900	0.20 (<−0.2−1.7) [c]	0.05 (<−0.05−0.4) [c]
Cervical cancer case-control [d] [B1]	56	n.a.	7.10	n.a.	−0.10 (<0−0.23) [c]	n.a.
Benign lesions in the locomotor system [D12]	65	67.5	0.39	392 900	−0.09 [c]	−0.16 [c]
Mortality						
Life Span Study [P9]						
Sex Male	16	14	0.23	614 997	1.13 (<0−6.41)	0.15 (<0−0.51)
Female	35	31	0.23	972 359	1.16 (0.01−3.9)	0.19 (0.001−0.5)
All	51	45	0.23	1 587 355	1.15 (0.12−3.27) [c]	0.17 (0.02−0.4) [c]
Benign lesions in the locomotor system [D12]	80	63.8	0.39	439 400	0.65 [c]	0.95 [c]
Ankylosing spondylitis [W1] [e]	22	13.6	4.38	287 095	n.a.	n.a.
Benign gynaecological disease [I6]	14	12.4	1.19	246 821	0.11 (<−0.2−0.6) [c]	0.05 (<−0.1−0.3) [c]
Peptic ulcer [G6]	3	2.2 [f]	1.55	35 815	0.23 (95% CI: −0.6−10)	0.13
Metropathia haemorrhagica [D7] [g]	9	3.5	1.30	47 144	1.23 (0.3−2.7) [c]	0.90 (0.2−2.0) [c]
Nuclear workers in Canada, United Kingdom, and United States [C11]	44	n.a.	0.04	2 142 526	4.2 (0.3−14.4)	n.a.

Study	*Observed cases*	*Expected cases*	*Mean dose (Sv)*	*Person-years*	*Average excess relative risk at 1 Sv*	
INTERNAL LOW-LET EXPOSURES						
Incidence						
Diagnostic ^{131}I [H27]	50	45.9	0.00019 [h]	527 056	n.a.	
Swedish ^{131}I Hyperthyroid [H23]	21	20.0	0.06	139 018	n.a.	
Mortality						
United States thyrotoxicosis [i] [R14]	28	n.a.	0.042	735 255	11 [j]	

Table 20 (continued)

Study	*Observed cases*	*Expected cases*	*Mean dose*	*Person-years*	*Average relative risk* [k]	
INTERNAL HIGH-LET EXPOSURES						
Incidence						
Danish thorotrast patients [A5]	4	0.95	n.a.	19 365	4.34 (0.85–31.3) [l]	
Mortality						
German thorotrast patients [V8]	10 [m]	n.a.	20.6 ml [n]	n.a.	~4.1 [o]	

a Mean dose to red bone marrow.
b 90% CI in parentheses derived from published data for Life Span Study and using exact Poisson methods for the other studies.
c Estimates based on method described in the introduction to Chapter III.
d Based on one-year survivors. The observed number of cases covers both exposed and unexposed persons.
e The values given exclude the period within five years of first treatment. Mean dose to bone marrow taken from [W2].
f Based on unirradiated patients.
g The values given exclude the period within five years of irradiation.
h Mean dose to bone marrow given in [H12].
i Some patients from the United Kingdom were included in this analysis [R14].
j Not statistically significantly different from zero (p=0.3).
k 95% CI in parentheses.
l Risk relative to an unexposed control group, in which two cases were observed compared with 2.1 expected.
m Diagnosis of plasmacytoma.
n Mean amount of thorotrast administered, based on hospital records.
o Crude relative risk, based on two cases in an unexposed control group (p>0.05).

Table 21
Risk estimates for cancer incidence and mortality from studies of radiation exposure: leukaemia
The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this Table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.01 Sv or more for incidence.

Study	*Observed cases*	*Expected cases*	*Mean dose (Sv)*	*Person-years*	*Average excess relative risk [a] at 1 Sv*	*Average excess absolute risk [a] (10^4 PYSv)$^{-1}$*
EXTERNAL LOW-LET EXPOSURES						
Incidence						
Life Span Study [P4]						
Sex Male	71	35.3	0.26	412 300	3.91	3.35
Female	70	32.1	0.25	664 500	4.75	2.29
Age at exposure <20 years	46	17.9	0.26	478 100	6.11	2.28
>20 years	95	49.5	0.25	598 700	3.70	3.06
Time since exposure 5-10 years	29	5.1	0.25	160 900	18.69	5.87
11-20 years	45	40.3	0.25	367 200	0.46	0.50
21-30 years	34	18.5	0.25	277 900	3.32	2.21
31-42 years	33	28.1	0.25	270 800	0.70	0.72
All	141	67.4	0.25	1 076 800	4.37 (3.2–5.6) [b]	2.73 (2.0–3.5) [b]
Cervical cancer case-control [c e] [B12]	141	n.a.	7.2	n.a.	0.74 (0.1–3.8)	0.50 (0.1–2.6)
Cancer of the uterine corpus [d, e] [C10]	118	n.a.	5.4	n.a.	0.10 (95% CI: <0.0–0.23)	n.a.
Benign lesions in the locomotor system [D12]	116	98.5	0.39	392 900	0.46 [b]	1.14 [b]
Hodgkin's disease [e, f] [K40]	60	n.a.	n.a.	n.a.	0.24 (95% CI: 0.04–0.43)	n.a.
Breast cancer therapy [g] [C9]	38	n.a.	7.5	n.a.	0.19 (0.00–0.6)	0.89 (0.00–3.0)
Techa River population [K27]	37	19.3	0.5	388 880	1.84 (0.9–3.1) [b]	0.91 (0.4–15) [b]
UK childhood cancers [f, h] [H11]	21	n.a.	n.a.	n.a.	0.241 (95% CI: 0.01–1.28)	n.a.
International childhood cancer [h, i] [T7]	25	n.a.	10	n.a.	0.0 (0.0–0.004)	n.a.
Chernobyl recovery operation workers in Russian Federation [j] [I14]	24	n.a.	0.115	n.a.	1.67 (–5.90–9.23)	n.a.
Mortality						
Benign lesions in the locomotor system [D12]	115	95.5	0.39	439 400	0.52 [b]	1.14 [b]
Ankylosing spondylitis [e, k] [W2]	53	17.0	4.38	245 413	6.00 [l]	n.a.
Benign gynaecological disease [e] [I6]	47	27.6	1.19	246 821	2.97 (2.2–4.0)	1.25 (0.9–1.7)
Massachusetts TB fluoroscopy [e] [D4]	17	18	0.09	157 578	<–0.2 (<–0.2–4.5) [b]	<–0.2 (<–0.2–5.1) [b]
Israeli tinea capitis [h, m] [R5]	14	6	0.3	279 901	4.44 (1.7–8.7) [b]	0.95 (0.4–1.9) [b]
Stockholm skin haemangioma [h] [L24]	14	~11	0.2	373 542	1.6 (95% CI: (–0.6–5.5) [n]	n.a.
Metropathia haemorrhagica [o] [D7]	12	5.6	1.3	53 144	0.74 (95% CI: –0.11–1.59)	0.85 [b]
Peptic ulcer [e] [G6]	8	2.9 [p]	1.55	35 815	1.13 (95% CI: –0.2–6.5)	0.92 [b]
Nuclear workers [e] in Canada, United Kingdom, United States [C11]	119	n.a.	0.04	2 142 526	2.18 (0.13–5.7) [q]	n.a.

Table 21 (continued)

Study	*Observed cases*	*Expected cases*	*Mean dose (Sv)*	*Person-years*	*Average excess relative risk* [a] *at 1 Sv*	*Average excess absolute risk* [a] *(10^4 PYSv)$^{-1}$*
Nuclear workers in Japan [r] [E3]	23	25.5	0.014	533 168	>0 [s]	n.a.
Yangjiang background radiation [T25, T26]	33	29.7	n.a. [t]	1 246 340	1.61 (95% CI: <0–28.4) [u]	n.a.
Mayak workers (cohort study) [K10]						
Radiochemical plant	27	10.8	1.71	162 556	1.65 [v]	0.89 [r]
Plutonium production	11	5.19	0.72	67 086	n.a.	n.a.
Reactors	6	6.74	0.87	87 307	n.a.	n.a.
Study	*Observed cases*	*Expected cases*	*Mean dose (Sv)*	*Person-years*	*Average excess relative risk at 1 Sv*	
INTERNAL LOW-LET EXPOSURES						
Incidence						
Diagnostic and therapeutic ^{131}I [H12]	130	119	0.014	943 944	n.a. [s]	
Mortality						
United States thyrotoxicosis [e] [w] [R14]	82	n.a.	0.042	735 255	~1 [s]	
Study	*Observed cases*	*Expected cases*	*Mean dose*	*Person-years*	*Average relative risk* [x]	
INTERNAL HIGH-LET EXPOSURES						
Incidence						
Danish thorotrast patients [A5]	20 [ab]	1.3	n.a.	19 365	12.7 (2.4–138.4) [y]	
^{224}Ra ankylosing spondylitis patients [W20]	13	4.2	n.a.	32 800	2.4 [z]	
Mortality						
Radon-exposed miners[D8]	69	59.5	155 WLM [aa]	1 085 000	n.a. [s]	
German thorotrast patients [V8]	42 [ab]	n.a.	20.6 ml [ac]	n.a.	~4.9 [ad]	
Portuguese thorotrast patients [D31]	11 [ab]	n.a.	26.3 ml [ac]	16 963	15.2 (1.28–181.7) [ae]	
Japanese thorotrast patients (combined data) [M14]	10	n.a.	17 ml [af]	10 685	12.5 (4.5–34.7)	

a 90% CI in parentheses derived from published data for Life Span Study and using exact Poisson methods for the other studies.
b Estimates based on method described in the introduction to Chapter III.
c The observed number of cases covers both exposed and unexposed persons. The excess relative risk was estimated using a linear-exponential dose-response model, and the associated CI was estimated from the confidence region curves in [B9]; the excess absolute risk estimate uses incidence estimates from the cohort study [B11].
d Risk estimate based on a linear dose-response model fitted to data for all radiation types [C10].
e Excludes cases of chronic lymphatic leukaemia.
f Risk estimate based on analysis in [L52].
g The excess absolute risk for this study is computed based on annual incidence estimates and average follow-up times reported in [C9].
h Population exposed as children.
i The observed number of cases covers both exposed and unexposed persons. Risk estimates based on an unmatched analysis of data given in [T5].
j Excludes cases of chronic lymphatic leukaemia. Results are not restricted according to the date of starting work.
k The values given exclude the one-year period following the treatment.
l Risk estimate based on a linear exponential dose-response model averaged over the period 1–25 years after exposure [W2].
m A re-estimate of the dose to bone marrow in this study indicates a mean dose of 0.60 rather than 0.30 Sv. Consequently the excess relative risk becomes 2.22 Sv^{-1} [R7].
n Based on those with doses above 0.1 Sv.
o The values given exclude the period within two years of irradiation.

Table 21 (continued)

p Based on unirradiated patients.
q Doses lagged by two years.
r No cases of chronic lymphatic leukaemia (CLL) in cohort. Expected number based on rates for leukaemia excluding CLL.
s Trend not statistically significant.
t Mean annual effective dose = 6.4 mSv.
u Based on a two-year latent period.
v Based on male workers followed to the end of 1993, as given in [K11].
w Some patients from the United Kingdom were included in this analysis [R14].
x 95% CI in parentheses.
y Relative to unexposed controls, adjusted for gender, age at administration and calendar period [A5].
z In the control group, seven leukaemias were observed, compared with 5.4 expected [W20].
aa Mean cumulative radon exposure.
ab Excludes cases of chronic lymphatic leukaemia.
ac Mean amount of thorotrast administered, based on hospital records.
ad Crude relative risk, based on seven cases in the control group.
ae Based on two deaths in the control group, and excluding the first five years after administration of thorotrast [D31].
af Mean amount of thorotrast administered in the first series of Japanese patients [M47].

Table 22
Estimates of the projected lifetime risk of cancer mortality following an organ dose of 1 Sv, based on studies of radiation exposure

PART A: STOMACH

Study	*Gender*	*Risk of exposure-induced death (REID) (%) [a] for a projection method with a 10−year latent period and a relative risk for exposure at ages*			
		<20 years		*≥20 years*	
		Assumed constant from 10 years after exposure	*Declining to zero risk at age 90 years [b]*	*Assumed constant from 10 years after exposure*	*Declining to zero risk at age 90 years [b]*
EXTERNAL LOW-LET EXPOSURES					
Values based on incidence studies					
Life Span Study [T1]	Both	0.38	0.17	0.10	0.08
Cervical cancer case-control [B1]	Females	–	–	0.18 (0.03−0.49)	0.14 (0.03−0.39)
Mayak workers [Z1]	Males	–	–	0.15 (95% CI: 0−0.5) [c]	0.12 (95% CI: 0−0.4) [c]
Swedish benign breast disease [M28]	Females	–	–	0.43 (0−1.4)	0.34 (0−1.1)
Values based on mortality studies					
Life Span Study [P9]	Males Females Both	0.11 (<0−0.76) 0.40 (<0−0.93) 0.26	0.05 (<0−0.37) 0.17 (<0−0.40) 0.11	0.06 0.13 0.09	0.05 0.09 0.07
Ankylosing spondylitis [W1]	Males	–	–	<0 (95% CI: <0−0.03)	<0 (<0−0.02)
Peptic ulcer [G6]	Both	–	–	0.07	0.05
Metropathia haemorrhagica [D7]	Females	–	–	0.33 (<0−0.92)	0.26 (<0−0.73)
Benign gynaecological disease [I16]	Females	–	–	0.09 (<0−1.57)	0.07 (<0−1.2)

a Estimated percentage of population that would die of radiation-induced cancer. Computed using relative risks estimated from the relevant studies (split by gender and age at exposure where possible), and applied to Japanese death rates for 1985 [J3]. The calculations have been performed for the gender and age-specific groupings that predominate in the relevant study. 90% CI in parentheses unless otherwise stated.

b Constant relative risk for first 45 years after exposure. Relative risk then decreases linearly with increasing attained age to zero at age 90 years.

c Based on the excess relative risk among those with external gamma doses in excess of 3 Gy relative to those with lower doses, divided by an (arbitrary) value of 4 in order to estimate risks at 1 Gy.

Table 22 (continued)

PART B: COLON

Study	*Gender*	*Risk of exposure-induced death (REID) (%) [a] for a projection method with a 10 −year latent period and a relative risk for exposure at ages*			
		<20 years		*≥20 years*	
		Assumed constant from 10 years after exposure	*Declining to zero risk at age 90 years [b]*	*Assumed constant from 10 years after exposure*	*Declining to zero risk at age 90 years [b]*
EXTERNAL LOW-LET EXPOSURES					
Values based on incidence studies					
Life Span Study [T1]	Both	0.55	0.25	0.51	0.42
Cervical cancer case-control [B1]	Females	–	–	0.00 (−0.01−0.02)	0.00 (−0.01−0.02)
Stockholm skin haemangioma [L16]	Both	0.33 [c]	0.15	–	–
Values based on mortality studies					
Life Span Study [P9]	Males Females Both	1.5 (<0−4.6) 2.2 (<0−6.7) 1.8	0.73 (<0−2.3) 0.95 (<0−2.9) 0.84	0.35 0.48 0.42	0.28 0.34 0.31
Benign gynaecological disease [I16]	Females	–	–	0.31 (<0−3.5)	0.25 (<0−2.7)
Metropathia haemorrhagica [D7]	Females	–	–	0.08 (95% CI: 0.01−0.21)	0.06 (95% CI: 0.00−0.17)
Peptic ulcer [G6]	Both	–	–	0.04 (95% CI: −0.04−0.18)	0.03 (95% CI: −0.03−0.13)

a Estimated percentage of population that would die of radiation-induced cancer. Computed using relative risks estimated from the relevant studies (split by gender and age at exposure where possible) and applied to Japanese death rates for 1985 [J3]. The calculations have been performed for the gender and age-specific groupings that predominate in the relevant study. 90% CI in parentheses unless otherwise stated.

b Constant relative risk for first 45 years after exposure. Relative risk then decreases linearly with increasing attained age to zero at age 90 years.

c Not statistically significant.

Table 22 (continued)

PART C: LUNG

Study	*Gender*	*Risk of exposure-induced death (REID) (%)* [a] *for a projection method with a 10 –year latent period and a relative risk for exposure at ages*			
		<20 years		*≥20 years*	
		Assumed constant from 10 years after exposure	*Declining to zero risk at age 90 years* [b]	*Assumed constant from 10 years after exposure*	*Declining to zero risk at age 90 years* [b]
EXTERNAL LOW-LET EXPOSURES					
Values based on incidence studies					
Life Span Study [T1]	Both	2.1	1.0	3.3	2.9
Hodgkin's disease (Netherlands) [V2]	Both	–	–	~3 (<0 – ~30)	~3 (<0 – ~30)
Breast cancer [I7]	Females	–	–	0.19 (95% CI: <0–0.52)	0.16 (95% CI: <0–0.45)
Swedish benign breast disease [M28]	Females	–	–	0.43 (95% CI: 0–1.4)	0.34 (95% CI: 0–1.1)
Stockholm skin haemangioma [L16]	Both	5.2	2.5	–	–
Values based on mortality studies					
Life Span Study [P9]	Males Females Both	1.1 (<0–8.7) 1.1 (<0–7.5) 1.1	0.52 (<0–4.1) 0.48 (<0–3.4) 0.50	1.5 1.2 1.3	1.3 1.0 1.2
Ankylosing spondylitis [W1]	Males	–	–	0.20 (95% CI: 0.01–0.36)	0.18 (95% CI: 0.01–0.32)
Canadian TB fluoroscopy [H7]	Both	0.00 (95% CI: <0–0.26)	0.00 (95% CI: <0–0.12)	0.00 (95% CI: <0–0.22)	0.00 (95% CI: <0–0.19)
Peptic ulcer [G6]	Both	–	–	1.2 (95% CI: 0.34–2.4)	1.1 (95% CI: 0.31–2.2)
Massachusetts TB fluoroscopy [D4]	Both	<0 (<0–0.15)	<0 (<0–0.07)	<0 (<0–0.13)	<0 (<0–0.11)

a Estimated percentage of population that would die of radiation-induced cancer. Computed using relative risks estimated from the relevant studies (split by gender and age at exposure where possible), and applied to Japanese death rates for 1985 [J3]. The calculations have been performed for the gender and age-specific groupings that predominate in the relevant study. 90% CI in parentheses unless otherwise stated.

b Constant relative risk for first 45 years after exposure. Relative risk then decreases linearly with increasing attained age to zero at age 90 years.

Table 23
Lung cancer mortality in the Canadian fluoroscopy study and in the study of survivors of the atomic bombings

Lung dose (Sv)	*Canadian fluoroscopy study (1950–1987) [H7]*			*Study of survivors of atomic bombings (1950–1990) [P9, P11]*		
	Observed deaths	*Relative risk* [a] [b]	*95% CI*	*Observed deaths*	*Relative risk* [a] [b]	*95% CI*
0 [c]	723	1.00		349	1.00	
>0–0.49	180	0.87	0.74–1.03	477	1.16	1.02–1.34
0.50–0.99	92	0.82	0.66–1.02	43	1.35	0.97–1.83
1.00–1.99	114	0.94	0.77–1.15	39	2.05	1.40–2.96
2.00–2.99	41	1.09	0.80–1.50	11	2.80	1.41–5.06
≥3.00	28	1.04	0.72–1.53	5	1.65	0.61–3.70

a Adjusted for age at risk, calendar year at risk and sex.
b Excludes person-years for age at risk <20 years and deaths and person-years at risk within 10 years of exposure.
c Defined as less than 0.01 Sv for the fluoroscopy study and less than 0.005 Sv for the study on survivors of atomic bombings.

Table 24
Lung cancer cases and parameters for risk estimates in studies of radon-exposed underground miners [a]
[L6, L45]

Study cohort	*Cases* [b]	*Average cumulative exposure (WLM)*	*Excess relative risk per 100 WLM ($\beta \times 100$)*	*Modification factor (γ)*	*Test of significance (p)* [c]
China tin miners	980	277.4	0.59	−0.79	<0.001
Western Bohemia uranium miners	661	198.7	5.84	−0.78	<0.001
Colorado Plateau uranium miners	294	595.7	14.5	−0.79	<0.001
Ontario uranium miners	291	30.8	2.40	−0.55	0.002
Newfoundland fluorspar	118	367.3	5.14	−0.53	<0.001
Sweden iron miners	79	80.6	1.55	−1.02	0.03
New Mexico uranium miners	69	110.3	6.56	−0.30	0.17
Beaverlodge uranium miners	65	17.2 [d]	7.42	−0.67	0.001
Port Radium uranium miners	57	242.8	1.15	−0.42	0.24
Radium Hill uranium miners	54	7.6	5.68	−0.63	0.30
France uranium miners	45	68.7	1.92	0.57	0.57

a Background lung cancer rates are adjusted for attained age (all studies), other mine exposures [China, France, Ontario, United States (Colorado, New Mexico)], and indicator of radon progeny exposure (Beaverlodge) and ethnicity (New Mexico). United States (Colorado) data are restricted to exposures under 3,200 WLM. The relative risk is modelled by the form $RR = 1 + \beta \times WLM \times (WL)^{\gamma}$.
b Total number of cases is 2,701 and omits 12 cases that were included in both United States studies (New Mexico and Colorado).
c P-value for test of significance of continuous variation of ERR/WLM by WL.
d Howe and Stager [H18] quote a revised mean of 81.3 WLM for exposed miners, compared with an earlier mean of 50.6 WLM for miners with non-zero exposure.

Table 25
Parameter values used by BEIR Committees in risk models for lung cancer following radon exposure
[C2, C21]

Parameter	*Parameter value*		
	BEIR VI preferred models [a]		*BEIR IV model*
	Exposure-age-duration	*Exposure-age-concentration*	
Time since exposure, θ (years)			
5–14	1	1	1
15–24	0.72	0.78	0.5
≥25	0.44	0.51	0.5
Attained age, φ_{age} (years)			
<55	1	1	1
55–64	0.52	0.57	0.83
65–74	0.28	0.29	0.33
≥75	0.13	0.09	0.33
Duration of exposure, γ_z (years)			
<5	1	1	1
5–14	2.78	1	1
15–24	4.42	1	1
25–34	6.62	1	1
≥35	10.20	1	1
Exposure rate (WL)			
<0.5	1	1	1
0.5–1.0	1	0.49	1
1.0–2.99	1	0.37	1
3.0–4.99	1	0.32	1
5.0–14.99	1	0.17	1
≥15.0	1	0.11	1

a ERR = β ($w_{5-14} + \theta_{15-24}\, w_{15-24} + \theta_{25+} w_{25+}$)$\varphi_{age}\ \gamma_z$, i.e. a product of terms representing: (a) exposure in three time periods, i.e. 5-14, 15–24 and 25+ years previously *(Note: BEIR IV used 5–14 and 15+)*; (b) attained age (φ_{age}); (c) duration of exposure or average concentration (γ_z) *(Note: not included in BEIR IV model)*.

Table 26
Basal-cell skin cancer incidence in the Life Span Study
[R15]

Variable	*Observed cases* [a]	*Average excess relative risk at 1 Sv*	*90% CI*
All [b]	80	1.9	0.83–3.3
Gender			
Male	32	2.7	0.5–9.1
Female	48	1.6	0.5–4.1
	(Heterogeneity [c] p > 0.5)		
Age at exposure			
<10 years	3	21	4.1–73
10–19 years	8	6.7	2.1–17
20–30 years	28	1.7	0.5–3.8
>40 years	41	0.7	–0.05–2.2
	(Heterogeneity [c] p = 0.03)		

a Includes exposed and non-exposed cases.
b Estimates are for a person exposed to the atomic bombings at age 30 years. The estimates depend on age at exposure with larger risks for those exposed earlier and smaller risks for thoses exposed later in life. The risks change by about 11% for a one-year change in age at exposure.
c Test of the hypotheses that effects differ across categories.

Table 27
Numbers and rates of tumours of the brain and central nervous system in the Life Span Study of atomic bomb survivors (1958–1994)
[P19]

Histology	*Brain dose* [a] *(Gy)*	*Number of cases*	*Incidence rate per 10,000 person years*
Glioma, astrocytoma	<0.0005	19	0.24
	0.0005–0.099	12	0.16
	0.1–0.99	7	0.20
	>1	3	0.46
Meningioma	<0.0005	33	0.42
	0.0005–0.099	28	0.38
	0.1–0.99	19	0.53
	>1	5	0.76
Neurilemmoma	<0.0005	18	0.23
	0.0005–0.099	11	0.15
	0.1–0.99	17	0.48
	>1	9	1.37
Not specified and other	<0.0005	15	0.19
	0.0005–0.099	18	0.24
	0.1–0.99	9	0.25
	>1	3	0.46

a Total person years at <0.0005 Sv: 791,456; at 0.0005–0.099 Sv:7425,831; at 0.1–0.99 Sv: 355,877; and at >1 Sv: 65,844.

Table 28
Thyroid cancer risk in patients receiving diagnostic administration of ^{131}I [a]
[H4]

Dose [b] *(Gy)*	*Observed number of cases*	*Standardized incidence ratio (SIR)*	*95% CI*
Referred for suspicion of a thyroid tumour			
≤0.25	6	3.57	1.31–7.77
0.26–0.50	12	4.30	2.22–7.51
0.51–1.00	4	1.39	0.38–3.56
>1.00	20	2.72	1.66–4.20
All	42	2.86	2.06–3.86
Referred for other reasons			
≤0.25	5	0.55	0.18–1.29
0.26–0.50	4	0.68	0.18–1.73
0.51–1.00	5	0.47	0.20–1.46
>1.00	11	1.04	0.52–1.86
All	25	0.75	0.48–1.10
All patients			
≤0.25	11	1.03	0.51–1.83
0.26–0.50	16	1.84	1.05–2.98
0.51–1.00	9	0.46	0.38–1.57
>1.00	31	1.60	1.09–2.27
All	67	1.35	1.05–1.71

a The first five years after exposure were excluded.
b Estimated without considering thyroid weight.

Table 29
Childhood thyroid cancer in Belarus, Russian Federation and Ukraine before and after the Chernobyl accident [a] [S9]

Country / region	*Number of cases*			*Incidence rate (10^{-6})*			*Number of children with thyroid cancer born since 1986*	*Cases found by annual medical examination since 1986 (%) [b]*	*Range of estimated thyroid doses (Gy)*	*Cases of papillary cancer (%)*	*Cases confirmed by international review*
	1981–1985	*1986–1990*	*1991–1994*	*1981–1985*	*1986–1990*	*1991–1994*					
Belarus [c]	3	47	286	0.3	4.0	30.6	7	62	n.a.	96	91
Gomel	1	21	143	0.5	10.5	96.4	5	n.a.	0.15–5.7	n.a.	n.a.
Russian Federation	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Bryansk and Kaluga regions	0	3	20	0	1.2	10.0	0	n.a.	0.06–1.8	n.a.	n.a.
Ukraine	25	60	149	0.5	1.1	3.4	2	n.a.	n.a.	95	n.a.
Five most northerly regions [d]	1	21	97	0.1	2.0	11.5	n.a.	40	0.05–2.0	n.a.	n.a.

a Aged under 15 years at diagnosis; rates are expressed as annual averages per million children under 15 in the regions and periods specified.
b Annual medical examination includes palpation and ultrasound scanning of neck and, in some cases, thyroid hormone tests.
c Data made available by Drs. Demidchik, Astakhova, Okeanov, and Kenigsberg.
d Kiev, Chernikov, Cherkassy, Rovno, and Zhitomir.

Table 30
Fitted risks of leukaemia (other than chronic lymphatic leukaemia) in four studies of low-LET irradiation of adults

Risk parameter	*Ankylosing spondylitis study [a]*		*Uterine corpus cancer study [b]*		*Cervical cancer study [c]*	*Life Span Study [d]*	
	Time since exposure = 10 years	*Time since exposure = 25 years*	*Brachytherapy irradiation*	*Any external irradiation*		*Time since exposure = 1–25 years*	*Time since exposure >25 years*
Linear component of excess relative risk Gy^{-1}	12.37 (2.25–52.07) [e]	5.18 (0.81–23.63)	4.69 (1.10–13.4)	0.05 (<0–0.55)	0.88 (–0.50–2.23)	-	-
Reduction in excess relative risk at 1 Gy due to cell sterilization	47% (17–79%)	47% (17–79%)	59% (30–75%)	–4% (–40–23%)	8% (1–14%)	-	-
Predicted excess relative risk at a uniform dose of 1 Gy	6.00 [f]	1.88 [f]	1.91	0.05	0.74	5.13	1.56

a Estimates derived from the compartmental linear-exponential model allowing for the effect of time since first treatment, assuming that each bone marrow compartment received the same dose and using national rates as baseline risk [W2].
b Estimates derived from the linear-exponential model [C10].
c Estimates based on case-control analysis [B12].
d Estimates for survivors of the atomic bombings in Japan aged over 20 years at exposure [P11].
e 95% CI.
f Predicted relative risks in the two periods are the average relative risks at 1–25 years and 25–40 years after first treatment, respectively.

Table 31
Models for risks of solid cancer mortality and incidence used in the lifetime risk computations based on the Life Span Study

Cancer type	*Age-at-exposure model*				*Attained-age model*			
	Excess relative risk per Sv [a]		*Sex ratio (female/ male)*	*Change in risk per 10-year increase in age at exposure (%)*	*Excess relative risk per Sv* [b]		*Sex ratio (female/ male)*	*Power of age*
	Male	*Female*			*Male*	*Female*		
Cancer mortality risks								
All solid cancer	0.38	0.77	2.1	−32	0.38	0.88	2.3	−1.5
Oesophagus	0.91	1.88	2.1	−32	1.04	2.37	2.3	−1.5
Stomach	0.26	0.54	2.1	−32	0.27	0.63	2.3	−1.5
Colon	0.46	0.95	2.1	−32	0.68	1.56	2.3	−1.5
Liver	0.61	1.66	1.0	−13	0.29	0.29	1.0	1.4
Lung	0.30	0.99	3.3	26	0.68	1.55	2.3	−1.5
Breast	0.00	1.34	-	−32	0.00	2.35	-	−1.5
Bladder	0.46	0.94	2.1	33	0.97	2.21	2.3	−1.5
Other cancer	0.38	0.77	2.1	−32	0.32	0.74	2.3	−1.5
Cancer incidence risks								
All solid cancer	0.38	0.79	2.1	−33	0.58	1.10	1.9	−2.1
Oesophagus	0.41	0.84	2.1	0	0.78	1.48	1.9	−2.1
Stomach	0.29	0.60	2.1	0	0.39	0.73	1.9	−2.1
Colon	0.46	0.95	2.1	0	0.83	1.56	1.9	−2.1
Liver	0.58	0.58	1.0	−7	0.66	0.66	1.0	−0.6
Lung	0.50	2.18	4.3	7	0.51	2.19	4.3	0.2
Breast	0.00	1.55	-	0	0.00	2.22	-	−2.1
Bladder	1.18	0.98	0.8	−61	1.53	2.90	1.9	−2.1
Thyroid	0.89	1.84	2.1	0	1.14	2.15	1.9	−2.1
Other cancer	0.47	0.28	0.6	−50	0.65	0.38	0.6	−3.2

a For age at exposure 30 years.
b For attained age 50 years (ages at exposure <40 years).

Table 32
Estimated lifetime probabilities of solid cancer and leukaemia in unexposed populations

Cancer type	*Lifetime probability (%)*									
	China		*Japan*		*Puerto Rico*		*United Kingdom*		*United States*	
	Male	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*
Incidence										
Solid cancer	24.3	16.2	37.2	15.3	26.2	19.9	39.6	33.6	33.9	30.4
Leukaemia	0.3	0.3	0.4	0.3	0.6	0.5	0.7	0.5	0.6	0.5
Mortality										
Solid cancer	12.8	9.5	23.3	25.2	13.9	11.1	24.0	20.1	21.6	17.9
Leukaemia	0.1	0.1	0.4	0.3	0.1	0.1	0.6	0.5	0.6	0.5

Table 33
Estimates of lifetime risk of exposure-induced death (REID) or exposure-induced cancer incidence following an acute whole-body exposure to a population of all ages

Projection model [a]	*Risk transport model*	*REID (%)*														
		China			*Japan*			*Puerto Rico*			*United Kingdom*			*United States*		
		Male	*Female*	*Both*	*Male*	*Female*	*Both*	*Male*	*Female*	*Both*	*Male*	*Female*	*Both*	*Male*	*Female*	*Both*
Dose of 1 Sv																
Solid cancer mortality																
Age-at-exposure	RR [b]	8.2	11.7	9.9	9.5	12.9	11.2	7.3	11.9	9.6	9.5	19.3	14.4	8.5	16.4	12.5
	AR [c]	8.6	10.5	9.5	9.5	12.9	11.2	9.9	12.8	11.3	10.8	14.4	12.6	8.2	11.5	9.9
Attained-age	RR	4.9	7.1	6.0	6.2	8.5	7.4	4.4	7.9	6.1	6.6	13.5	10.1	6.2	12.4	9.3
	AR	5.3	6.8	6.0	6.2	8.5	7.4	6.1	8.2	7.2	6.7	9.1	7.9	5.4	7.6	6.5
UNSCEAR 1994 [U2]	RR				10.4	11.4	10.9									
Leukaemia mortality																
Age- and time-varying	AR	0.94	0.56	0.75	1.04	0.79	0.92	0.91	0.52	0.72	1.02	0.87	0.95	1.13	1.25	1.19
UNSCEAR 1994 [U2]	AR						1.1									
Solid cancer incidence																
Age-at-exposure	RR	14.8	17.6	16.2	18.6	21.0	19.8	17.5	19.8	18.6	22.1	29.9	26.0	18.7	27.4	23.0
	AR	18.7	19.7	19.2	18.6	21.0	19.8	20.4	21.7	21.1	22.1	23.2	22.7	14.1	17.0	15.5
Attained-age	RR	10.2	13.8	12.0	13.3	16.2	14.7	8.6	13.8	11.2	12.9	22.6	17.8	12.3	23.1	17.7
	AR	13.0	14.7	13.8	13.3	16.2	14.7	14.0	16.2	15.1	14.6	17.0	15.8	10.7	13.5	12.1
Leukaemia incidence																
Age- and time-varying	AR	1.27	0.84	1.06	1.00	0.73	0.87	1.29	1.12	1.21	1.19	0.96	1.08	1.24	0.94	1.09
Dose of 0.1 Sv [d]																
Solid cancer mortality																
Age-at-exposure	RR	0.9	1.3	1.1	1.0	1.4	1.2	0.8	1.3	1.1	1.1	2.3	1.7	0.9	1.9	1.4
	AR	0.9	1.2	1.1	1.0	1.4	1.2	1.1	1.4	1.3	1.2	1.6	1.4	0.9	1.3	1.1
Attained-age	RR	0.5	0.7	0.6	0.7	0.9	0.8	0.5	0.8	0.6	0.7	1.5	1.1	0.7	1.4	1.0
	AR	0.6	0.7	0.6	0.7	0.9	0.8	0.6	0.9	0.8	0.7	1.0	0.8	0.6	0.8	0.7

Table 33 (continued)

Projection model [a]	*Risk transport model*	*REID (%)*														
		China			*Japan*			*Puerto Rico*			*United Kingdom*			*United States*		
		Male	*Female*	*Both*	*Male*	*Female*	*Both*	*Male*	*Female*	*Both*	*Male*	*Female*	*Both*	*Male*	*Female*	*Both*
Leukaemia mortality																
Age- and time-varying	AR	0.04	0.02	0.03	0.05	0.03	0.04	0.04	0.02	0.03	0.04	0.04	0.04	0.06	0.06	0.06
Solid cancer incidence																
Age-at-exposure	RR	1.8	2.1	1.9	2.4	2.6	2.5	2.3	2.5	2.4	3.0	4.1	3.5	2.6	3.8	3.2
	AR	2.4	2.4	2.4	2.4	2.6	2.5	2.7	2.7	2.7	2.9	2.9	2.9	1.7	2.1	1.9
Attained-age	RR	1.1	1.5	1.3	1.5	1.8	1.6	0.9	1.5	1.2	1.4	2.6	2.0	1.4	2.8	2.1
	AR	1.4	1.6	1.5	1.5	1.8	1.6	1.6	1.8	1.7	1.6	1.9	1.8	1.2	1.5	1.3
Leukaemia incidence																
Age- and time-varying	AR	0.05	0.03	0.04	0.04	0.03	0.04	0.06	0.05	0.06	0.05	0.04	0.05	0.06	0.04	0.05

a The projection models are described in Section IV.B.1 of this Annex, with the exception of those cited from the UNSCEAR 1994 Report [U2].
b Relative risk transportation.
c Absolute risk transportation.
d The estimates presented for solid cancers at 0.1 Sv do not involve a reduction factor for low doses or low dose rates. In contrast, the leukaemia estimates at 0.1 Sv are based on a linear-quadratic dose response.

Table 34
Estimates of REID for an acute whole-body dose of 1 Sv to a Japanese population

Projection model	*Age at exposure (years)*	*REID (%)*					
		Solid cancer mortality		*Solid cancer incidence*		*Leukaemia incidence*	
		Male	*Female*	*Male*	*Female*	*Male*	*Female*
Age-at-exposure model	10	13.9	19.6	31.0	36.5	1.9	1.0
	30	8.6	11.9	15.4	18.8	0.8	0.9
	50	6.2	8.8	9.1	10.7	0.6	0.6
	All	9.5	12.9	18.6	21.0	1.0	0.7
Attained-age model	10	6.7	9.7	14.9	20.1	1.9	1.0
	30	6.7	9.5	13.3	18.1	0.8	0.9
	50	6.3	8.2	11.4	13.0	0.6	0.6
	All	6.2	8.5	13.3	16.2	1.0	0.7

Table 35
Estimates of measures of radiation detriment associated with an acute whole-body dose of 1 Sv to a male Japanese population

Age at exposure (years)	*Cause of death*	*Unexposed*	*Exposed*							
			Age-at-exposure model				*Attained-age model*			
		Lifetime risk	*Lifetime risk*	*Radiation-associated deaths, REID (%)*	*Excess lifetime risk, ELR (%)*	*Loss of life expectancy, LLE (years)*	*Lifetime risk*	*Radiation-associated deaths, REID (%)*	*Excess lifetime risk, ELR (%)*	*Loss of life expectancy, LLE (years)*
10	Solid cancer	23.6	34.6	13.9	11.0	12.7	28.6	6.7	5.0	15.0
	Leukaemia	0.5	2.4	2.0	1.9	53.1	2.4	2.0	1.9	53.0
	Other causes	75.9	63.0	0.0	−12.9	0.0	69.0	0.0	−6.9	0.0
30	Solid cancer	23.8	30.7	8.6	6.9	12.0	29.1	6.7	5.3	13.9
	Leukaemia	0.5	1.3	0.9	0.9	29.0	1.3	0.9	0.9	28.9
	Other causes	75.7	68.0	0.0	−7.7	0.0	69.6	0.0	−6.1	0.0
50	Solid cancer	23.9	28.9	6.2	5.0	10.3	28.9	6.3	5.0	11.4
	Leukaemia	0.4	1.0	0.6	0.6	13.9	1.0	0.6	0.6	14.0
	Other causes	75.7	70.1	0.0	−5.6	0.0	70.1	0.0	−5.7	0.0
All ages	Solid cancer	23.3	30.9	9.5	7.6	11.1	28.2	6.2	4.9	12.8
	Leukaemia	0.4	1.4	1.0	1.0	30.6	1.5	1.0	1.0	30.6
	Other causes	76.3	67.7	0.0	−8.6	0.0	70.4	0.0	−5.9	0.0

Table 36
Estimates of REID for cancer mortality under the attained-age model, based on acute whole-body exposure at age 30 years [a]

Cancer type	*REID (%)*								
	China		*Japan*	*Puerto Rico*		*United Kingdom*		*United States*	
	RR [b]	*AR* [c]		*RR*	*AR*	*RR*	*AR*	*RR*	*AR*
Dose of 1 Sv (males)									
Oesophagus	2.6	0.6	0.7	1.2	0.7	0.5	0.8	0.3	0.7
Stomach	0.7	0.9	1.0	0.5	1.0	0.3	1.1	0.1	0.9
Colon	0.2	0.3	0.4	0.3	0.4	0.6	0.4	0.9	0.4
Liver	0.6	1.5	1.2	0.9	1.7	0.1	1.3	0.2	1.0
Lung	0.5	1.0	1.8	0.2	1.1	3.6	2.0	3.1	1.6
Breast	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Bladder	0.1	0.2	0.2	0.2	0.2	0.5	0.3	0.4	0.2
Other solid cancer	0.7	1.1	1.3	1.4	1.2	1.4	1.4	1.8	1.1
All solid cancers	5.3	5.6	6.7	4.8	6.4	7.1	7.3	6.8	5.9
Leukaemia	0.5	0.5	0.9	0.5	0.5	0.7	0.7	1.0	1.0
Total	5.9	6.1	7.6	5.3	6.9	7.8	8.0	7.8	6.9
Dose of 0.1 Sv (males) [d]									
Oesophagus	0.27	0.07	0.08	0.13	0.07	0.06	0.08	0.03	0.07
Stomach	0.07	0.09	0.11	0.05	0.10	0.03	0.12	0.01	0.10
Colon	0.02	0.04	0.04	0.03	0.04	0.06	0.05	0.10	0.04
Liver	0.06	0.16	0.12	0.09	0.18	0.01	0.14	0.02	0.11
Lung	0.05	0.10	0.19	0.02	0.12	0.38	0.21	0.33	0.17
Breast	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Bladder	0.01	0.02	0.02	0.03	0.02	0.06	0.03	0.04	0.02
Other solid cancer	0.07	0.11	0.14	0.15	0.13	0.15	0.15	0.19	0.12
All solid cancers	0.55	0.59	0.70	0.50	0.66	0.75	0.77	0.71	0.62
Leukaemia	0.02	0.02	0.04	0.02	0.02	0.03	0.03	0.05	0.05
Total	0.57	0.61	0.74	0.5	0.7	0.78	0.80	0.76	0.67
Dose of 1 Sv (females)									
Oesophagus	3.2	0.4	0.6	1.3	0.5	0.7	0.6	0.2	0.5
Stomach	0.9	1.0	1.4	0.6	1.3	0.4	1.5	0.2	1.2
Colon	0.3	0.5	0.7	0.8	0.6	1.5	0.7	1.9	0.6
Liver	0.6	1.8	0.6	1.0	2.4	0.1	0.6	0.2	0.5
Lung	0.3	0.4	2.5	0.1	0.5	3.5	2.6	3.2	2.3
Breast	0.6	1.2	1.3	2.2	1.3	5.8	1.4	5.2	1.3
Bladder	0.1	0.2	0.2	0.3	0.2	0.5	0.3	0.3	0.2
Other solid cancer	1.8	1.8	2.3	2.8	2.3	2.8	2.5	3.2	2.2
All solid cancers	7.7	7.2	9.5	9.0	9.1	15.2	10.1	14.4	8.8
Leukaemia	0.5	0.5	1.0	0.5	0.5	1.0	1.1	1.5	1.6
Total	8.1	7.6	10.4	9.6	9.7	16.2	11.2	15.9	10.3
Dose of 0.1 Sv (females) [d]									
Oesophagus	0.34	0.04	0.06	0.14	0.06	0.08	0.06	0.03	0.05
Stomach	0.09	0.11	0.14	0.07	0.14	0.04	0.16	0.02	0.13
Colon	0.03	0.05	0.07	0.09	0.07	0.17	0.08	0.22	0.06
Liver	0.06	0.19	0.06	0.10	0.25	0.01	0.06	0.02	0.06
Lung	0.03	0.04	0.26	0.01	0.06	0.38	0.28	0.34	0.24
Breast	0.06	0.12	0.14	0.23	0.14	0.63	0.14	0.56	0.13
Bladder	0.01	0.02	0.02	0.03	0.02	0.05	0.03	0.04	0.02
Other solid cancer	0.19	0.19	0.25	0.29	0.24	0.32	0.27	0.36	0.23
All solid cancers	0.81	0.76	1.00	0.96	0.98	1.68	1.08	1.58	0.93
Leukaemia	0.02	0.02	0.04	0.02	0.02	0.04	0.04	0.06	0.06
Total	0.83	0.78	1.04	1.0	1.0	1.72	1.12	1.64	0.99

a Owing to rounding errors, the sum of the individual values in each column sometimes differs from the total, which has been calculated to greater accuracy. Also, in a few instances, the mortality estimates in this Table are greater than the corresponding incidence values in Table 37 owing to the use of baseline rates that differ by the region studied within a country or that differ by time period (see Section IV.B.4).

b Relative risk transportation.

c Absolute risk transportation.

d The estimates presented for solid cancers at 0.1 Sv do not involve a reduction factor for low doses or low dose rates. In contrast, the leukaemia estimates at 0.1 Sv are based on a linear-quadratic dose response.

Table 37
Estimates of REID for cancer incidence under the attained-age model, based on acute whole-body exposure at age 30 years [a]

Cancer type	*REID (%)*								
	China		*Japan*	*Puerto Rico*		*United Kingdom*		*United States*	
	RR [b]	*AR* [c]		*RR*	*AR*	*RR*	*AR*	*RR*	*AR*
Dose of 1 Sv (males)									
Oesophagus	0.6	0.5	0.5	0.5	0.5	0.5	0.6	0.2	0.4
Stomach	1.1	1.7	1.9	0.4	1.9	0.5	2.1	0.2	1.5
Colon	0.6	1.3	1.4	0.8	1.4	1.2	1.6	1.1	1.2
Liver	0.7	2.4	2.6	0.3	2.5	0.2	2.8	0.1	2.1
Lung	3.2	2.4	2.8	1.3	2.9	5.0	3.4	2.9	2.0
Breast	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Thyroid	0.2	0.3	0.3	0.1	0.3	0.4	0.9	0.4	0.6
Bladder	0.5	0.7	0.8	0.7	0.8	0.1	0.3	0.4	0.3
Other solid cancer	2.6	2.7	2.9	4.0	2.9	5.1	3.2	6.8	2.5
All solid cancers	9.4	12.0	13.3	8.0	13.1	12.9	14.9	12.1	10.6
Leukaemia	0.8	0.8	0.8	0.9	0.9	0.9	0.9	0.7	0.7
Total	10.2	12.8	14.1	8.9	14.0	13.8	15.8	19.7	13.8
Dose of 0.1 Sv (males) [d]									
Oesophagus	0.06	0.05	0.05	0.05	0.05	0.05	0.06	0.02	0.04
Stomach	0.12	0.19	0.21	0.04	0.20	0.05	0.23	0.02	0.17
Colon	0.07	0.14	0.16	0.09	0.15	0.13	0.17	0.13	0.13
Liver	0.08	0.26	0.28	0.03	0.27	0.02	0.31	0.02	0.23
Lung	0.35	0.27	0.32	0.14	0.33	0.55	0.39	0.32	0.23
Breast	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Thyroid	0.02	0.03	0.04	0.02	0.03	0.04	0.10	0.04	0.07
Bladder	0.05	0.08	0.09	0.07	0.09	0.01	0.04	0.04	0.03
Other solid cancer	0.27	0.29	0.32	0.43	0.31	0.55	0.35	0.74	0.26
All solid cancers	1.01	1.30	1.46	0.85	1.44	1.40	1.65	1.33	1.16
Leukaemia	0.04	0.04	0.04	0.04	0.04	0.02	0.02	0.05	0.05
Total	1.05	1.34	1.50	0.89	1.48	1.42	1.67	1.38	1.21
Dose of 1 Sv (females)									
Oesophagus	0.4	0.1	0.2	0.3	0.2	0.4	0.2	0.1	0.1
Stomach	1.0	1.6	1.9	0.4	1.9	0.4	2.0	0.1	1.6
Colon	1.1	1.6	2.0	1.5	2.0	2.0	2.1	1.9	1.7
Liver	0.6	0.6	0.8	0.1	0.8	0.1	0.9	0.1	0.7
Lung	4.7	3.4	4.6	2.4	4.5	7.4	5.1	7.5	3.5
Breast	4.6	4.9	5.3	8.4	5.3	12.3	5.4	13.6	4.9
Thyroid	0.6	1.2	1.3	0.5	1.3	0.5	0.4	0.5	0.3
Bladder	0.2	0.3	0.4	0.5	0.4	0.3	1.3	1.0	1.2
Other solid cancer	1.1	1.4	1.6	1.4	1.6	2.4	1.6	2.2	1.4
All solid cancers	14.4	15.1	18.1	15.5	17.9	25.7	19.0	27.0	15.4
Leukaemia	0.8	0.8	0.9	1.2	1.2	1.1	1.2	1.0	1.1
Total	15.2	15.9	19.0	16.7	19.0	26.8	20.1	30.2	17.9
Dose of 0.1 Sv (females) [d]									
Oesophagus	0.05	0.02	0.02	0.03	0.02	0.05	0.02	0.01	0.02
Stomach	0.11	0.17	0.21	0.04	0.21	0.05	0.22	0.02	0.17
Colon	0.12	0.18	0.22	0.17	0.22	0.24	0.24	0.24	0.19
Liver	0.07	0.07	0.10	0.02	0.09	0.01	0.10	0.01	0.41
Lung	0.54	0.39	0.54	0.28	0.53	0.91	0.61	0.95	0.07
Breast	0.49	0.52	0.56	0.90	0.56	1.39	0.57	1.57	0.52
Thyroid	0.06	0.12	0.14	0.06	0.14	0.06	0.05	0.06	0.04
Bladder	0.03	0.04	0.05	0.05	0.05	0.03	0.14	0.11	0.13
Other solid cancer	0.12	0.15	0.17	0.15	0.17	0.27	0.18	0.26	0.15
All solid cancers	1.58	1.67	2.02	1.70	1.99	3.01	2.13	3.23	1.70
Leukaemia	0.03	0.03	0.04	0.05	0.05	0.02	0.02	0.05	0.05
Total	1.61	1.70	2.06	1.75	2.04	3.03	2.15	3.28	1.75

a Owing to rounding errors, the sum of the individual values in each column sometimes differs from the total, which has been calculated to greater accuracy.
b Relative risk transportation.
c Absolute risk transportation.
d The estimates presented for solid cancers at 0.1 Sv do not involve a reduction factor for low doses or low dose rates. In contrast, the leukaemia estimates at 0.1 Sv are based on a linear-quadratic dose response.

Table 38
Comparison of elicited high dose and high-dose-rate lifetime low-LET fatal cancer risks for a general population (European Union / United States) with those derived from other sources
(Risks expressed per 100 at 1 Sv)
(Based on [L27])

Cancer type	*Elicited risk* [a]	*BEIR V* [b]	*ICRP 60* [c]	*UNSCEAR 1994* [d]	*UNSCEAR 2000 (Age-at-exposure)* [e]	*UNSCEAR 2000 (Attained age)* [f]
Bone	0.035 (<10^{-3}– 0.88)					
Colon	0.98 (0.011–3.35)		3.24	0.6		0.6
Breast [g]	0.78 (0.11–3.78)	0.35	0.97	1.0		0.6
Leukaemia	0.91 (0.026–2.33)	0.95	0.95	1.1		1.0
Liver	0.86 (<10^{-3}–2.02)			1.2		0.9
Lung	2.76 (0.59–8.77)	1.7	2.92	2.5		2.1
Pancreas	0.17 (<10^{-3}–1.26)					
Skin	0.039 (<10^{-3}–0.37)		0.03			
Stomach	0.30 (<10^{-3}–4.01)		0.51	1.4		1.2
Thyroid	0.059 (<10^{-3}–0.71)					
All other cancers	2.60 (<10^{-3}–10.8)					
All cancers	10.2 (3.47–28.5)	7.9	12.05	12	12	9

a REID for a joint European Union / United States population (90% CI in parentheses). Elicitation of risks involved questioning a range of experts.
b ELR for a United States population [C1].
c REID averaged over United Kingdom and United States populations, using a relative risk projection model (data extracted from [I1]).
d REID for a Japanese population, using an age-at-exposure model [U2].
e REID for a Japanese population of both genders and all ages, using an age-at-exposure model (derived from Table 34 of this Annex).
f REID for a Japanese population of both genders and all ages, using an attained-age model (derived from Table 36 of this Annex).
g Averaged over genders.

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