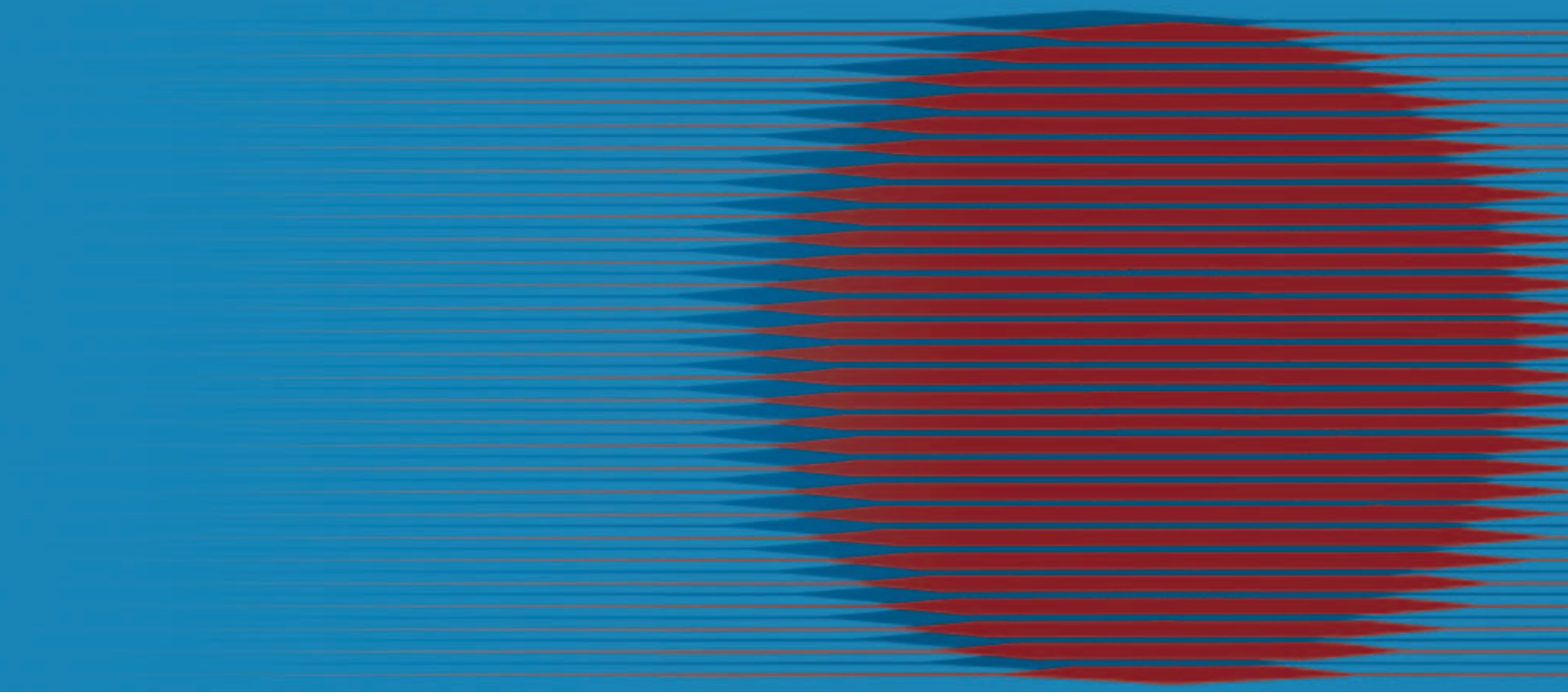
# EFFECTS OF IONIZING RADIATION

United Nations Scientific Committee on the Effects of Atomic Radiation

## UNSCEAR 2006 Report

### Volume I

Report to the General Assembly
Scientific Annexes A and B



UNITED NATIONS

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United Nations Scientific Committee on the
Effects of Atomic Radiation

UNSCEAR 2006
Report to the General Assembly,
with Scientific Annexes

VOLUME I

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New York, 2008

NOTE

The report of the Committee without its annexes appears as Official Records of the General Assembly, Sixty-first Session, Supplement No. 46 and corrigendum (A/61/46 and Corr. 1). The report reproduced here includes the corrections of the corrigendum.



The country names used in this document are, in most cases, those that were in use at the time the data were collected or the text prepared. In other cases, however, the names have been updated, where this was possible and appropriate, to reflect political changes.

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# Contents

# Report of the United Nations Scientific Committee on the Effects of Atomic Radiation to the General Assembly

## Contents

# I. Deliberations of the United Nations Scientific Committee on the Effects of Atomic Radiation at its fifty-fourth session

1. Since the creation of the United Nations Scientific Committee on the Effects of Atomic Radiation by the General Assembly in its resolution 913 (X) of 3 December 1955, the mandate of the Committee has been to undertake broad reviews of the sources of ionizing radiation and its effects on human health and the environment. Exposure to radiation occurs from sources such as nuclear weapon testing; natural background radiation; nuclear electricity generation; accidents such as the one at Chernobyl in 1986; occupations that entail increased exposure to man-made or naturally occurring sources; and medical screening, diagnostic and therapeutic procedures. The Committee[1] thoroughly reviews and evaluates global and regional exposures to such sources of radiation and the doses that result from them. It evaluates the evidence of radiation-induced health effects from studies of the health of survivors of the atomic bombings of Japan and of other exposed groups. It also reviews advances in understanding of the mechanisms by which radiation-induced health effects can occur. These assessments provide the scientific foundation used, inter alia, by the International Commission on Radiological Protection (ICRP) in developing its recommendations on radiation protection and by the relevant agencies within the United Nations system in formulating International Basic Safety Standards for Protection against Ionizing Radiation and for the Safety of Radiation Sources.

2. The Committee held its fifty-fourth session[2] in Vienna from 29 May to 2 June 2006. Peter Burns (Australia), Norman Gentner (Canada) and Christian Streffer (Germany) served as Chairman, Vice-Chairman and Rapporteur, respectively. The Committee reviewed advanced versions of documents that were last considered at the fifty-third session of the Scientific Committee (26–30 September 2005), as reported to the General Assembly in the Committee's report on that session.[3] The Committee had originally envisaged that those documents would be published by 2005, but the limited availability of resources had delayed their development. Nevertheless, five scientific annexes were approved for publication in the 2006 report of the Committee. The Committee also scrutinized drafts of the other outstanding documents, namely those on exposures of the public and workers to various sources of radiation; exposures from radiation accidents; exposures from medical uses of radiation; and effects of ionizing radiation on non-human biota.

3. The Committee took note that, in its resolution 60/98 of 8 December 2005, the Assembly, inter alia, reaffirmed its decision to maintain the present functions and independent role of the Committee; endorsed the intentions and plans of the Committee for its future activities of scientific review and assessment on behalf of the Assembly; emphasized the need for the Committee to hold regular sessions on an annual basis; requested the United Nations Environment Programme (UNEP) to continue to provide support for the effective conduct of the work of the Committee and for the dissemination of its findings to the Assembly, the scientific community and the public; and urged UNEP to review and strengthen the present funding of the Committee.

4. The date 14 March 2006 had marked the fiftieth anniversary of the first session of the Committee. As part of the commemoration of that event, the Government of Japan and the Chairman of the fifty-third session of the Committee, Yasuhito Sasaki, had arranged for publication of all the past reports of the Committee to be made available electronically on its website; the structure, design and content of the website was also generally overhauled. Moreover, during the fifty-fourth session of the Committee, the Mayor and Governor of the City of Vienna hosted a reception for invited dignitaries, scientists and diplomats at the Vienna Town Hall to commemorate the anniversary. On that occasion, the Director-General of the United Nations Office at Vienna delivered a message from the Secretary-General; the special guest speaker was Hans Blix; and other speakers attended from the International Atomic Energy Agency (IAEA), the World Health Organization (WHO) and UNEP. The speakers, especially Hans Blix, highlighted the importance of the Committee's scientific work over the past 50 years, recognizing its achievements and reputation for

[1] The United Nations Scientific Committee on the Effects of Atomic Radiation was established by the General Assembly at its tenth session, in 1955. Its terms of reference are set out in resolution 913 (X) of 3 December 1955. The Committee was originally composed of the following Member States: Argentina, Australia, Belgium, Brazil, Canada, Czechoslovakia, Egypt, France, India, Japan, Mexico, Sweden, Union of Soviet Socialist Republics, United Kingdom of Great Britain and Northern Ireland and United States of America. The membership of the Committee was subsequently enlarged by the Assembly in its resolution 3154 C (XXVIII) of 14 December 1973 to include the Federal Republic of Germany, Indonesia, Peru, Poland and the Sudan. By its resolution 41/62 B of 3 December 1986, the Assembly increased the membership of the Committee to a maximum of 21 members and invited China to become a member.

[2] The fifty-fourth session was also attended by observers from the United Nations Environment Programme (UNEP), the International Atomic Energy Agency (IAEA), the International Commission on Radiological Protection (ICRP), and the International Commission on Radiation Units and Measurements (ICRU).

[3] *Official Records of the General Assembly, Sixtieth Session, Supplement No. 46* (A/60/46).

scientific independence and credibility. He reflected that, with the important developments in radiation science and major environmental challenges, there was a need to strengthen support for the Committee. The Director and Regional Representative, Regional Office for Europe, of UNEP undertook actively to explore options for enhanced future support. He considered that a more apparent relationship between the scientific appraisals made by the Committee and UNEP-led policy exchanges would facilitate joint efforts to strengthen and broaden the Committee's resource base.

5. The Committee had participated in the work of the Chernobyl Forum (which involved eight United Nations entities and the Governments of Belarus, the Russian Federation and Ukraine), whose important mission covered many aspects of the Chernobyl accident, including the review of the health effects of radiation. The Committee reiterated that the recent findings of that Forum confirmed its own essential scientific conclusions,[4] reached six years earlier, on the health and environmental consequences of radiation exposure due to the Chernobyl accident. For the general population, the main adverse health consequence that had been observed was the dramatic increase in the incidence of thyroid cancer among people who had received high thyroid doses as children in 1986. The Committee recognized that it was often difficult for the public and the media to appreciate that the radiation risks, while serious for some exposed groups, were for the general population not as significant from a radiological health point of view as they were often represented to be. Uninformed reporting of postulated numbers of projected exposure-related deaths as a result of the accident, especially reporting before and at the time of the twentieth anniversary of the accident in April 2006, had created confusion among the public. With the exception of the early deaths among emergency workers that were clinically attributable to acute radiation syndrome and the small proportion of cases of thyroid cancer (which could be attributed on epidemiological grounds to radiation exposure) that were fatal, it was not possible to attribute any specific death to late effects of exposure to radiation as a result of the accident. The Committee expressed its intention to clarify further the assessment of potential harm owing to chronic low-level exposures among large populations and also the attributability of health effects. It also recognized that some outstanding details merited further scrutiny and that its work to provide the scientific basis for a better understanding of the radiation-related health and environmental effects of the Chernobyl accident needed to continue. However, owing to its participation in the Chernobyl Forum, the Committee would now extend the work on updating its own assessments of the health and environmental consequences of the Chernobyl accident in order to scrutinize information that had become available more recently. To do so effectively, it would need to increase the participation of scientists from Belarus, the Russian Federation and Ukraine. The work could not be conducted properly without additional resources.

6. The need for restoration of an operating budget adequate to allow the Committee to fulfil its mandate from the General Assembly, expressed most recently in Assembly resolutions 60/98, 59/114 of 10 December 2004, 58/88 of 9 December 2003 and 57/115 of 11 December 2002, and in anticipation of a growing need for the Committee's expertise, was now at a critical point. The Committee reiterated its concern that reliance on a single professional in the secretariat left the Committee seriously vulnerable which in the past had hampered the efficient implementation of the approved programme of work. The Committee considered that funding in the biennium 2008–2009 had to be strengthened pursuant to resolutions 60/98, 59/114, 58/88 and 57/115. Moreover, no additional resources had as yet been provided in the biennium 2006–2007 to allow the plans endorsed by the General Assembly to be carried out effectively.[5]

7. The Committee recognized the importance of information from Member States and relevant international organizations for its work. It calls upon all Member States, specialized agencies of the United Nations system and other international and national scientific bodies, to continue to make available relevant and authorized information for its reviews, whose quality and completeness critically depend on such information.

8. The Committee decided to hold its fifty-fifth session in Vienna from 21 to 25 May 2007.

[4] See *Official Records of the General Assembly, Fifty-fifth Session, Supplement No. 46* (A/55/46).

[5] *Official Records of the General Assembly, Sixtieth Session, Supplement No. 7* (A/60/7), sect. IV, para. IV.46.

# II. Scientific report

9. The Committee summarized the main conclusions of five scientific annexes for inclusion in its report for 2006, entitled "Epidemiological studies of radiation and cancer", "Epidemiological evaluation of cardiovascular disease and other non-cancer diseases following radiation exposure", "Non-targeted and delayed effects of exposure to ionizing radiation", "Effects of ionizing radiation on the immune system", and "Sources-to-effects assessment for radon in homes and workplaces". The 2006 report and its annexes should be considered taking into account the context provided by earlier substantive reports[6] of the Committee. The overall view of the Committee is that the data reviewed for its 2006 report do not necessitate changes in its current risk estimates for the cancer and the hereditary effects of radiation.

10. The present report and its scientific annexes were developed between the fiftieth and fifty-fourth sessions of the Committee, on the basis of working papers prepared by the Secretariat. Serving as Chairman, Vice-Chairman and Rapporteur respectively at those sessions were:

Fiftieth and fifty-first sessions: J. Lipzstein (Brazil), Y. Sasaki (Japan) and R. Chatterjee (Canada);

Fifty-second session: Y. Sasaki (Japan), R. Chatterjee (Canada) and P. Burns (Australia);

Fifty-third session: Y. Sasaki (Japan), P. Burns (Australia) and N. Gentner (Canada);

Fifty-fourth session: P. Burns (Australia), N. Gentner (Canada) and C. Streffer (Germany).

The names of the members of national delegations who attended the fiftieth to fifty-fourth sessions of the Committee are listed in appendix I below. The Committee wishes to acknowledge the help and advice of a small group of consultants (see appendix II below) who helped in the preparation of the material and the contributions in kind of national experts and staff of international organizations. They were responsible for the preliminary reviews and evaluations of the technical information received by the Committee or available in the open literature, on which rested the final deliberations of the Committee.

11. The sessions of the Committee held during the period under review were attended by representatives of the following United Nations specialized agencies and other organizations: WHO, IAEA and UNEP; and by the following international organizations: ICRP and the International Commission on Radiation Units and Measurements (ICRU). The Committee wishes to acknowledge their contributions to the discussions.

12. Following established practice, the present annual report of the Committee to the General Assembly does not include the scientific annexes. The full report of the Scientific Committee for 2006, including the scientific annexes, will be issued as a United Nations sales publication. This practice is intended to achieve a wider distribution of the findings for the benefit of the international scientific community. The Committee wishes to draw the attention of the Assembly to the fact that the main text of the Committee's 2006 report is presented separately from its scientific annexes in the present document simply for the sake of convenience. It should be understood that the scientific information contained in the annexes is important because it forms the basis for the conclusions of the report.

[6] For the previous substantive reports of the United Nations Scientific Committee on the Effects of Atomic Radiation to the General Assembly, see *Official Records of the General Assembly, Thirteenth Session, Supplement No. 17* (A/3838); ibid., *Seventeenth Session, Supplement No. 16* (A/5216); ibid., *Nineteenth Session, Supplement No. 14* (A/5814); ibid., *Twenty-first Session, Supplement No. 14* (A/6314 and Corr.1); ibid., *Twenty-fourth Session, Supplement No. 13* (A/7613 and Corr.1); ibid., *Twenty-seventh Session, Supplement No. 25* (A/8725 and Corr.1); ibid., *Thirty-second Session, Supplement No. 40* (A/32/40); ibid., *Thirty-seventh Session, Supplement No. 45* (A/37/45); ibid., *Forty-first Session, Supplement No. 16* (A/41/16); ibid., *Forty-third Session, Supplement No. 45* (A/43/45); ibid., *Forty-eighth Session, Supplement No. 46* (A/48/46); ibid., *Forty-ninth Session, Supplement No. 46* (A/49/46); ibid., *Fifty-first Session, Supplement No. 46* (A/51/46); ibid., *Fifty-fifth Session, Supplement No. 46* (A/55/46 and Corr.1 Arabic only); and *Fifty-sixth Session, Supplement No. 46* (A/56/46). These documents are referred to as the 1958, 1962, 1964, 1966, 1969, 1972, 1977, 1982, 1986, 1988, 1993, 1994, 1996, 2000 and 2001 reports, respectively. The 1972 report, with scientific annexes, was published as *Ionizing Radiation: Levels and Effects, Volume I: Levels and Volume II*: *Effects* (United Nations publication, Sales Nos. E.72.IX.17 and 18). The 1977 report, with scientific annexes, was published as *Sources and Effects of Ionizing Radiation* (United Nations publication, Sales No. E.77.IX.1). The 1982 report, with scientific annexes, was published as *Ionizing Radiation: Sources and Biological Effects* (United Nations publication, Sales No. E.82.IX.8). The 1986 report, with scientific annexes, was published as *Genetic and Somatic Effects of Ionizing Radiation* (United Nations publication, Sales No. E.86.IX.9). The 1988 report, with scientific annexes, was published as *Sources, Effects and Risks of Ionizing Radiation* (United Nations publication, Sales No. E.88.IX.7). The 1993, 1994 and 1996 reports, with scientific annexes, were published as *Sources and Effects of Ionizing Radiation* (United Nations publication, Sales Nos. E.94.IX.2, E.94.IX.11 and E.96.IX.3, respectively). The 2000 report, with scientific annexes, was published as *Sources and Effects of Ionizing Radiation, Volume I: Sources and Volume II: Effects* (United Nations publication, Sales Nos. E.00.IX.3 and 4). The 2001 report, with scientific annex, was published as *Hereditary Effects of Radiation* (United Nations publication, Sales No. E.01.IX.2).

### A. Epidemiological studies of radiation and cancer

13. The Committee has always relied heavily upon results of epidemiological investigations in estimating the risks of radiation-induced cancer. Much attention has been given by the Committee to the criteria that define good-quality epidemiology studies and to the various features of such studies that must be taken into consideration for the Committee to improve its estimates. The concept of statistical power, that is the probability that an epidemiological study will detect a given level of elevated risk with a specific degree of confidence, and various factors that affect it were summarized in the Scientific Committee's 2000 report. Further elaboration of this issue in annex A of the 2006 report, entitled "Epidemiological studies of radiation and cancer", shows that the statistical power of a study is greatly affected by the sample size, the dose level(s) of the exposed group and the magnitude of the risk coefficient, such that most low dose studies reported in the literature have inadequate statistical power. Also, for low dose studies with numbers of effects that are expected to be small and which do not have any statistical power, the value of the relative risk found for any supposedly "statistically significant" results is likely to be a substantial overestimate of the "true" risk.

14. Numerous sources of uncertainty in epidemiological studies were considered, together with methods for dealing with them. A new generation of epidemiological studies has begun to provide estimates of radiation risks corrected for uncertainties in dose assessment and corrections for other uncertainties are beginning to be made. An important issue when interpreting studies that make multiple comparisons (for example, for many different types of cancer) is that the probability of obtaining a statistically significant result purely by chance increases with the number of comparisons.

15. The cancer risk estimates calculated in the Committee's 2000 report were based on data on Japanese atomic bombing survivors and used the set of survivor dose estimates produced in the mid-1980s, the so-called DS86 dosimetry. For some time, it was thought that the DS86 neutron dose estimates for the Hiroshima atomic bombing survivors were systematic underestimates, while the DS86 gamma dose estimates were thought to be more reliable. Recent analysis of the available data suggests that there are no appreciable systematic errors in the DS86 Hiroshima neutron dose estimates. The most current set of dose estimates, the so-called DS02 dosimetry, differs only slightly from the DS86 system, by amounts generally of no more than 20 per cent. Analyses using the new dosimetry indicate that estimates of cancer risk factors might fall by about 8 per cent as a result, but with no appreciable change in the shape of the dose response or in the patterns of excess risk with age or time.

16. Although the resolution of dosimetric inconsistencies in the data on Japanese atomic bombing survivors has reduced one source of uncertainty in estimating cancer risks to a population from low doses of radiation, a considerable number of other sources of uncertainty remain. A major source relates to extrapolation from the moderate dose but high dose-rate exposures received by the Japanese atomic bombing survivors to low doses and dose rates. This is also true for interpreting data on many therapeutically exposed groups. There is also uncertainty relating to the extrapolation of cancer risk to the end of lifetime. In particular, about half of the cohort of Japanese atomic bombing survivors are still alive. In estimating risk factors from the data on this cohort it is vital to determine the pattern of variation of radiation-associated cancer risk for those exposed in childhood, who are now reaching the age at which larger numbers of cancers would be expected to arise spontaneously. Another source of uncertainty relates to the transfer of radiation-induced cancer risk estimates between populations with different spontaneous cancer rates.

17. Annex A of the Committee's 2006 report reassesses the risk of incidence and the mortality of cancer from the data on Japanese atomic bombing survivors, wherever possible making use of the latest DS02 dosimetry and follow-up. It also comprehensively reviews all the evidence from studies of groups of people exposed therapeutically, diagnostically and occupationally. Annex A considers risks of cancers of the salivary gland, oesophagus, stomach, small intestine (including duodenum), colon, rectum, liver, pancreas, lung, bone and connective tissue, female breast, uterus, ovary, prostate, urinary bladder, kidney, brain and central nervous system, and thyroid; and risks of non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, leukaemia, cutaneous melanoma, and non-melanoma skin cancer. This somewhat extends the list of organ sites from those that had been considered in the Committee's 2000 report (cancers of the salivary gland, small intestine, rectum, pancreas, uterus, ovary and kidney, and cutaneous melanoma were not considered in that report). As with the Committee's 2000 report, annex A assesses separately the risks arising from internal and external exposure to radiation, and from so-called low-LET and high-LET (linear energy transfer) radiation.

18. There are still problems in characterizing cancer risks for some sites, owing to the low statistical precision associated with relatively small numbers of excess cases. This can limit, for example, the ability to estimate trends in risk in relation to factors such as sex, age at exposure and time since exposure. 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, for which a comparison of data on the Japanese atomic bombing survivors and on medically exposed women in North America points to a so-called "absolute" model for the transfer of risk estimates between populations. There are some cancer sites for which there is no evidence for an association with radiation and others where excess risks have only been seen following very high dose (radiotherapeutic) exposures. 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, which is also a rare disease.

19. The increased statistical precision associated with the longer follow-up of the above studies and the resulting larger number of cancers observed has assisted in the examination of dose-response relationships, in particular for lower levels of dose. For example, the most recent data for the Japanese atomic bombing survivors are largely consistent with linear or linear-quadratic risk-dose trends over a wide range of dose levels. However, analyses restricted solely to low doses are complicated by the limitations of statistical precision, the potential for misleading findings arising from any small, undetected biases and the problem of observing statistically significant results purely by chance when performing multiple tests to establish a minimum dose at which elevated risks can be detected. Longer follow-up of large groups such as the atomic bombing survivors will provide more information on effects for low doses. However, epidemiology alone will not be able to resolve the issue of whether there are dose thresholds for radiation risks. A better understanding of biological mechanisms is necessary. In particular, the inability to detect increases in risks at very low doses using epidemiological methods does not mean that the cancer risks are not elevated.

20. New findings have also been published from analyses of fractionated or chronic low-dose exposure to low-LET radiation; in particular, a study of nuclear workers in 15 countries, studies of persons living in the vicinity of the Techa River in the Russian Federation who were exposed as a consequence of radioactive discharges from the Mayak plant, a study of persons exposed to fallout from the Semipalatinsk nuclear test site in Kazakhstan, and studies in regions with high natural background levels of radiation. Cancer risks are generally statistically compatible with, although in some studies they are somewhat higher than, those derived from the data on Japanese atomic bombing survivors. However, there are concerns about bias in all of these studies, which may explain why the cancer risk estimates are elevated in comparison with those derived from the Japanese data.

21. The results presented in annex A to the Committee's 2006 report illustrate the sensitivity of estimates of lifetime cancer risk due to radiation exposure to variations in the background rates of spontaneous cancers. These findings suggest that this variability can lead to differences that are comparable with those associated with different methods of transferring risk estimates between populations or methods of risk projection. The variability in all these projections highlights the difficulty of choosing a single value to represent the lifetime risk of radiation-induced cancer. Furthermore, uncertainties in estimates of risks for specific types of cancer are generally greater than the uncertainties in estimates of risks for all cancers together.

22. Despite these difficulties, risk estimates are of considerable value for use in characterizing the impact of radiation exposure on a population. The Committee's 2000 report emphasized, for the purpose of risk projection, models that simulated the relative risk due to radiation according to age-at-exposure or attained age. With longer follow-up studies it has become clear that these models do not fit well. The Committee's 2006 report indicates that best fits are currently obtained if the models for the risk of mortality from solid cancer simulate the relative or absolute excess risk due to radiation exposure as proportional to a product of functions involving powers of time since exposure and attained age. The current preferred leukaemia mortality models imply that the relative excess risk is proportional to a power of attained age, and absolute excess risk is proportional to a power of time since exposure. When these models are applied to any of five specific populations (China, Japan, Puerto Rico, the United States of America and the United Kingdom of Great Britain and Northern Ireland) of all ages, the lifetime risk of death from all solid cancers together following an acute dose of 1 sievert (Sv) is estimated to be about 4.3–7.2 per cent, and for leukaemia 0.6–1.0 per cent. The calculations in annex A to the 2006 report show that these values vary among different populations and with different risk models; the variation being most substantial for solid cancers. These cancer risk estimates are somewhat lower, although not by much, than those previously published in the Committee's 2000 report. Some of the reduction in cancer risk estimates may be due to the new atomic bomb dosimetry and follow-up, although a larger part is probably due to the different risk projection and transport models used, in particular for solid cancers. Lifetime cancer risk estimates for those exposed as children might be a factor of 2 to 3 times higher than 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 results from analysing the data on the Japanese atomic bombing survivors are consistent with a linear or linear-quadratic dose-response relationship for the risk of all solid cancers together and with a linear-quadratic dose response relationship for leukaemia.

### B. Epidemiological evaluation of cardiovascular disease and other non-cancer diseases following radiation exposure

23. Annex B to the Committee's 2006 report, entitled "Epidemiological evaluation of cardiovascular disease and other non-cancer diseases following radiation exposure", considers epidemiological investigations that have addressed diseases other than cancer. A statistically significant association between radiation dose and mortality from diseases other than cancer was first reported in 1992 from the analysis of the Life Span Study of the data on the Japanese atomic bombing survivors for the period 1950–1985. Significant associations were seen for cardiovascular disease and other non-cancer diseases. The excess mortality from those diseases could not be explained by the effects

of smoking or other possible factors and thus the possibility that radiation was the direct cause of those effects needed to be considered. Annex B concentrates primarily on the findings from that Life Span Study and others that relate to cardiovascular diseases.

24. Effects of exposure to radiation on conditions other than cancer were most recently reviewed in the Committee's 1982 and 1993 reports, showing the presence of a minimum dose—a threshold dose—below which no radiation effects are detected clinically. Although a value for the threshold dose is difficult to define and may vary according to tissues and measuring techniques, the atomic bombing survivor data show that associations between radiation exposure and the incidence of diseases other than cancer can occur at levels of dose below those hitherto considered as thresholds for various so-called deterministic effects.

25. Annex B to the Committee's 2006 report reviews current epidemiological data and attempts to characterize the nature of the risk of non-cancer disease associated with exposure to radiation. It discusses several methodological issues that are especially relevant for assessing epidemiological data for non-cancer diseases. It then provides a general overview of currently available data on major diseases other than cancer from some 50 irradiated populations. Epidemiological data have been reviewed in detail for cardiovascular disease, which is one of the most common diseases and the one for which relatively more information on possible causation by radiation exposure is currently available. Annex B also identifies important gaps in knowledge regarding the nature of this risk and discusses the possible impact on future radiation risk assessment.

26. There is an increased risk of cardiovascular disease associated with high radiation doses to the heart, which may be incurred during radiotherapy, although newer treatment techniques resulting in lower cardiac doses have reduced the risk substantially. To date, the evidence for an association between fatal cardiovascular disease and radiation exposure at doses in the range of less than about 1–2 gray (Gy) comes only from the analysis of the data on the Japanese atomic bombing survivors. Other studies provide no clear or consistent evidence of a risk of cardiovascular diseases for radiation doses of less than about 1–2 Gy. The Committee judges that, overall, the data are not sufficient to determine appropriate risk models for these end points. The scientific data are also not at present sufficient to conclude that there is a causal relationship between exposure to ionizing radiation and the incidence of cardiovascular disease for doses of less than about 1–2 Gy.

27. Because of the high occurrence of cardiovascular disease in non-exposed populations, and its multifactorial nature and heterogeneity, as well as the need to account for major confounding factors (such as tobacco use, genetics and cholesterol level), it is uncertain whether epidemiological studies alone will be able to add significantly to the understanding of the potential for and nature of any possible causal relationship between the incidence of cardiovascular disease and radiation exposure.

28. For mortality from the group of all diseases apart from cardiovascular disease and cancer, the evidence for an association with radiation exposure at doses of less than about 1–2 Gy is also only derived from the analysis of the atomic bombing survivor data. Scientific evidence from other studies for inferring a causal relationship with radiation exposure for doses of less than about 1–2 Gy is even less sufficient than that for cardiovascular disease in these populations. This is in part because of limited data, the large heterogeneity of diseases and the various pathological mechanisms and aetiologies, as well as a multitude of confounding factors.

### C. Non-targeted and delayed effects of exposure to ionizing radiation

29. The risks of cancer after high and moderate doses of radiation are relatively well understood from detailed epidemiological studies of the Japanese atomic bombing survivors and others. However, risks at the lower doses more typical of environmental and occupational exposures are generally extrapolated from the high dose data by incorporating factors to account for low dose and low dose rates. The estimation of the human health risks associated with radiation exposures are based mechanistically on the view that the detrimental effects of irradiation have their origin in irradiated cells or, in the case of heritable effects, in cells directly descended from them. However, a number of so-called non-targeted and delayed effects of radiation exposure have been described that may challenge this view. Annex C to the Committee's 2006 report, entitled "Non-targeted and delayed effects of exposure to ionizing radiation", reviews the evidence for such effects and reflects on how they may influence the mechanistic judgements required for the estimation of risk at low doses and dose rates.

30. The effects considered include radiation-induced genomic instability, bystander effects, abscopal effects, induced clastogenic factors and hereditary effects, as follows:

*(a)* If a single cell is irradiated and survives, it may produce daughter cells that over generations have increasing numbers of alterations in their genomes, even though the daughter cells themselves were not irradiated. This effect is termed "induced genomic instability". The alterations in the genomes of the daughter cells can include alterations in their chromosomes, changes in the numbers of their chromosomes, mutation of their genes and other deozyribonucleic acid (DNA) sequences and a reduction in the number of subsequent cells generated through daughter cell replication;

*(b)* The so-called "bystander" effect is the ability of irradiated cells to convey manifestations of damage to neighbouring cells not directly irradiated;

*(c)* An abscopal effect is said to occur if there is a significant response in a tissue that is physically separate from the region of the body exposed to radiation;

*(d)* There is a large body of evidence that blood plasma from irradiated animals and humans can contain so-called "clastogenic factors" capable of inducing chromosomal damage in unexposed cells;

*(e)* Heritable effects are those effects observed in offspring born after one or both parents has or have been irradiated prior to conception. Transgenerational effects are those that are expressed beyond the first generation;

*(f)* Finally, some of the manifestations of non-targeted and delayed effects noted above can arise spontaneously and after exposure to other agents.

31. In spite of the large body of new information, there continues to be considerable debate regarding the causal relationship between these non-targeted effects and the observed health effects attributable to radiation. The Committee concludes that at present the available data provide some support for concluding that there are disease associations, but not for causation. In arriving at this conclusion, the Committee stresses that the estimation of the health effects of radiation is based on epidemiological and experimental observations where there is a statistically significant dose-related increase in disease incidence. These direct observations of adverse health outcomes implicitly take account of mechanistic elements relating not only to the targeted (direct) effects of irradiation but also to the non-targeted and delayed effects described in annex C to the 2006 report.

32. The Committee continues to hold the view that mechanistic information is important for its judgements on radiation-induced health effects at doses below about 0.2 Gy. However, to ascribe a mechanism for the development of a particular health-related biological effect, the data in question need to be independently replicated and to show strong coherence with the particular disease considered. In this respect, the data on microdosimetric energy distribution in the cell nucleus and the subsequent cellular processing of directly induced DNA damage, reviewed in the Committee's 2000 report, are considered to provide a suitable foundation for judgements on mechanisms that affect risk estimation. However, the Committee recognizes that a variety of mechanistic processes will contribute to the development of radiation-induced health effects.

33. The Committee will maintain surveillance of scientific developments in the area of non-targeted and delayed effects and recommends generally that future research pay particular attention to designing studies that emphasize reproducibility, low dose responses and causal associations with health effects. Ultimately, understanding the range and nature of cellular and tissue responses to radiation will provide insights into the mechanisms by which radiation exposure induces detrimental health effects, thereby improving the scientific basis for the quantitative estimation of the risk of health effects for low doses and low dose-rates.

### D. Effects of ionizing radiation on the immune system

34. The effects of ionizing radiation on the immune system were first reviewed in detail in the Committee's 1972 report and then briefly described in the 1977, 1982, 1986, 1988, 1994 and 2000 reports. Concepts in immunology have developed and changed considerably in the last three decades and so the Committee had proposed that a completely new review of the effects of ionizing radiation on the immune system was necessary. Thus, annex D to the 2006 report, entitled "Effects of ionizing radiation on the immune system", reviews data related to radiation-induced alterations of immune responses, considers the possible mechanisms involved and reviews epidemiological studies of the effects of ionizing radiation on the human immune system.

35. The immune system, one of the most complex systems of the human body, is composed of cells of several types (lymphocytes and accessory cells) strategically spread throughout the body, perfectly positioned to recognize antigens (non-self or foreign substances and cells) and to neutralize or destroy them; this protects against infections and cancer. There are two different but interrelated forms of immunity: innate and acquired immunity. Innate immunity is fully functional before any foreign agent enters the body and thereby provides a rapid defence. Acquired immunity develops after a pathogen has entered the body and maintains memory of previous exposures, yielding a stronger response following subsequent exposure to the same antigen. Acquired immune responses are mainly executed by B-lymphocytes (humoral responses) and T-lymphocytes (cell-mediated responses).

36. The effects of ionizing radiation on the immune system can be assessed by estimating changes in cell numbers or by using a variety of functional assays. The impact of such alterations in immune response depends on factors such as dose of radiation, its temporal relation to immunization and genetic disposition. Thus:

*(a)* High doses of radiation produce immunosuppression mainly due to the destruction of cells. Lymphocytes are very radiosensitive and their reduction is currently used as an early indicator of the level of an accidental acute exposure. Radiation-induced changes in immune parameters seem to be more dependent on total dose than on dose rate. Persisting effects on the immune system have been observed after exposure to ionizing radiation;

*(b)* At low doses and dose rates, the effects of ionizing radiation on the immune system may be suppressive or stimulatory. The long-term impacts of low radiation doses

on the immune functions in relation to human health need to be evaluated.

37. Annex D to the 2006 report discusses some possible mechanisms by which radiation can induce alterations in the immune system and their role in the promotion and control of cancer. The immune system is able to remove aberrant cells that are potentially capable of forming tumours. It is unclear whether cancer results from a deficiency of the immune system. Immune dysfunction, however, has been associated with several types of human tumour. Understanding the interactions of ionizing radiation with the immune system may open new possibilities for cancer prevention and treatment.

38. Annex D to the 2006 report describes studies of the effects of ionizing radiation on the human immune system for Japanese atomic bombing survivors, Chernobyl workers and residents, Techa river residents, the population near the Hanford nuclear site and patients undergoing radiotherapy. A cross-comparison of these data indicates some common findings: impairment of cellular immunity, increased humoral immunity and a shift towards an inflammatory profile. Atomic bombing survivors show perturbations to stable immune systems; this was not evident in workers and residents exposed to radiation resulting from the Chernobyl accident.

39. While the suppressive effects of high doses of ionizing radiation are well documented, annex D to the 2006 report concludes that uncertainty exists regarding the effects of low radiation doses on the immune system; both stimulatory and suppressive effects have been reported.

### E. Sources-to-effects assessment for radon in homes and workplaces

40. Everyone is exposed in daily life to radon, a chemically inert radioactive gas that occurs naturally and is present in the atmosphere everywhere. Levels of radon indoors vary widely both within countries and between countries, with (nominal) geometric mean concentrations of radon in indoor air ranging from less than 10 becquerel per cubic metre (Bq $m^{-3}$) in the Middle East to more than 100 Bq $m^{-3}$ in several European countries.

41. The annual per capita dose from inhalation of radon gas (and its decay products) represents typically about half of the effective dose received by members of the public from all natural sources of ionizing radiation. For certain occupations, radon gas is the predominant source of occupational radiation exposure. In the nuclear fuel cycle, the release of radon from uranium mine tailings makes a substantial contribution to the effective dose from this practice.

42. Radon and its decay products are well established as lung carcinogens. However, the doses to other organs and tissues arising from the inhalation of radon and its decay products are quite small, usually at least an order of magnitude smaller than the doses to the lung. Moreover, epidemiological data provide little evidence for increased risks of mortality other than for that due to lung cancer.

43. Annex E to the 2006 report, entitled "Sources-to-effects assessment for radon in homes and workplaces", discusses potential sources of exposure to radon for workers and the public; issues of current interest in radon dosimetry; information from animal experiments and experiments at the cellular and sub-cellular level, which are important in understanding mechanisms of carcinogenesis; epidemiological studies of miners' exposure and residential exposure to radon; and approaches to risk projection.

44. For general risk management, a factor for calculating the dose from a given exposure to radon is needed for regulatory purposes and to allow comparison with other sources of radiation exposure. There are two approaches for deriving this so-called dose factor. A "dosimetric approach" derives the dose from a given exposure on the basis of atmospheric and breathing characteristics relevant for radon and its decay products. An "epidemiological approach" has been used by ICRP to derive the factor from epidemiological studies using the ratio of the risk of lung cancer in miners to the overall risk of cancer in the atomic bombing survivors. In the Committee's 2000 report there appeared to be a difference of a factor of about two between the results for the two approaches. However, the most recent data published on the risks to underground miners (derived from updated studies of cohorts of uranium miners) suggest that the results for the two approaches are less different than initially thought. Nonetheless, more work is necessary to better understand and account for the influence of modifying factors—such as the time since exposure, the attained age and the influence of dose rate—and of confounding factors (especially tobacco smoking).

45. Studies of miners exposed to radon and its decay products provide a direct basis for assessing their lung cancer risk. The United States National Research Council's Committee on Health Risks of Exposure to Radon in its sixth report in the study series Biological Effects of Ionizing Radiation (BEIR VI), entitled *Health Effects of Exposure to Radon*, reported an excess relative risk from exposure to radon that was equivalent[7] to 1.8 per cent per megabecquerel hours per cubic metre (MBq h $m^{-3}$) (95 per cent confidence interval: 0.3, 35) for miners with cumulative exposures below 30 MBq h $m^{-3}$. There are various sources of error in the assessment of miners' exposures, especially for the earliest years of mining when exposures were highest. Other factors that complicate the analyses of data on

[7] Equilibrium equivalent concentration using Système International (SI) units. Most historic, and indeed current, measurements of exposure to radon in mines are expressed in terms of the so-called working level month (WLM). 1 WLM is equivalent to 0.637 MBq h $m^{-3}$.

miners include the high percentage of miners who smoke; workplace exposure to dust contaminants, such as arsenic, diesel exhaust in the dust and other pollutants; and periods spent working in non-uranium mines. The power to detect any excess risks in miners nowadays is likely to be small, in part because the exposures are much smaller than in the early years of mining and in part because of improved monitoring and record-keeping. Because of the high exposures in the early days of mining, it is possible to detect trends in the risk of lung cancer and to investigate factors that affect the dose-response relationship, such as the age at exposure, the effect of dose rate and the reduction of risk with increasing time since exposure, as well as the effect of confounding factors such as smoking.

46. The BEIR VI model developed from the pooled analysis of 11 cohorts of underground miners provides a well-established basis for estimating risks from exposure to radon and accounts for factors such as the reduced risk with increasing time since exposure. Since the BEIR VI report, studies of various miner cohorts have been updated and these confirm the general patterns of risk with dose and with time since exposure that were reported by BEIR VI, including updated coefficients to take account of the time since exposure. Studies of miners therefore provide a strong basis for evaluating risks from exposure to radon and for investigating the effects of modifiers to the dose-response relationship. Biological and cellular models of the multistage process of carcinogenesis are used to analyse the data from studies on miners. They offer the possibility of assessing the uncertainties in our understanding of the mechanisms for the development of cancer and in modelling the mechanisms for the purposes of risk estimation.

47. The extrapolation of radon concentrations in the air in mines to those in homes provides an indirect basis for assessing the risks from residential exposure to radon. However, there have now been over 20 analytical studies of residential radon and lung cancer. These studies typically assess the relative risk from exposure to radon on the basis of estimates of residential exposure over a period of 25 to 30 years prior to diagnosis of lung cancer. Recent pooled analyses of residential case control studies support a small but detectable lung cancer risk from residential exposure and this risk increases with increasing exposure. The excess relative risk from long-term residential exposure to radon at 100 Bq $m^{-3}$ is established with reasonably good precision and is considered to be about 0.16 (after correction for uncertainties in exposure assessment) with about a three-fold factor of uncertainty higher or lower than that value. Because of the synergistic interaction between the effects of radon exposure and those of inhalation of tobacco smoke, smokers account for nearly 90 per cent of the population-averaged risk from residential exposure to radon.

48. Although there are major uncertainties in extrapolating the risks of exposure to radon from the studies of miners to assessing risks in the home, there is remarkably good agreement between the risk factors derived from studies of miners and those derived from residential case control studies. The recent pooling of residential case control studies in Europe and North America now provides a direct method for estimating the risks from long-term residential exposure to radon. On the basis of current information, the Committee considers the use of measurement-adjusted risk coefficients from pooling studies to be an appropriate basis for estimating the risks to people at home due to exposure to radon.

# Appendix I

## MEMBERS OF NATIONAL DELEGATIONS ATTENDING THE FIFTIETH TO FIFTY-FOURTH SESSIONS OF THE UNITED NATIONS SCIENTIFIC COMMITTEE ON THE EFFECTS OF ATOMIC RADIATION

| | |
|---|---|
| ARGENTINA | A. J. González (Representative), D. Beninson (Representative), P. Gisone (Representative), M. del Rosario Pérez |
| AUSTRALIA | P. A. Burns (Representative), S. Solomon, P. Thomas |
| BELGIUM | J. R. Maisin (Representative), H. Bosmans, A. Debauche, H. Engels, J. Lembrechts, P. Smeesters, J. M. Van Dam, H. Vanmarcke, A. Wambersie, H. Bijwaard, R. O. Blaauboer, M. J. Brugmans |
| BRAZIL | D. R. Melo (Representative), J. L. Lipsztein (Representative), E. R. Rochedo |
| CANADA | N. E. Gentner (Representative), R. P. Bradley, K. Bundy, D. B. Chambers, R. M. Chatterjee (Representative), R. J. Cornett, R. Lane, C. Lavoie, S. Vlahovich (Representative), D. Whillans |
| CHINA | Pan Z. (Representative), He Q., Hou P., Jia J., Li K., Li J., Liu S., Liu Q., Pan S., Shang B., Shi J., Su X., Sun J., Sun Q., Xiu B., Xuan Y., Yang G., Yang H., Yang X., Yu J. |
| EGYPT | M.A.M. Gomaa (Representative), A. M. El-Naggar (Representative) |
| FRANCE | A. Flüry-Hérard (Representative), E. Ansoborlo, A. Aurengo, D. Averbeck, M. Bourguignon, J. F. Lacronique (Representative), J. Lallemand, J. J. Leguay, C. Luccioni, R. Maximilien, A. Rannou, M. Tirmarche |
| GERMANY | C. Streffer (Representative), P. Jacob, A. Kellerer, J. Kiefer, G. Kirchner, W. Köhnlein, W. U. Müller, W. Weiss (Representative) |
| INDIA | K. B. Sainis (Representative) |
| INDONESIA | Z. Alatas (Representative), K. Wiharto (Representative) |
| JAPAN | Y. Sasaki (Representative), T. Asano, M. Doi, A. Iwama, K. Kodama, H. Kuniyoshi, T. Maeyama, M. Nakano, Y. Nakayama, O. Niwa, M. Sasaki, K. Sato, H. Tatsuzaki, S. Yoshinaga, M. Yoshizawa |
| MEXICO | H. Maldonado (Representative) |
| PERU | L. V. Pinillos Ashton (Representative) |
| POLAND | Z. Jaworowski (Representative), L. Dobrzyński, M. Janiak, M. Waligórski |
| RUSSIAN FEDERATION | L. A. Ilyin (Representative), R. M. Alexakhin, N. P. Garnyk, A. K. Guskova (Representative), V. K. Ivanov, I. I. Kryshev, B. K. Lobach, O. A. Pavlovsky, T. S. Povetnikova, M. N. Savkin, V. A. Shevchenko |
| SLOVAKIA | E. Bedi (Representative), P. Gaál, V. Klener, L. Tomasek, D. Viktory (Representative) |
| SUDAN | K.E.H. Mohamed (Representative) |
| SWEDEN | L. E. Holm (Representative), L. Moberg |
| UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND | R. Cox (Representative), S. Bouffler, R. H. Clarke (Representative), G. M. Kendall, T. McMillan, C. Muirhead, P. Shrimpton, J. W. Stather |
| UNITED STATES OF AMERICA | F. A. Mettler Jr. (Representative), L. R. Anspaugh, B. G. Bennett, J. D. Boice Jr., N. H. Harley, E. V. Holahan Jr., C. B. Meinhold, R. J. Preston, H. Royal, P. B. Selby, A. G. Sowder |

### SECRETARIAT OF THE UNSCEAR

N. E. Gentner
M. J. Crick

# Appendix II

## SCIENTIFIC STAFF AND CONSULTANTS COOPERATING WITH THE UNITED NATIONS SCIENTIFIC COMMITTEE ON THE EFFECTS OF ATOMIC RADIATION IN THE PREPARATION OF THE 2006 REPORT

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**Corrigendum**

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Vienna

# Effects of Ionizing Radiation: United Nations Scientific Committee on the Effects of Atomic Radiation 2006 Report

## Volume 1

### Corrigendum

#### Annex A

**1. Paragraph 541, line 9**

For the existing model *substitute*

$$EAR(a,y,s,D,e) = h(a,y,s,D,e) - h(a,y,s,0,e) \qquad (7)$$

**2. Paragraph 549, line 8**

For the existing model *substitute*

$$h_0(a,e,c,s)\cdot\left[1+(\alpha\cdot D+\beta\cdot D^2)\cdot\exp[\kappa_1\cdot 1_{s=female}+\kappa_2\cdot\ln[a-e]+\kappa_3\cdot\ln[a]]\right] \qquad (14)$$

# ANNEX A

## Epidemiological studies of radiation and cancer

## Contents

# INTRODUCTION

1. Epidemiological studies of cancer risks associated with internal and external exposure to ionizing radiation were reviewed extensively in the UNSCEAR 1994 and 2000 Reports [U4, U2]. The UNSCEAR 2000 Report assessed data on cancer incidence and mortality up to 1990 among the Life Span Study (LSS) cohort of survivors of the atomic bombings in Japan [P1, P4, T1], as well as many studies relating to other persons exposed occupationally, therapeutically or diagnostically.

2. The UNSCEAR 2000 Report presented cancer risk estimates based on the LSS data and using the set of survivor dose estimates produced in the mid-1980s, the "DS86 dosimetry" [R20]. For some time it was thought that the DS86 neutron doses for the survivors of the Hiroshima bombing were systematically underestimated, particularly for survivors beyond 1,000 m from the hypocentre [R20, S39]. This perception was largely based on the results of measurements of thermal neutron activation products in samples taken from the city [S39]. The DS86 estimates for the gamma doses at both Hiroshima and Nagasaki, as well as the estimates for the neutron doses at Nagasaki [S40], were thought to be more reliable than the estimates for the neutron doses at Hiroshima [R20]. Recent analysis of all the information, including that on fast-neutron activation products, suggests that there are no appreciable systematic errors in the DS86 neutron dose estimates for Hiroshima [C13, R12, S41]. The latest set of dose estimates for the survivors of the atomic bombings, the "DS02 dosimetry", differs slightly from the DS86 system, for both neutron and gamma doses. The difference is generally no more than 20% for distances of up to 1,500 m from the two hypocentres, where the doses were greatest [C13, R12]. The DS02 estimates of colon doses due to neutrons were lower for both cities but by no more than about 20% compared with the DS86 estimates. The DS02 estimates were progressively lower relative to the DS86 estimates with increasing distance from the hypocentre; this was particularly marked for Nagasaki [P10]. For Hiroshima survivors, the DS02 estimates for colon dose due to gamma radiation were lower by about 10% compared with the DS86 estimates at all distances; for Nagasaki survivors, the estimates for colon dose within 1,800 m from the hypocentre were about 10% higher, but were somewhat less than 10% higher for greater distances [P10]. Analyses of the LSS epidemiological data using the DS02 dosimetry indicate that cancer risk factors might be lower by about 8% as a result, but with no appreciable change in the shape of the dose response or in the patterns of excess risk with age or time [P10].

3. Although resolving inconsistencies in the dosimetry for the survivors of the atomic bombings has reduced one source of uncertainty in estimating cancer risks to a population from low doses of radiation, a considerable number of other sources of uncertainty remain. A major one relates to extrapolating risks from the moderate-dose but high-dose-rate exposures received by survivors of the atomic bombings to low doses and dose rates. This is also true for interpreting data on many therapeutically exposed groups. The topic has long been controversial, and was discussed in annex G, "Biological effects at low radiation doses", of the UNSCEAR 2000 Report [U2]. There is also uncertainty related to extrapolating cancer risk to the end of lifetime. In particular, about half of the LSS cohort is at present still alive [P10]. In estimating lifetime risk factors from the data on this cohort, it is vital to determine the pattern between radiation dose and expression of cancer risk for those who were exposed in childhood and who are now reaching the age at which larger numbers of cancers would be expected to arise spontaneously. Another source of uncertainty relates to the transfer of radiation-induced cancer risk estimates between populations with different underlying rates of cancer. For example, the rates of lung and breast cancer for the Japanese population tend to be lower than for many North American and Western European populations, whereas rates of stomach cancer tend to be much higher [P19]. The available evidence, most recently reviewed in the UNSCEAR 1994 Report [U4], did not suggest that there is an easy resolution of this problem.

4. This annex presents the Committee's reassessment of the LSS data for the estimation of the risks of cancer and cancer mortality due to radiation exposure, wherever possible making use of the latest DS02 dosimetry and follow-up. This annex also contains assessments of all the evidence from studies of groups exposed therapeutically, diagnostically or occupationally. The Committee has made assessments of the risks for cancer in a variety of organs, including the salivary gland, oesophagus, stomach, small intestine (including duodenum), colon, rectum, liver, pancreas, lung, bone and connective tissue, female breast, uterus, ovary, prostate, urinary bladder, kidney, brain and central nervous system, and thyroid, and for cutaneous melanoma, non-melanoma skin cancer, non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma and leukaemia. This somewhat extends the list of organ sites from those considered in the UNSCEAR 2000 Report [U2]. The Committee has attempted to consider separately the uncertainties associated with estimation of cancer risks arising from the sources listed above. As for the UNSCEAR 2000 Report, the Committee has assessed separately the risks

arising from internal and external exposure, and from low- and high-linear-energy-transfer (LET) radiation. It has made estimates of the population-averaged risks of cancer and cancer mortality for a variety of current populations. These estimates have been made using risk models fitted to the latest mortality and cancer incidence data from the follow-up of the survivors of the atomic bombings [P10, P48]; both sets of data use the latest DS02 dosimetry. The term incidence has two uses in this annex: in a general sense, often to contrast cancer incidence with cancer mortality, and in a specific sense, where the incidence of a disease is the number of cases of the disease that occur during a specified period of time (usually a year). The incidence rate is this number divided by a specified unit of population.

# I. FEATURES OF EPIDEMIOLOGICAL STUDIES

## A. Criteria for good-quality epidemiological studies

5. Epidemiology is the study of the distribution and determinants of disease in human populations [M26]. It is by its nature observational rather than experimental. In contrast to randomized controlled trials (which are largely experimental in design), in epidemiological studies there is always the possibility that biases or confounding factors of various sorts may give rise to spurious results, as discussed in more detail below. A well-designed study should attempt to minimize these. A good investigator will design a study to have adequate statistical power, and this is discussed in greater detail in section I.B below. Epidemiological studies are commonly of two types: the cohort study and the case-control study. In a "cohort study", a defined population (preferably with a wide range of radiation exposures) is followed forward in time to examine the occurrence of many possible health end points. Such a study can be performed either prospectively, by following a current cohort into the future, or retrospectively, by using registers to construct a cohort of persons alive at some time in the past, and then following it forward, possibly to the current time and beyond. The LSS of the survivors of the atomic bombings in Japan is an example of a cohort study, partly retrospective and partly prospective in nature. The LSS data were assembled in the late 1950s using questions posed in the Japanese national census of October 1950 to ascertain those persons who were in either Hiroshima or Nagasaki at the time of the atomic bombings. This cohort and other related cohorts were then followed forward in time, and are still being followed up, for mortality due to all causes [P1, P9, P10], cancer incidence [P4, P48, T1] and various other end points [O3, O4, W17, Y3]. A "correlation study" is a particular type of cohort study that is based on data averaged over groups, and in particular uses data grouped on exposure. In a "randomized controlled trial (RCT)", people are assigned at random to various groups before planned exposure to radiation (e.g. radiotherapy treatment [F10]), and these groups are then followed up to assess their response to the treatment over some defined period. An RCT may be regarded as a special form of cohort study; however, its essentially experimental design, as opposed to the more observational design of most cohort studies, should be noted. In a "case-control study", data on persons with some specified disease (e.g. some class of cancers) are assembled (the "cases") together with data on a suitably matched (e.g. by age and sex) set of persons otherwise similar to these cases but without the disease (the "controls"). These two groups are then compared to assess differences in the distribution of a number of exposure variables. The advantage of a case-control study is that detailed histories of radiation exposure and other information (e.g. history of smoking), which may be difficult to collect for a cohort, can be collected relatively easily for the specific cases and controls. The International Radiation Study of Cervical Cancer Patients (IRSCCP) is an example of a series of nested case-control studies of the occurrence of a second primary cancer in a cohort of women followed after treatment for a first primary cancer of the cervix [B5, B7, B8]. Another form of study, not so frequently used, is the "case-cohort" or "case-base" study [P13], in which information is collected on all cases with a certain disease status (e.g. cancer) as well as on a sample of persons from the underlying cohort, sampled without regard to their disease status. This type of study is particularly useful when one is interested in a number of different end points, because one can reuse the cohort sample for each disease end point under consideration. This study design was used in an early analysis of the IRSCCP [H31]. Other, more novel designs, which generalize the above, have recently been proposed [L38]. An RCT, if the randomization is conducted properly, should not be subject to any bias, and is generally regarded as the epidemiological "gold standard". The case-control study is prone to more biases (e.g. recall bias and investigation bias—see below) than the cohort study, and for this reason cohort studies are regarded as the next most reliable type of study after the RCT.

6. "Bias" in a study may be defined as any process at any stage in the conduct of the study that tends to produce results or conclusions that differ systematically from the truth [S34]. One sort of bias is "follow-up bias", which arises when there is a lack of follow-up information, for example if persons have, unknown to the investigator, migrated outside of the study area, so that their health status cannot be reported. In this instance, they still apparently contribute to the number of person-years (PY) of follow-up in the study, but in reality there is no chance of observing any detrimental effect to their health, making them appear "effectively immortal". Unless corrected for, by censoring members of the study cohort (i.e. stopping their contribution to the total number of person-years) when they are lost to follow-up, estimates of disease risks will generally be biased downwards and therefore be underestimates of the true risk. This form of bias applies equally to cohort studies and case-control studies. It is sometimes supposed that case-control studies are immune to this bias, but this is not so; case and control selection will be biased if certain members of the full cohort are not available to be selected. Related to follow-up bias is "ascertainment bias", also sometimes known as "selection bias", which arises when there is variation in ascertainment of disease status, perhaps correlated with exposure variables. For this

reason, much the strongest studies are those that rely on independently maintained registers of disease and health status, e.g. the mortality and cancer incidence registers maintained in many developed countries. As an example, certain tumours, such as those of the thyroid, are notoriously difficult to detect, so that the recorded incidence of thyroid cancer in a cohort will very much depend on the diligence with which clinical examinations have been conducted in the underlying cohort. In the LSS cohort of the survivors of the atomic bombings, the detection of thyroid tumours is better in the higher-dose groups, because many people in these groups are subject to biennial screening [T1], as they are also members of the Adult Health Study (AHS), a subcohort of the LSS. Unless corrected for, this ascertainment bias, which is correlated with dose, would bias the slope of the dose–response curve upwards; however, in this case the ascertainment bias can be corrected for by stratification of the cohort according to membership in the AHS, and conducting a suitably adjusted analysis [T1]. Another example of such bias occurred in a study of workers involved in the recovery from the Chernobyl accident, for whom a statistically significant increase in the incidence rate of leukaemia was reported compared with the incidence rate for the general population [I5]. However, the workers received frequent medical examinations, so that the accuracy and completeness of their leukaemia diagnoses are likely to differ from those for the general population. Indications that ascertainment biases may have produced this result come from a case-control study nested within the Chernobyl recovery operation worker cohort, which found no evidence of an increase in the incidence of leukaemia [I6]. Again, it should be pointed out that ascertainment bias applies equally to both cohort and case-control studies. In the context of case-control studies, ascertainment bias can arise if the selection of cases or controls is influenced by exposure status. In such studies it is therefore important that there be comparable ascertainment for cases and controls, and in particular that ascertainment be as complete as possible for both groups. For example, when it is necessary to approach potential study subjects, or their relatives, for interviews, it is important that the refusal rate for both cases and controls be as low as possible.

7. It is sometimes necessary to approach cohort members, or their relatives, to recall exposures. This is very likely to be the situation when studies, in particular case-control studies, are organized retrospectively. "Recall bias" arises when information, for example on exposure, is collected retrospectively, and patients, or their relatives, are subject to differential recall of this information, depending on their disease status. For this reason, much the strongest studies are those that rely on independently maintained registers of exposure, for example the registers of radiation dose that are maintained for regulatory purposes for many cohorts of nuclear workers [M12]. Related to recall bias is "investigation bias", which results if investigators scrutinize exposures more thoroughly for cases than for controls. Although register-based studies are not prone to recall or investigation bias, they are subject to errors due, for example, to inaccurate diagnostic information. To the extent that such studies should not be biased by knowledge of radiation exposures, one would expect that random misclassification due to inaccurate diagnosis would not affect values of the ratio of the excess disease rate to the underlying disease rate in the absence of radiation exposure, that is to say the excess relative risk (ERR), although values of the excess disease rate itself, or excess absolute risk (EAR), might be biased, either positively or negatively.

8. A "confounding factor" is one that is correlated both with the disease under study and with an exposure of interest. Confounding factors can lead to bias. In many studies there is no reason to expect correlations between most factors and the radiation exposure, so that confounding ought not to be a problem. In studies of medical exposures, confounding may arise if the clinical indications that lead to the exposures are related to a subsequent diagnosis of the relevant disease; 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 observed [H14]. However, this risk was not related to dose and was concentrated among patients referred because of a suspected thyroid cancer [H14], indicating that the apparent elevated risk was probably due to the underlying condition. There are known to be correlations between smoking rate and the DS86 radiation dose among female survivors of the atomic bombing of Hiroshima, although there are no such correlations for the male survivors in this city, or for either males or females in Nagasaki [P14]. This may be connected with the (statistically non-significant) indications that the radiation-associated excess relative risk (ERR) of lung cancer increases with increasing age at exposure and attained age in this data set [L39], findings at odds with the customary reduction of ERR with increasing values of these variables [U2, U4]. Cigarette smoking is one of the most serious confounding factors that have to be dealt with in epidemiological studies. As shown in table 1 (reproduced from reference [P17]), the ratio of the disease rate to the underlying disease rate in the absence of the relevant exposure (in this case to cigarette smoke), i.e. the relative risk (RR), of lung cancer associated with cigarette smoking (which for moderate to heavy smokers generally exceeds 10 [P8, P17]) is much greater than the RR associated with exposure to high doses of radiation (which rarely exceeds 2). Therefore even slight confounding by factors related to cigarette smoking can seriously bias studies of lung cancer or other smoking-related cancers. Confounding factors can usually be dealt with at the analysis stage, either by incorporation of such factors into the regression model, or by stratifying the data according to levels of the confounding factor.

9. RCTs, cohort and case-control studies all use individual-related data, in particular data on individual exposures. By contrast, correlation studies are based on data averaged over groups, as noted above. A particular form of this type of study is the "geographical correlation study" (often referred to as an "ecological study"), in which disease rates based on data aggregated over

geographical areas are compared with aggregated data on levels of exposure, for example to natural radiation or to man-made increases in environmental radiation levels. The possibilities for bias in such studies are well known. The principal cause of bias (sometimes termed "ecological bias") is the failure to take account of correlations within each area between multiple risk factors (e.g. radiation and smoking) [G13, P15]. Examples of such studies include ones of leukaemia [H32] and lung cancer [C14] in relation to environmental radon daughter exposure. The possibilities for bias in such studies are illustrated by a study of lung cancer in relation to environmental radon daughter exposure in Sweden, which when analysed as a case-control study yielded a positive slope for lung cancer risk versus radon daughter concentration, but when analysed as a correlation study, with grouped exposure estimates, yielded a negative slope [L40].

### B. Impact of dose level on statistical power and sample size

10. The concept of statistical power and various factors that affect it were summarized in the UNSCEAR 2000 Report [U2] and have also been addressed in a recent report [B26]. However, a few points merit further elaboration and illustration, especially in relation to the dose levels in a study. Under an assumption of a linear association between radiation dose and the probability of cancer induction, the sample size required to detect a radiation effect with adequate statistical power (e.g. 80% power) is approximately proportional to the inverse of the dose squared, or approximately proportional to the inverse square of the ERR coefficient (see appendix A). For example, if the dose distribution is that among the survivors of the atomic bombings (table A1) and the anticipated ERR is 4.0 $Sv^{-1}$ (similar to that observed for leukaemia mortality from the latest follow-up of the LSS data [P10]), about 34 cancer deaths would be needed in order for the probability of observing a statistically significant (1-sided p = 0.05) excess risk to be at least 80% (figure I). However, if the ERR is assumed to be 0.4 $Sv^{-1}$ (similar to that observed for solid cancer mortality from the latest follow-up of the LSS data [P10]), 765 cancer deaths would be needed for the excess to be observed with the same probability (figure I). If the ERR is assumed to be 0.04 $Sv^{-1}$, about 50,000 cancer deaths would be needed for the excess to be observed with the same probability. Further calculations along these lines are given in reference [B26]. If the dose–response relationship were instead linear–quadratic with an upward curvature, then the number of cancer deaths or cases needed to detect radiation effects for the aforementioned low-dose studies would be even larger.

**Figure I. Influence of the ERR on the number of cancer deaths or cases required by a study to detect an increasing trend of risk with dose**

The curves are for 80% power of detecting a statistically significant (1-sided $p = 0.05$) increasing trend of risk with dose. The assumed distributions for colon and bone marrow doses are as in the latest LSS data (see table A1 in appendix A)

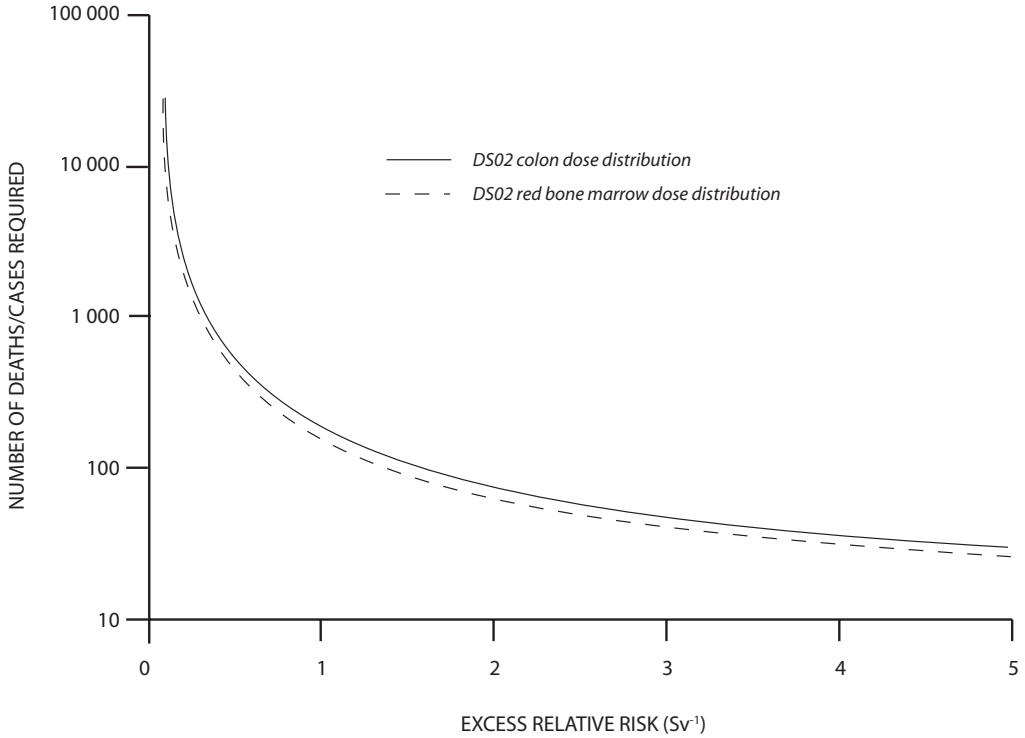
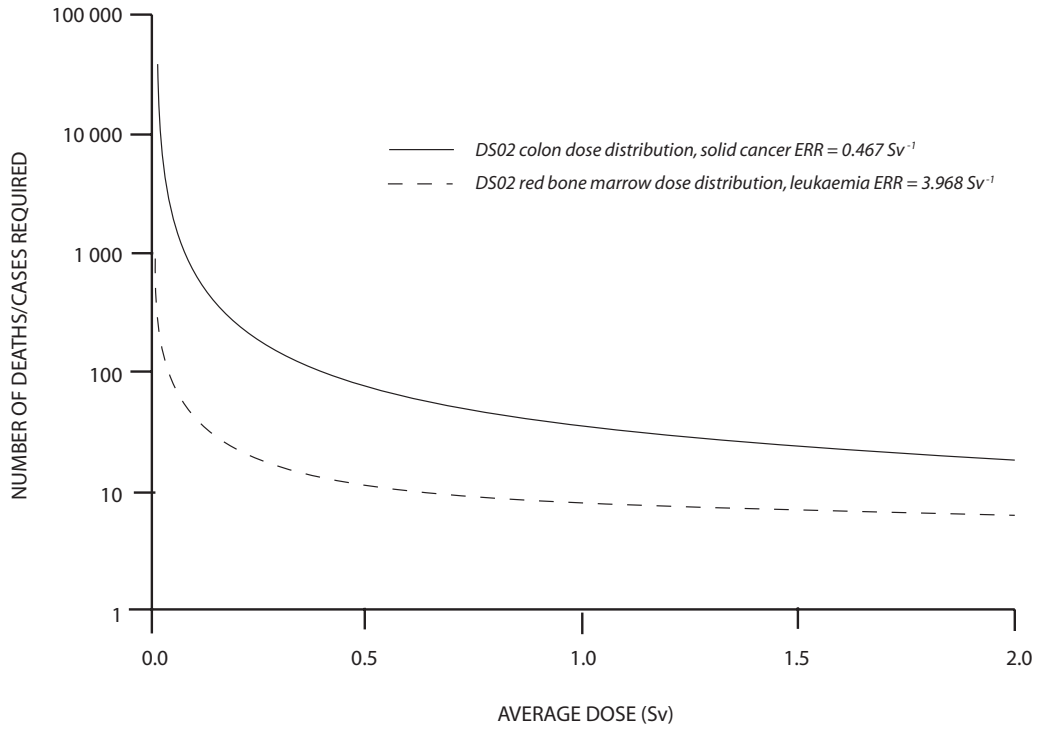


**Figure II. Influence of the average dose on the number of cancer deaths or cases required by a study to detect an increasing trend of risk with dose**

The curves are for 80% power of detecting a statistically significant (1-sided $p = 0.05$) increasing trend of risk with dose. The assumed distributions for colon and bone marrow doses are some multiple of those in the latest LSS data (see table A1 in appendix A)




11. A corollary of the large sample sizes needed at low doses is that, for a given sample size, the statistical power of a study is affected dramatically by the dose levels of the exposed group. In this regard, most low-dose studies reported in the literature have inadequate statistical power. Figure II shows the influence of the average dose in a study on the number of cancer deaths or cases needed to detect an excess risk. For example, at an average dose of 0.1 Sv (about that of the LSS, for both colon and bone marrow dose), and assuming an ERR for solid cancers of 0.467 $Sv^{-1}$, and for leukaemias of 3.968 $Sv^{-1}$ (as observed from the LSS data [P10]), about 700 solid cancer deaths or cases would be needed to have an 80% power of observing a significant excess (figure II), whereas only 43 leukaemia deaths would be needed for this purpose. If the average dose is 1.0 Sv, only 37 solid cancers and 9 leukaemias would be needed (figure II). If on the other hand the average dose is only 0.01 Sv, then the numbers needed increase to about 45,700 solid cancers and 910 leukaemias (figure II).

12. The duration of follow-up is often the crucial determinant of how many cases will be observed in a cohort, and therefore of the statistical power. Cancer rates generally increase substantially with age [D44]. This means that in many cohorts the cancer deaths and cases are concentrated in the final years of follow-up. For example, in the LSS, about 25% of all solid cancer deaths have occurred in the last 10 years of follow-up (1991–2000) [P10]. Figure III illustrates how the statistical power to detect a positive trend with dose varies with the duration of follow-up. It is assumed that the cohort accumulates cancers over time in accordance with the distribution observed for solid cancers in the LSS [P10]. Four different values for the total numbers of cancers within 50 years after exposure (500, 1,000, 1,500 and 2,000) are considered. The figure demonstrates that even if a total of 2,000 cancers were to arise within 50 years after exposure, a statistical power of 80% or more is achieved only after about 20–25 years of follow-up.

13. Another factor that may complicate statistical power is possible heterogeneity of risk expression within the cohort. However, as can be seen from figure IV, in practice this may not greatly affect calculations of statistical power, even when the ERR varies by nearly 20-fold within the cohort. Statistical power is slightly lower in the group with heterogeneous ERR (comprised of three equal subgroups of cases arising from ERR = 0.1 $Sv^{-1}$, 1.0 $Sv^{-1}$ and 1.9 $Sv^{-1}$) compared with a group with homogeneous ERR (= 1.0 $Sv^{-1}$). However, the difference is no more than a few per cent.

14. To the degree that a given sample of exposed people has variation in individual dose levels, there can be a modest improvement in the statistical power when a dose–response analysis is performed, providing the estimated individual doses are reasonably accurate and there is some spread among them [S6]. However, the mean dose is still an important limiting factor in determining the degree of statistical power achievable.

**Figure III. Influence of the duration of follow-up on the power of a study to detect an increasing trend of risk with dose**
The curves are for various numbers of total deaths after 50 years. The power illustrated is to detect a statistically significant (1-sided $p = 0.05$) increasing trend of risk with dose. The assumed distributions for colon dose are as in the latest LSS data (see table A1 in appendix A), assuming ERR = 0.467 $Sv^{-1}$ (as observed for solid cancers in reference [P10])

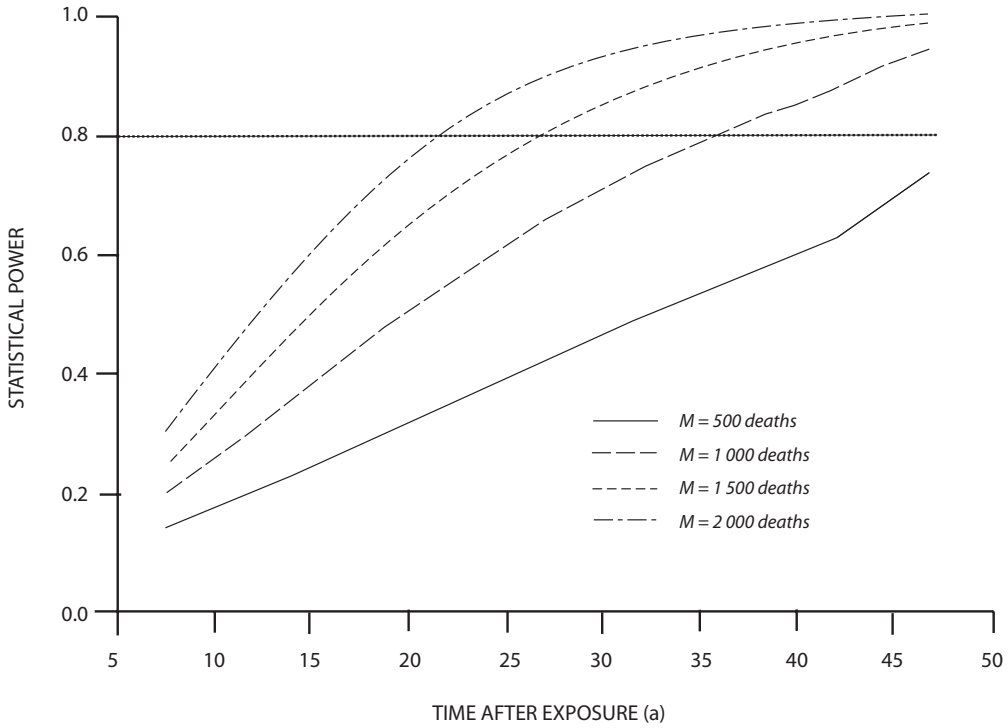
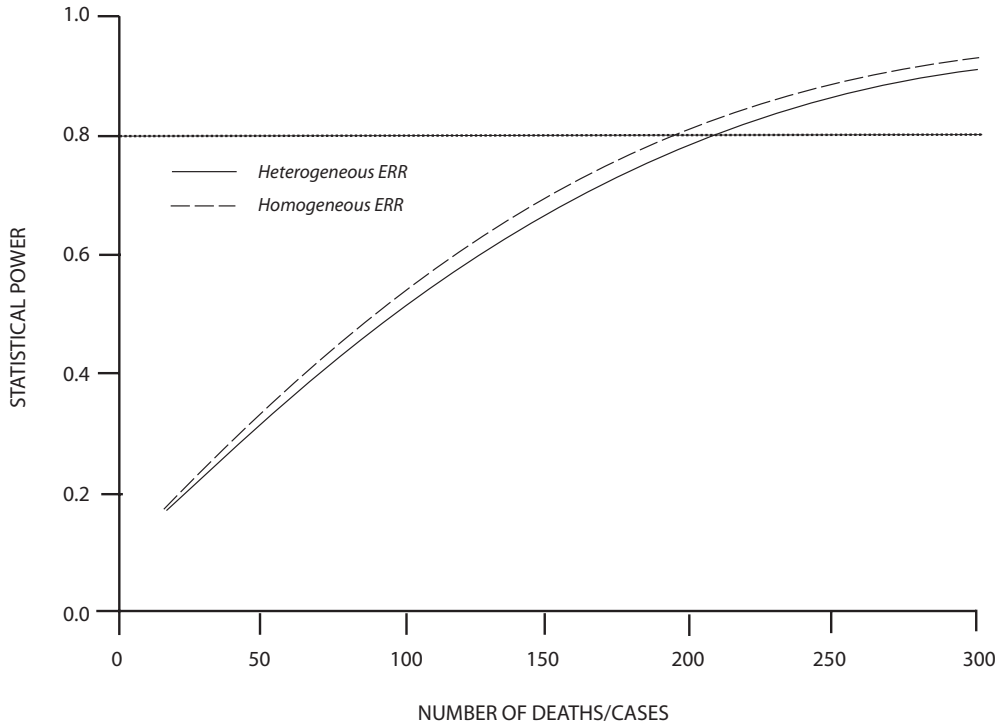



**Figure IV. Influence of the heterogeneity of ERR in a cohort on the power of a study to detect an increasing trend of risk with dose**
Two curves are presented: one for a cohort with assumed homogeneous ERR (1.0 $Sv^{-1}$) and one for a cohort with assumed heterogeneous ERR (three equal strata with ERR = 0.1 $Sv^{-1}$, 1.0 $Sv^{-1}$ and 1.9 $Sv^{-1}$). The power illustrated is to detect a statistically significant (1-sided $p = 0.05$) increasing trend of risk with dose. The assumed distributions for colon doses are as in the latest LSS data [P10] (see table A1 in appendix A)



15. When the dose levels are low, two other phenomena affect the study results. The first occurs because epidemiological studies are based on natural human populations with their extraneous variability in genetic make-up, diet, lifestyle and other exposures, rather than having tightly controlled experimental conditions. This means there may be subtle differences between exposed and unexposed groups in some unmeasured factors that affect cancer risk. For a high-dose study with a large expected radiation effect, such variations are fairly inconsequential, but for a low-dose study with a small expected radiation effect, the magnitude of such extraneous variations may equal or surpass the size of the expected radiation effect. Hence for a low-dose study there is great potential for a false negative or false positive result, with little way of even knowing whether such an effect has occurred; this reduces the credibility of the results. Assessment of the pattern of results in low-dose studies may sometimes provide indications of artefactual findings. For example, on the basis of an analysis of results for non-malignant respiratory diseases related to smoking, which exhibited negative trends with radiation dose, Muirhead et al. [M12] suggested that smoking may confound the radiation dose–response relationship for some smoking-related cancers, e.g. lung cancer.

16. Secondly, for a low-dose study with small numbers of cases or deaths expected and therefore with inadequate statistical power, if any result for RR is found to be "statistically significant", its magnitude is in all likelihood a substantial overestimate of the "true" risk. For instance, Land [L3] showed that if women received a 10 mGy dose to both breasts at age 35 and were followed up for 20 years thereafter, the prediction from high-dose studies may be that about 60 excess breast cancers per million exposed women could be expected between years 10 and 20 of follow-up, compared with 19,100 spontaneous breast cancers during that same period. If the study were on a cohort of a million such women, the statistical power would still be only a little above 5%. (Adequate statistical power is usually taken as at least 80%.) If such a study were to be repeated numerous times, for the occasions when there was a nominal "statistically significant" excess, the RR estimates would be about nine times greater on average than the "true" relative risk. However, in a single given study, the authors will usually derive the best estimate of the "true" risk from their own central estimate, which is likely to be a substantial overestimate.

### C. Impact of dose levels on the precision of risk estimates

17. The precision of a risk estimate is normally defined by the width of the confidence interval (CI) around the central estimate of the risk. Risk estimates with narrow confidence intervals are more informative than those with wide confidence intervals. Technically, a 95% confidence interval implies that there is a 95% chance that the confidence interval includes the "true" value of the parameter (e.g. a relative risk) under investigation. One can also think of the confidence interval as indicating the possible values the 'true' risk may have that are consistent with the observed data.

18. The width of the confidence interval for the observed RR is largely dependent on the number of cancers observed in that study, and the width of this confidence interval would be approximately equal (on a logarithmic scale) for a low-dose and a high-dose study if the two studies involved equal numbers of observed cancers. However, the kinds of risk estimate useful for radiation risk assessment are typically expressed per unit dose (with units of, for example, $Gy^{-1}$), and the RR estimate and its confidence interval are explicitly divided by the mean dose for the exposed group (or else a similar division by dose occurs implicitly in dose–response analyses that directly estimate the ERR per unit dose). As an example, suppose the underlying ERR at 1 Gy for some cancer of interest was 1.0 (i.e. the RR at 1 Gy was 2.0), and a study was performed of people incurring a 1 Gy dose and an unexposed group with an equal number of persons and length of follow-up. Suppose that 800 cancers of this type were found in total, distributed between the exposed and the unexposed group (see scenario E in table 2). A calculation of the estimated ERR would yield 1.00 $Gy^{-1}$ with a 95% likelihood-based confidence interval of (0.73, 1.32) $Gy^{-1}$. This is a fairly narrow confidence interval that would be useful information to help define risk estimates. Suppose, however, that the same group of people had received only 0.05 Gy instead. Scenario J in table 2 shows the expected result. The ERR per unit dose is similar (1.03 $Gy^{-1}$), but now the confidence interval is very wide: (–1.70, 4.16) $Gy^{-1}$. In fact, to achieve confidence intervals for ERR per unit dose as narrow as that shown in scenario E with a dose of 0.05 Gy would require a study large enough to have over 70,000 cancers of the type of interest. As with any study in which such small RRs are being assessed, the influence of any uncontrolled confounding factors would be appreciable. If now one assumes that a dose of 1 Gy is given to the exposed groups, but that this represents only 10% of the total cohort in terms of numbers of persons and length of follow-up (scenario O), then the estimated ERR is much the same (0.99 $Gy^{-1}$), with an only slightly wider confidence interval for the ERR (0.66, 1.38) $Gy^{-1}$ than in the base case. This shows that the loss of statistical power occasioned by an uneven distribution of dose within a cohort need not be very marked.

19. The conclusion from this discussion is that exceptionally large studies are required to provide bounds on the risk estimate at low doses that will be informative and useful. In addition, the probable influence of confounding factors becomes increasingly important at low doses. For example, heavy cigarette smoking is associated with a risk of lung cancer that is more than 20 times higher than that for never smoking [P8]. Therefore even a slight imprecision in knowledge of smoking habits could easily produce artificial elevations (or mask true elevations) in estimates

of the lung cancer risk anticipated from very low doses of radiation. These are important considerations to bear in mind when proposing or evaluating low-dose studies.

### D. Impact of dose measurement error and other uncertainties on study associations

20. In recent years there has been much development of methods for evaluating the impact of uncertainties in individual dose estimates upon the associations between dose and cancer risk [C12, F9]. A primary distinction is between random errors and systematic ones. Systematic errors in dose measurement could result, for example, from incorrect calibration of a dosimetry badge reader or from incorrect assumptions or coefficients in an algorithm to reconstruct doses. Such errors would be specific to a particular case and might bias the dose–response association in a positive or negative direction, depending on the particular error. Systematic and random errors are either differential, when they are statistically dependent on the disease end point being considered, or non-differential, when the errors are statistically independent of the disease. More precisely, if the "true" (unobserved) dose is $D$, the "nominal" or measured dose is $d$ and outcome for the disease end points measured by the binary variable $Y$, then the measurement errors are non-differential if $P[d \mid D,Y = P[d \mid D,Y = 1]$, or equivalently if $P[Y \mid d,D] = P[Y \mid D]$; otherwise they are differential. Differential measurement errors can arise, for example, if a pathologist codes a death certificate being aware of the subject's exposure history. These errors can introduce serious and unpredictable bias into the analysis of a study [T17]. Fortunately such errors can usually be eliminated by careful study design, for example by a blind assessment of the study variables.

21. However, even when the errors are non-differential, random measurement error affects virtually all quantitative radiation epidemiological studies to one degree or another, and can introduce bias. Two types of measurement error model have been customarily assumed, classical and Berksonian. Classical measurement error arises when the "nominal" (assigned) dose, $d$, is assumed to vary around the "true" (usually unknown) dose, $D$. For example, in the data for the survivors of the atomic bombings in Japan, the errors are assumed to be of classical form [J3]. This is because the "nominal" dose, derived as a result of survivors' recall, a few years after the event, of where they were and their orientation with respect to the bomb detonation, will contain errors, probably random and non-differential. There are other (random, non-differential) errors associated with shielding uncertainties, and with the radiation energy spectrum and magnitude of the source term, which result in the logarithm of the "nominal" dose, $1n[d]$, being distributed approximately normally around the logarithm of the "true" dose, $1n[D]$ [J3, R20]. Berkson error, on the other hand, arises when classification of individuals into groups results in the distribution of individual "true" doses, $D$, around the "nominal" mean dose, $d$. A Berkson error structure is often assumed for occupational studies, because the classification of individuals into groups results in the distribution of individual "true" doses around a "nominal" film badge mean dose [T17]. There may be a variety of sources and types of random measurement error in a given study. When the dose measurement error in a study is Berksonian, and a linear model is fitted, failing to account for it means the variance of the slope of a linear dose–response regression line will be underestimated but the slope itself will be unaffected (i.e. the risk estimate will be unbiased). However, this may not be the case for non-linear models [T17]. When classical measurement error occurs, failure to take it into account generally means that not only will the variance of the slope be underestimated but the slope estimate itself will also be biased towards the null (i.e. closer to zero than it should be). The direction of the slope, however, would not be expected to change [A1]. Error models combining classical and Berkson error have been developed [R19].

22. Classical measurement error generally reduces the statistical power of a study because it increases the variance of the risk estimate while simultaneously biasing the estimate itself towards the null [M7]. This can be understood intuitively: random measurement error will tend to blur the dose differences among people. This reduces the correlation with the "true" doses (where ideally the correlation should be 1.0) and thereby tends to reduce any correlation between the nominal doses and a disease outcome.

23. There are typically other uncertainties in evaluating the association between radiation exposure and cancer risk. To name a few, there may be uncertainties associated with the completeness of cancer case or mortality ascertainment, uncertainties in the accuracy of diagnoses, uncertainties associated with instrument error in making radiation measurements, uncertainties in the degree to which a radiation film badge measurement estimates dose to some organ, uncertainties in estimating various parameters in performing a dose reconstruction, uncertainties in the "transfer" of risk estimates from one population to another, uncertainties in behavioural factors that affect exposure to radioactive deposits after an accident or residential radon exposure, and uncertainties in the uptake and metabolism of specific radionuclides. In theory, a complete model to correct for uncertainties would need to take into account all the applicable sources of uncertainty in a given study. However, frequently only limited information is available on the magnitude of these uncertainties, so the researcher has to use whatever information is available to make judgements about the distributions of the relevant uncertainties. This requires that the researcher make use of information available in the literature. Ideally it would require cooperation between experts from a variety of disciplines, for example between statisticians, epidemiologists and dosimetrists, in order to correctly identify the forms and magnitudes of the uncertainty distributions. Statistical estimates of the composite "credibility interval" that take into account the various measured and judged uncertainties can then be made.

There can be serious systematic error (or bias) in studies that can produce spurious or misleading results and that may be difficult or impossible to properly account for in analyses. For example, if persons who developed thyroid cancer years after exposure to fallout had better recall of past events and habits, such as of their milk consumption at the time, than similar persons who are disease-free, or if persons living in high-dose areas were screened for thyroid cancer but persons living in low-dose areas were not, this can lead to serious bias.

24. Methods to deal with the complexities of measurement error corrections are still evolving. Estimating the combination of various sources of measurement error and their magnitude with respect to individual dose estimates often requires sophisticated Monte Carlo simulations [H4]. Nevertheless, the new generation of epidemiological studies has begun to provide estimates of radiation risk corrected for dose uncertainties (e.g. [G1, L1, L93, P2, S1]), and corrections for other uncertainties are beginning to be made. A method of wide applicability is first-order regression calibration, in which one substitutes for the "true" dose, $D$, in fitted models the expectation of the "true" dose given the "nominal" (measured) one, $E[D] \mid [d]$ [C12]. As emphasized by Carroll et al. [C12], this is an approximate method in non-linear dose–effect relationships. It leads to reasonable adjusted point estimates of the model parameters but does not fully take account of all the variability induced by the measurement errors. Within many contexts, for example that of the LSS data, the extra variability not taken into account is relatively small [P2, P16]. It is well known that when dosimetric errors are not too large, the first-order regression calibration parameter estimates are a good approximation to the full likelihood-based estimates [C12, K26, R21]. A Bayesian approach to the measurement error problem has recently been developed [R22, R23, R24] that rests on the formulation of conditional independence relationships between different model components, following the general structure outlined by Clayton [C15]. In this approach, three basic submodels are distinguished and linked: the disease model, the measurement model and the exposure model. The power of this Bayesian approach is that the dosimetric uncertainty is reflected in the variability of the model parameters. An adapted Bayesian method of correction for measurement error, the two-stage Bayesian method, has already been applied to the fitting of generalized relative and absolute risk models to the LSS data on cancer mortality and incidence; estimates of population cancer risk and associated uncertainties have been derived from the posterior distribution of the risk parameters [B18, L17]. The Committee outlines in Appendix E how this method has been used to fit models to the latest LSS cancer mortality data [P10], and thereby to evaluate uncertainties in population cancer risks.

25. Dosimetric uncertainty analyses do not correct for methodological biases that distort observations and produce spurious results. Statistical methods to deal with multiple sources of bias, such as those arising from methodological issues, have recently been developed [G11, G14]. However, these are still controversial, as they tend to produce very large uncertainties in risks, are not perhaps completely transparent, and avoid reliance on a full probability model by using a series of more or less ad hoc "adjustments" (see the remarks of Copas, Spiegelhalter and de Stavola in reference [G11]).

26. Another type of dose measurement error that may have an impact on studies involving occupational exposure to radiation, but that has received limited attention, occurs in the assigning of a value for a dose when the dosimeter reading is below the limit of detection. Designating such doses as zero will tend to overestimate the risk per unit dose and distort the dose–response relationship. Statistical methods to assign values for such doses in an unbiased manner have recently been proposed [M9, X1].

27. Very few studies attempt to take account of natural background exposure simultaneously with the effect of the other radiation exposures being considered. Low-LET natural background radiation might be expected to contribute a dose of about 70–80 mSv over a lifetime. These levels of dose are small in relation to radiotherapeutic doses, although not in relation to the average doses received in occupational settings, or to those received by the survivors of the atomic bombings. In most cohorts, such doses should not be correlated with the other doses received, or with other modifying factors, so that they should not materially affect inferences on radiation risk. For those cancers that are extremely radiogenic, such as thyroid cancer or leukaemia, natural background exposure may contribute materially to the risk, particularly in cohorts, such as the LSS, in which the average doses approach background levels [L96]. A recent analysis of thyroid cancer incidence among the survivors of the atomic bombings demonstrated that a substantial proportion (up to 32%) of thyroid cancer appearing at young age in this cohort might be attributed to natural background exposure [L96]. Doses from radiological examinations or from radiation therapy are also generally not considered. Surveys of both exposure types have been conducted in the LSS [K60, K61], although as yet no account has been taken of these doses in any analysis of health end points. Cumulative doses to specific organs (e.g. colon, stomach) due to radiological examinations in some persons in the AHS are of the order of 100 mSv or more, which is comparable to the average dose to this cohort due to the atomic bombings [K60]. However, the doses due to radiological examination are not generally expected to be correlated with those due to the bombings, thus bias in risk estimates is unlikely to be appreciable.

### E. Use of biodosimetry for epidemiological studies of radiation risk

28. When individual dose measurements are unavailable or incomplete, a biodosimetric measure of radiation exposure would be desirable. Ideally the biodosimeter would:

register uniformly low values in the absence of a radiation exposure; be sensitive, precise and unbiased in estimating radiation exposure; and use a biological indicator that has a long half-life, so that dose estimates could be made some years after exposure. There are currently no biodosimetric methods that fulfil all these criteria, although the method employing electron paramagnetic resonance (EPR) to measure doses to teeth (see below) arguably comes closest. The measurement of chromosome aberrations in peripheral lymphocytes, whether stable (balanced translocations) or unstable (dicentrics, ring chromosomes), has been much used, for example in studies of the survivors of the atomic bombings in Japan [K22, S81], in a study of women irradiated for treatment of benign and malignant gynaecological disease [K21] and in Chernobyl recovery operation workers [N23, S27]. G-banding of chromosomes to detect such aberrations has been performed for a number of groups, including those of patients receiving radiotherapy [T20]. The technique, developed relatively recently, of fluorescence in situ hybridization (FISH) is particularly useful for assessment of stable chromosome aberrations, and has been used in various studies of nuclear workers [M20, T19], of persons exposed as a result of nuclear weapons tests [S26] and of Chernobyl recovery operations worker populations [J4, L18]. The hypoxanthine phosphoribosyltransferase (HPRT) gene mutation frequency in lymphocytes is also sometimes used in an assay of radiation damage [J4]. The glycophorin A (GPA) assay measures somatic radiation inactivation of the GPA gene in erythroid progenitor cells in the bone marrow and has been used in studies of Chernobyl recovery operation workers [B19, J4]. It has the weakness that it can only be used among those (about 50%) of the general population with the M/N blood type, and it has wide variability in sensitivity between individuals. EPR, also known as electron spin resonance (ESR), can be used to measure cumulative radiation doses to tooth enamel. Under experimental conditions and using the latest refinements [H54, H55], the technique has a minimum detectable dose of approximately 10 mGy. EPR/ESR has been used in assessing radiation doses in the LSS cohort [I22, I23], in groups exposed to radiation due to the Chernobyl accident [I24, S82] and in workers at the Mayak nuclear complex in the Russian Federation [R44, R45]. All these techniques and their applications to biodosimetry are discussed in a recent report of the International Commission on Radiation Units and Measurements (ICRU) [I21].

29. Biodosimetric data pose at least five particular problems. First, most such measurements show some variability in background levels. The most important source of variability for stable chromosome translocations is age. In particular, a recent collaborative analysis involving a number of laboratories using the FISH technique demonstrated that age is the main determinant of translocation yield; other variables, such as smoking and sex, had little if any influence on aberration yield [E5, L44, W19]. A comparison of measurement results among some laboratories has been reported [L44] as part of the follow-up to the 1994 accident in Estonia involving the exposure of a family to radiation from a powerful $^{137}Cs$ source. After correction to full genome, yields from the participating laboratories were in reasonable agreement [L44]. A similar comparison of results for blood samples taken from non-irradiated populations has likewise demonstrated a large measure of agreement among laboratories [W19]. A second problem with biodosimeters is that they integrate dose from all sources. While in certain circumstances this might be thought advantageous, the lack of information on the temporal distribution of exposure can cause difficulties, particularly as for most sites the probability of cancer occurring varies substantially as a function of age at exposure [U2]. Moreover, the dose under study (for example that received occupationally) may be similar in magnitude to the cumulative dose that individuals have received due to background radiation. Since the dose from external penetrating background radiation averages about 1 mGy in a year, by age 50, study subjects have received about 50 mGy on average from background radiation, with perhaps a twofold variation around that value. If the extra dose under study (e.g. that resulting from occupational exposure to radiation) is of a similar magnitude, it becomes difficult to discriminate between the two components. A third problem with biodosimeters is that, compared with physical dosimeters such as film badges, collection, storage and analysis of the biological material are relatively expensive. At present it is not practicable to store and analyse samples for more than a small proportion of most cohorts. Storing samples and then analysing data from the cases and from a suitably structured set of controls from within the same cohort could alleviate somewhat the problem of expense of analysis. However, it is important that samples be taken and stored in comparable conditions, and if possible at a comparable time. It is also important that subsequent modifying exposures to radiation or other agents be avoided. This implies that samples should be taken from all members of an exposed cohort as soon after the relevant exposure as possible, before disease status is known. A fourth problem with biodosimeters is the difficulty in estimating organ doses following partial body irradiation. This can be a problem also for physical dosimeters, unless multiple dosimeters are used. A fifth problem, but only for certain end points, in particular unstable chromosome aberrations [L19], is that the signal decays over time. Knowledge of when the dose was received is needed to reliably infer dose. Some early studies of HPRT mutations also suggested that the signal decayed over time [D26, U18], but later studies did not show this [J4].

30. This last point is very much linked with the lowest detectable dose, as is also the intrinsic variability in aberration yield. In general, cytogenetic dosimetry based on the assay of chromosome aberrations in peripheral lymphocytes cannot reliably detect doses below about 100 mGy [L14]. For example, in spite of more than 258,000 painted metaphases being analysed, there was no association between aberration yield and recorded dose

among a population of 118 Estonian workers performing recovery operations after the Chernobyl accident, who had an average dose of about 103 mSv, although there was a significant increase in aberration yield among older recovery operation workers and among smokers [L18]. A recent acute dose of about 100 mGy can be fairly easily measured by counting dicentric chromosomes, because such a dose would treble the background level of ~1 dicentric among 1,000 cells. Dicentrics have a half-life of about 3 years, but this can be much shorter following high doses. Therefore, any doses received more than about 5 years before blood sampling cannot be measured using this indicator.

31. When translocation yields are measured many years after an accident, the lymphocytes drawn in the blood sample will have been derived from stem cells, which at the time of irradiation are presumed to have been in the bone marrow. This raises two questions. If there is a difference in sensitivity between mature lymphocytes and precursor cells in the bone marrow, it would not be appropriate to derive in vitro calibration curves using mature lymphocytes. Secondly, the irradiated cells have passed through an unknown number of divisions to become mature lymphocytes. This means that unstable cells will have been removed and, if some of these also contained translocations, the yield of translocations might have changed. The work that has been done on persistence in vivo, particularly when stable cells only have been scored, shows that neither of these problems is of great practical importance [L19, T20]. As indicated above, the major confounding factor for control levels is age, but there is still some extra variation unaccounted for.

32. The minimum detectable dose is to some extent related to the number of cells the investigator is prepared to score. If one is prepared to score translocations in a large number of cells (for example on a group basis), then one might detect an average dose of 200 mGy, although 500 mGy is a more realistic lower limit. Scoring 1,000 genome equivalents (3,000 cells with 3 pairs of the largest chromosomes painted, giving 33% efficiency in detecting translocations [I36]), one would expect to see a control level of about 10 translocations (in a 60-year-old) and a further 10 from an added dose of 500 mGy; these are just about measurable, bearing in mind the Poissonian variability. However, increasing the number of cells scored will reduce only the Poissonian variability in counts, and will do nothing to eliminate the intrinsic variability in control levels.

33. In summary, the biodosimetric methods available at present seem useful to estimate only moderate to high individual historical doses (doses of perhaps 0.2 Gy or above), although their use to estimate group-averaged doses of above 0.1 Gy may be meaningful. Perhaps the most useful measure, which is stable over time and between laboratories, is the assay of chromosome translocations using the FISH technique.

## F. Problem of multiple comparisons in epidemiological studies of radiation risk

34. For a study that makes numerous comparisons (e.g. a study of radiation exposure and cancer mortality that provides results for many types of cancer), it is popularly supposed that 1 statistical test out of 20 will be statistically significant (at the 5% level) by chance. This is not strictly true. Not so widely known are the probabilities of obtaining 1, 2, 3,…*n* statistically significant results by chance when there is no real effect at all. If the comparisons are independent of each other (as appropriately calculated estimates of excess mortality or incidence due to various types of cancer approximately are), then table 3 gives illustrative results.

35. Table 3 shows, for example, that the probabilities of obtaining one or more statistically significant results purely by chance are about 40.1%, 64.2%, 78.5%, 87.1%, 92.3% and 99.4% with 10, 20, 30, 40, 50 or 100 comparisons, respectively. The corresponding probabilities of obtaining two or more statistically significant results by chance are 8.6%, 26.4%, 44.6%, 60.1%, 72.1% and 96.3%, respectively, and so forth. There is no simple way to distinguish with certainty real effects from chance effects. Other criteria must be used to assess whether a particular association is likely to be causal or due to chance.

36. In assessing the results of analyses, in particular those that may have come from multiple testing of a variety of end points, the Bradford Hill criteria for assessing whether an association is plausibly causal should always be considered [B20]. Specifically these are as follows: *(a)* consistency and unbiasedness of findings: confirmation of the association by different investigators, in different populations, using different methods; *(b)* strength of association, and in particular two aspects: the frequency with which the factor (in this case radiation) is found in association with the disease, and the frequency with which it is found in the absence of the disease; the larger the relative risk, the more the hypothesis is strengthened; *(c)* temporal sequence: obviously, exposure to the factor (in this case radiation) must occur before onset of the disease; in addition, if it is possible to show a temporal relationship, as between exposure to the factor in the population and the frequency of the disease, the case is strengthened; *(d)* biological gradient (dose–response relationship): finding a quantitative relationship between exposure to radiation and the frequency of the disease; the intensity or the duration of exposure may be measured; *(e)* specificity: if the factor being studied can be isolated from others and shown to produce changes in the incidence of the disease, for example if thyroid cancer can be shown to have a higher incidence specifically associated with radiation exposure, this is convincing evidence of causation; *(f)* coherence with biological background and previous knowledge: the evidence must fit the facts that are thought to be related, e.g. the rising incidence of dental fluorosis and the rising consumption of fluoride are coherent; *(g)* biological plausibility: the statistically significant

association fits well with previously existing knowledge; *(h)* reasoning by analogy: sometimes a commonly accepted phenomenon in one area can be applied to another area; *(i)* experimental evidence: are similar effects observed in carefully controlled experiments in a variety of model systems? Criteria *(a)*, *(d)* and *(i)* are critical in evaluating whether a putative radiation effect is likely to represent a causal association. Sometimes a Bayesian analysis will also help give a better indication of the meaningfulness of particular results, in that it can present a more realistic picture of relative risk [G5, W1].

37. Statistical approaches are available to address the problem of multiple comparisons (e.g. the highly conservative Bonferroni criterion [T2] or the improved approach of Benjamini and Hochberg [B1]) but have seldom been used, for a number of reasons. One reason is that they reduce statistical power for any given comparison. Epidemiological studies commonly have limited statistical power for many cancer end points, and using such approaches to address the problem of multiple comparisons would reduce it further. The assumption of independence of the various tests is also often questionable. Although such methods facilitate the adjustment of tests of statistical significance, they provide no way to adjust the corresponding confidence intervals. Notwithstanding these problems, attempts should generally be made to account for this in assessing the significance of claimed findings.

## G. Measures of radiation risk, including lifetime risk

38. Appendix B details the six commonly used measures of population cancer risk, and their relation to the instantaneous cancer mortality rate, $\mu_c(s,t \mid a,D)$, expressed as cancer deaths per year that result for a given cancer type $c$ at age $t$ for persons of sex s following some instantaneously administered radiation dose $D$ given at age $a$. This quantity is typically evaluated by fitting a model for radiation risk to data corresponding to some exposed cohort. As outlined in appendix B, fundamental to the assessment of cancer risk for a population, one must assume certain underlying mortality rates that the population would experience in the absence of radiation exposure, both overall and for each cancer type. For calculations of population risk for cancer incidence, cancer incidence rates must also be specified. These underlying rates are generally estimated from national morbidity and mortality rates. It is usual to calculate the consequence of an instantaneous exposure to a "test" dose, $D_t$, that is assumed to be administered at some age, $a$. However, other, more general patterns of exposure are possible. By far the most commonly used population risk measure is the risk of exposure-induced death (REID) per unit dose; this has been employed by many scientific committees [I11, U2, U4] and others [L15, L16, L17]. As discussed in appendix B, this and the other five measures of risk considered there are non-constant as a function of the test dose $D_t$.

## H. Transfer of radiation risk estimates between populations, and interactions of carcinogens

39. Despite the relatively large number of data on radiation risk, the question of how to transfer risk estimates derived from one population to a different population remains unanswered. The available data suggest that there is no simple solution to the problem [M23, U4], as indicated below.

40. There does not appear to be an obvious, consistent relationship between underlying and radiation-related cancer risk, either across cancer sites within a single population or across populations for a single cancer site. In the female Japanese population generally, age-standardized (world) incidence is similar for stomach cancer and breast cancer, about 31 and 34, respectively, per 100 000 per year whereas in the United States of America the incidence is about 3 and 90, respectively [P19]. Among survivors of the atomic bombings, the radiation-related ERR at exposure age 30 at 1 Gy ($ERR_{1\,Gy}$) is 0.34 for stomach cancer incidence and 0.87 for breast cancer incidence [P48]. Stomach cancer contributes a substantial proportion of the total radiation-related risk (about 18%), but that proportion is considerably less than the proportion of underlying stomach cancer incidence to total underlying cancer incidence (about 27%) among survivors of the atomic bombings [P48] and among Japanese people generally [P19]. In the United States, the ratio is 2% for males and 1% for females [P19]. For female breast cancer the opposite is true. The underlying rate in Japan is among the lowest in the world for developed countries, whereas the total cancer rate is not much different from that in most other countries [P19], while among survivors of the atomic bombings, breast cancer contributes a disproportionately large fraction (about 17%) of the total radiation-related cancer burden [P48]. In the United States and many Western European populations, by contrast, underlying breast cancer rates are high [P19], but the radiation-related excess risk (in absolute terms) per unit dose among medically exposed women is similar to that among the survivors of the atomic bombings [L5, P3] (see also table 10). That is, the dose-specific, radiation-related component of the total breast cancer risk is likely to be similar in absolute magnitude for exposed Japanese and Western populations but, in Western populations, smaller as a proportion of the total breast cancer risk. For stomach cancer, on the other hand, the United States underlying rate is an order of magnitude lower than that in Japan [P19], whereas the limited information on dose-specific, radiation-related excess risk suggests that, as a multiple of the underlying risk, it may be comparable to that in the survivors of the atomic bombings [C4, G6].

41. The above information suggests that, for breast cancer, the radiation-related ERR per unit dose (i.e. the excess risk per unit dose expressed as a multiple of the underlying risk for the Japanese population) based on the data from the survivors of the atomic bombings in Japan would overestimate the risk for an exposed United States population. On the other hand, for stomach cancer, the radiation-related EAR

(i.e. the difference between the risk following exposure and the Japanese underlying risk) would result in an overestimate for the United States population. For most other cancers there is almost no information of a similar nature. This is not a trivial matter, because any transfer of a risk estimate from one population to another requires an assumption, explicit or implicit, about the relation between the excess and the underlying risk. Moreover, for some sites (e.g. stomach, liver and oesophagus) the underlying rates can differ markedly between populations [P19].

42. The available information suggests that, depending on circumstances, relative or absolute transfer of risk between populations, or indeed the use of some sort of hybrid approach, such as that employed by Muirhead and Darby [M24] and Little et al. [L21], may be appropriate. Many regulatory bodies implicitly assume that risk transfer is intermediate between additive and multiplicative [I11, M23]. In the updated United States National Institutes of Health (NIH) radioepidemiological tables report [L45], for most cancer sites population cancer risk was calculated by weighting equally all possible linear combinations of the multiplicative ($M$) and additive ($A$) transfer model estimates, $p \times M + (1 - p) \times A$, by assuming $p$ to be a random variable distributed approximately uniformly between 0 and 1. This subjective approach was motivated by: *(a)* the consideration that differences in underlying rates might reflect differential exposure to both cancer initiators (consistent with additive transfer) and cancer promoters (consistent with multiplicative transfer), and *(b)* an almost complete lack of relevant epidemiological information for most cancer sites. The general United States Environmental Protection Agency (EPA) approach for site-specific cancer risk was similar, but on a logarithmic scale, i.e. the logarithm of the excess risk was assumed to be a linear mixture between the logarithms of the multiplicative and additive transfer model estimates [E6], where the value of the uncertain mixture parameter $p$ was assumed to be uniformly distributed between 0 and 1. The EPA approach tends to yield somewhat lower risk estimates than the approach of the National Cancer Institute (NCI)/Center for Disease Control (CDC) [L45]. For the few sites where information on population transfer was available, the NCI/CDC approach was to favour one simple transfer model over the other. For example, for breast cancer, 0.5 probability was placed on additive transfer and 0.5 on the uniform model; for stomach cancer, 0.33 probability was placed on multiplicative transfer and 0.67 on the uniform model.

43. It should not be surprising that the relationship between radiation-related and underlying risk in different populations is not consistent for different cancer sites. There are reasons, as yet poorly understood, why underlying breast cancer rates are high in the United States, and why underlying stomach cancer rates are high in Japan. These reasons are almost certainly related to differences in lifestyle. Haenszel et al. [H35] found that migrants to Hawaii from Japan continued to have high levels of stomach cancer risk, but their children, especially those who had adopted Western-style diets, did not; this suggests that exposures early in life are critical determinants for this disease. On the other hand, colon cancer rates among migrants to the United States and Australia from countries with low underlying levels have tended, within their lifetimes, to converge to the higher levels characteristic of the country [H36, T39]. Similar findings have been reported for breast cancer risk among women migrating to the United States from European countries with low underlying rates, but for Japanese migrants to Hawaii and California the convergence was much slower [H34, Z5]. Generally breast cancer rates from non-white migrants to the United States remain below United States rates both in the migrants and in their descendants [T39]. In contrast, breast cancer rates in white migrants to the United States approximate those of United States whites in the first generation, except for rates in migrants from the former Yugoslavia [T39]. On the other hand, the breast cancer incidence rate in the San Francisco–Oakland metropolitan region among American-born women of Japanese descent was, by 1969–1971, approaching that for the Caucasian population [B24]. The lifestyle factors affecting the rates for breast and stomach cancer are probably different, at least in part, and probably interact differently with the radiation dose factor.

44. Related to this question is the issue of how one should model interactions between radiation and other agents in relation to cancer risk. This was the subject of an extensive review issued in annex H of the UNSCEAR 2000 Report [U2], which encompassed biological and epidemiological evidence for interactions and discussed in detail the implications for statistical modelling. Undoubtedly the most studied of these interactions is that between radiation and cigarette smoking in relation to lung cancer. Analysis by the BEIR (Biological Effects of Ionizing Radiation) VI Committee and others of the effects of cigarette smoking and radon progeny on lung cancer risk in 11 miner cohorts suggested an interaction that was intermediate between additive and multiplicative [C36, L39]. The preferred model of the BEIR VI Committee was submultiplicative [C36]. In fits to the data on Colorado Plateau uranium miners, models with multiplicative interaction between the effects of exposures to radon progeny and cigarette smoke were preferred to models with additive interactions, although it was not possible to rule out either submultiplicative or supramultiplicative models [L39]. Lung cancer mortality among Mayak workers could be better described with a model of carcinogenesis that was submultiplicative in relative risks of smoking and radiation than with a model that was multiplicative [J10]. Studies on domestic radon daughter exposure also suggest that the relationship between the effects of smoking and exposure to radon progeny in relation to lung cancer risk may be closer to multiplicative than additive [D24, P18]. Analysis of lung cancer in persons treated for Hodgkin's disease demonstrated a multiplicative interaction (on the logistic scale, i.e. where the disease probability, $p$, is transformed via the expression $\log[p/(1 - p)]$) between radiotherapy dose and cigarette smoke in relation to lung cancer risk; an additive interaction fitted statistically

significantly worse. Interactions between radiation and chemotherapy were more nearly additive (on the logistic scale); a model assuming a multiplicative interaction fitted statistically significantly worse [G23]. In contrast, analysis of the effects of radiation and smoking on lung cancer incidence in the survivors of the atomic bombings suggested that the interaction was approximately additive, although it was also consistent with a multiplicative interaction [P17]. However, with only a few tens of radiation-induced excess lung cancers, the LSS data at present lack the statistical power of the miner data to discriminate between multiplicative and additive models of interaction. The BEIR VII report [C37] also assessed interactions between radiation and a variety of other factors, including tobacco smoke, chemotherapy, heritable genetic risk factors, iodine insufficiency and ultraviolet radiation; in general, interactions ranged between additive and multiplicative effects. The BEIR VII Committee also adduced from consideration of stochastic quasi-mechanistic models why this should be so [C37]. However, as this analysis was based on an approximate (deterministic) version of the two-mutation model, which is known to poorly approximate the cancer risk from the exact (stochastic) model [H57], these inferences may not be correct. The arguments used by BEIR VII [C37] to justify invariance of relative risk break down when the exact hazard function is used instead of the approximate (deterministic) hazard function, although the arguments in favour of additive invariance of risk still hold (although not for the reasons given). Caution should be exercised in the application of such inferences to this model, and also to more general multistage cancer models [L25, L26].

45. In general it is not clear in terms of mechanisms or biology how data on excess risks for one population should be transferred to another population. If one supposes that radiation acts as the initiating mutation in generalized multistage models of the sort recently developed [L25, L26], then invariance of EAR would correspond to similar radiation-induced mutation rates between populations [L25, L26, L27]. Invariance of ERR would correspond to the ratio between the radiation-induced mutation rates and the underlying mutation rates being invariant [L25, L26, L27]. Mechanistic considerations imply that the interactions between radiation and the various other factors that modulate the multistage process of carcinogenesis may be complex [C35, L22], so that in general one would expect neither relative nor absolute risks to be invariant across populations. In fits of quasi-mechanistic multistage models to the data on the Colorado Plateau uranium miners, the model fitting best was one with three rate-limiting stages, with radon daughter exposure acting to vary the first and second mutation rates, and with cigarette smoking acting on the first mutation rate [L41]. This mixture of radon progeny and smoking actions on different stages implies that the interactions between these agents will not conform to a simple multiplicative or additive pattern. If this model is true, it would imply that the observed interaction between the effects of radiation and cigarette smoking will depend on their relative timing. This might explain why there are indications (admittedly not statistically significant) of differences between the forms of interaction in the LSS data, where an instantaneous radiation exposure was in general followed by cigarette smoke exposure, and in the miner data, where cigarette smoke exposure was concurrent with, but also preceded and followed, radiation exposure.

46. Much of environmental, nutritional and occupational cancer epidemiology is concerned with identifying risk factors that might account for some part of the variation of site-specific underlying cancer rates among populations. While there has been much progress, the problem is vast and there is only limited information on the interaction between radiation dose and lifestyle, or constitutional factors, in terms of cancer risk. The interactions between radiation exposure and cigarette smoking in relation to lung cancer risk discussed above are among the most well studied of such interactions, although other risk factors, in particular diet, have been studied in relation to radiation exposure [S42]. Interactions of radiation exposure with constitutional factors are discussed at greater length in section I.I and also in sections III.L and III.M (on cutaneous melanoma and non-melanoma skin cancer) below. Thus it is likely that, for the foreseeable future, the most useful information relevant to transferring radiation-related risk coefficients from one population to another will come from multinational comparisons of site-specific radiation-related risk, rather than from investigations of underlying cancer risk factors and their interactions with radiation dose.

47. In studies assessing the possible interaction of other factors with radiation risk, it can be useful to combine studies with similar designs to attempt to increase statistical power, for example by having a wider range of exposures to some other factor between populations than is available within any given population. Sometimes a “meta-analysis”, based on published findings from several studies, may be performed. Where feasible, as noted below, it is preferable to combine the original data and analyse them using a common format, in other words to perform a “pooled analysis”. Pooled analyses have been conducted of various cohorts of radiation workers [C3, C41], to assess the effects of radon daughter exposure in relation to lung cancer risk in underground miners [C36], to assess thyroid cancer risk in various (mainly medically exposed) cohorts [R6] and to assess breast cancer risk in various populations [H9, L5, P3]. Less commonly, analyses combining cohort and case-control data, for example in relation to leukaemia risk [L31], have been conducted.

48. The possible influence of confounding and residual bias needs to be considered. The greater power and therefore apparently greater precision of combined studies may be offset by increased bias resulting from uncontrolled confounding, for example inter-study confounding. Perhaps the most extreme instances of this are correlation studies, which as discussed in section I.A are prone to “ecological bias”. For example, this sort of bias is likely to explain the elevated risks, which are large and highly statistically

significant, in a meta-analysis of leukaemia in relation to radon daughter exposure [H32, M45]. Even where there is no inter-study confounding, if the individual studies are biased, meta-analysis based on their results can result in seriously biased and misleading results [B56, B57, L87]. One of the main problems in joint analysis can result from a lack of comparability of the component studies owing, for example, to differences in data collected on exposures and potential confounders. This is likely to be a particular problem for meta-analysis, or retrospectively assembled cohorts combined in a pooled analysis. Pooled analyses, in which the component cohorts are assembled using a common protocol and prospectively followed up, are therefore to be preferred. Another potential problem with retrospective pooling or meta-analysis is publication bias, i.e. selective reporting of results depending on whether the outcome was statistically significant. As noted in section I.B, this arises particularly in small, ad hoc cohorts. This is less likely to be a problem in a pooled analysis of large cohorts prospectively followed up.

### I. Impact of human genetic susceptibility on radiation risk

49. The International Commission on Radiological Protection (ICRP) [I12] and others [L9, L20, L23] have recently reviewed the issue of interaction between human genetic susceptibility and radiation risk. Little and colleagues [L9, L20, L23] paid particular attention to risks observed in medically exposed populations, where there is often (particularly in persons treated for cancer) a higher proportion of persons with heritable cancer syndromes than in the general population.

50. Only three of the studies considered by Little and colleagues [L9, L20, L23] contained adequate information to assess interactions between radiotherapy and cancer-prone conditions, all three studies relating to populations treated in childhood [L24, T10, W11]. The cancer incidence study of Wong et al. [W11] is an update of an earlier mortality study of Eng et al. [E7]. Tables 4 and 5 provide details on RRs of radiation-associated cancer in these studies in relation to whether the patients had a cancer-prone disorder (defined slightly differently in each study).

51. There were no indications in the studies of Little et al. [L24] or Tucker et al. [T10] that the RR of a second cancer is higher among those patients with a familial cancer syndrome. Indeed, in the study of Little et al. [L24], brain tumour RRs were markedly lower among the patients with cancer-prone disorders compared with those in the non-susceptible population, at borderline levels of statistical significance (2-sided $p = 0.06$) (table 4). In the study of Tucker et al. [T10] there were non-significant indications (2-sided $p = 0.67$) of a lower ERR of a bone tumour among patients with retinoblastoma (RB) than among those patients without, although, as is clear from table 5, EARs in the RB group were higher than among patients without RB. In that study, the RB group included both those patients treated for bilateral RB, which is presumed to be heritable, and those treated for unilateral RB, of which most cases are presumed to be non-heritable [W11]. About half of the RBs in this group would be expected to be bilateral [W11].

52. More limited information is available on the interaction between radiotherapy and heritable RB in the study of Wong et al. [W11]; unfortunately there is insufficient information on radiation dose in the published report. More information is given in a subsequent report [K43], although radiation dosimetry has still not been assessed. To assess the effects of heritable RB on RRs of a second cancer after radiotherapy for RB, Little et al. [L9] assumed that the expected numbers of second cancers in this cohort [W11] are given by:

$E_i$ in the non-irradiated, non-heritable-RB group;
$E_i \cdot \exp[\beta]$ in the irradiated, non-heritable-RB group;
$E_i \cdot \exp[\delta]$ in the non-irradiated, heritable-RB group;
$E_i \cdot \exp[\delta + \theta \cdot \beta]$ in the irradiated, heritable-RB group;

where $E_i$ is the (population) expected number of second cancers in group $i$. Here $\exp[\beta]$ is the ratio of the risk in the irradiated group to that in the non-irradiated group among the non-heritable-RB patients, $\exp[\delta]$ is the ratio of the risk in the heritable-RB patients to that in the non-heritable-RB patients, and $\exp[\theta \cdot \beta]$ is the ratio of the risk in the irradiated group to that in the non-irradiated group among the heritable-RB patients. The parameter of interest is the multiplier of radiosensitivity in the heritable-RB group, $\theta$, the maximum-likelihood estimate of which is 1.62 (95% CI: 0.70, >10,000) (table 5); i.e. there is weak evidence that the radiosensitivity of heritable-RB patients is higher than that of non-heritable-RB patients. The weakness of this evidence may in part be a consequence of the small number (nine) of cancers in the non-heritable-RB group. It should be emphasized that no account has been taken of radiotherapy dose in this analysis, reflecting the limitations of the published data. Consequently the conclusions drawn must be qualified. It is likely that similar conclusions would be drawn from the updated follow-up [K43]; unfortunately not enough information is given in the published report even to duplicate what has been attempted here for the more limited follow-up.

53. Although not shown in tables 4 and 5, additional information on the interaction between the risk of a radiation-related second cancer and cancer-prone conditions is given in a study of survivors of childhood cancer by Kony et al. [K25], in which there is weak evidence that RRs of radiation-associated second tumours in patients whose close relatives develop cancer more frequently than average (i.e. who belong to cancer-prone families) are lower than those in patients who are not from cancer-prone families [K25]. The ratio of RRs for second tumours between groups receiving ≥0.5 Gy and <0.5 Gy in the cancer-prone families is 1.9, whereas in the non-cancer-prone families it is 4.1 [K25].

54. Although there are indications of rather lower radiogenic ERRs among people with cancer-prone disorders [L9], the radiogenic EAR can be higher. For example, in the study of Tucker et al. [T10], the ERR can be calculated as 0.08 $Gy^{-1}$ among patients with a first cancer other than RB and as 0.05 $Gy^{-1}$ among those with RB as their first cancer [L9]; thus the ratio of ERRs for RB versus non-RB patients is 0.05/0.08 = 0.6. On the assumption that the underlying cancer risk in RB patients is 5.6 times that in non-RB patients (taken from the ratio of risk in heritable-RB patients to that in non-heritable-RB patients in the study of Wong et al. [W11]), this calculation implies that the ratio of EARs for RB versus non-RB patients is roughly (5.6 × 0.05)/0.08 = 3.5. As discussed in section I.H above, the fact that ERRs are lower in people with cancer-prone disorders is consistent with a more general pattern observed in epidemiological data, whereby higher underlying cancer risks are to some extent offset by lower ERRs of radiogenic cancer [U2, U4]. The ICRP [I12] has recently reviewed radiogenic cancer risks among genetically susceptible individuals, and suggests that EARs of radiogenic cancers in people with familial cancer syndromes may be higher by a factor of 5–100 than those in non-susceptible individuals, with the most appropriate value for this factor being about 10. The ICRP [I12] points out the serious implications of the higher EAR for such people receiving large doses of radiation, for example during radiotherapy. This elevated risk has to be balanced against the generally high underlying cancer risk in these individuals and the benefits accruing from radiotherapy.

### J. Effects of dose protraction or fractionation and radiation quality

55. The derivation of cancer risks after exposure to ionizing radiation at low doses and dose rates is critical to the setting of standards for radiological protection. In annex G of the UNSCEAR 2000 Report [U2], there was a detailed discussion of what constitutes "low dose" and "low dose rate", in part derived from previous UNSCEAR reports [U5, U7]. Curvature in the dose response to any end point can be measured by the ratio of quadratic to linear coefficients, $\beta/\alpha$, which defines the curvature, in fits of the equation:

$$F(D) = \alpha \cdot D + \beta \cdot D^2$$

(It should be noted that in annex G of the UNSCEAR 2000 Report [U2], curvature was defined as the inverse of this quantity, i.e. $\alpha/\beta$.)

56. For chromosome aberrations in peripheral blood lymphocytes exposed to $^{60}$Co gamma rays, typically $\beta/\alpha \approx 5\ Gy^{-1}$ [L88], implying that at doses of up to 40 mGy the quadratic term, $\beta \cdot D^2$, contributes less than 20% of the excess. For this reason, the UNSCEAR 2000 Report indicated that 20–40 mGy of low-LET radiation would be considered a low dose [U2]. Pierce and Vaeth [P11] analysed curvature in the LSS cohort adjusting for random dosimetric errors and obtained, for solid cancers, a value for $\beta/\alpha$ of 0.3 (95% CI: <0, 1.7) $Gy^{-1}$, and for leukaemia, a curvature of 0.6 (95% CI: 0.1, 3.3) $Gy^{-1}$. Little and Muirhead [L37] fitted a somewhat different model, arguably more plausible radiobiologically, to the LSS incidence data, also taking account of random dosimetric errors, and taking separate account of the effects of neutron dose, $D_n$, and gamma dose, $D_\gamma$, using:

$$F(D_\gamma, D_n) = \alpha \cdot [D_\gamma + RBE \cdot D_n] + \beta \cdot D_\gamma^{\,2}$$

Assuming a neutron relative biological effectiveness (RBE) of 10 and dose errors expressed as 35% geometric standard deviation (GSD) (similar to assumptions made by Pierce and Vaeth [P11]) $Gy^{-1}$, Little and Muirhead [L37] obtained, for solid cancers, curvatures of 0.10 (95% CI: –0.18, 0.70) and, for leukaemia, curvatures of 1.95 (95% CI: 0.31, >1000) $Gy^{-1}$. It has been shown that the curvature for leukaemia in the LSS is consistent with that seen in a number of data sets of chromosome aberrations in peripheral blood lymphocytes exposed to $^{60}$Co gamma rays, although this is not the case for solid cancers [L100]. These figures suggest that at a dose of 100 mGy the quadratic terms contribute 3–20% of the total excess, so that a low dose might consist of any value up to 100 mGy.

57. In the UNSCEAR 2000 Report [U2], microdosimetric analysis demonstrated that for $^{60}$Co gamma rays hitting a 4 μm diameter cell nucleus, doses of 0.8 mGy or less would ensure that on average no more than about 0.2 radiation tracks hit the nucleus, resulting in no more than 2% of cell nuclei having more than one radiation track. On this basis a low dose would correspond to no more than 0.8 mGy. The BEIR VII report [C37] defined (without justification) a low dose as 100 mGy or less. The principal definitions to date as to what constitutes a low dose are summarized in table 6.

58. The UNSCEAR 2000 Report [U2] employed microdosimetric analysis of the number of radiation track coincidences within a cell nucleus to estimate that, in the presence of DNA repair, dose rates of up to $10^{-3}$ mGy/min would be considered low dose rates, and in order to ensure only one track per cell in 60 years, dose rates of up to $10^{-8}$ mGy/min would be considered low dose rates. However, it was noted that these considerations only applied to end points such as chromosome aberrations, mutation or cell killing. For the multistage induction of cancer, where the probability of an effect might be influenced by a subsequent radiation track, these calculations break down. Assessment of fractionation effects for induction of leukaemia and solid tumours in animal studies was used in the UNSCEAR 1986 Report [U7] to suggest that 0.05 Gy/min of low-LET radiation can be considered a low dose rate. Comprehensive assessment of fractionation effects in experimental tumour systems and other data were used in the 1993 UNSCEAR Report [U5] to conclude that 0.1 mGy/min of low-LET radiation averaged over about an hour can be considered a low dose rate. The BEIR VII

report [C37] defined (without justification) a low dose rate as 0.01 mGy/min or less. The principal definitions to date as to what constitutes a low dose rate are summarized in table 7.

59. In extrapolating cancer risks observed in groups (such as the survivors of the atomic bombings in Japan) exposed at a high dose rate to low-LET radiation, the ICRP [I11] recommends application of a "dose and dose-rate effectiveness factor" (DDREF) to obtain cancer risks at low doses and low dose rates. The ICRP [I11] recommended a DDREF of 2 on the basis of data from studies of animals, the evidence for curvilinearity in the data from the Japanese survivors of the atomic bombings, and other epidemiological studies. The UNSCEAR 1993 Report reviewed epidemiological and experimental data to conclude that a DDREF should be applied to estimate tumour risk for low-LET exposures at a dose rate of 0.1 mGy/min or less, whatever the total dose, or if the total dose was less than 200 mGy, whatever the dose rate [U5]. UNSCEAR did not estimate tissue-specific DDREFs, but suggested that for tumour induction the available data suggested that the DDREF adopted should, on cautious grounds, "have a low value, probably no more than 3" [U5]. The BEIR VII Committee [C37] estimated what they termed an "LSS DDREF" to be 1.5 (95% CI: 1.1, 2.3), on the basis of estimates of curvature from experimental animal data and from the latest LSS data on solid cancer incidence. BEIR VII also conducted a detailed review of the experimental literature, and documented a substantial DDREF for chromosome aberrations and cell mutations (for example at the HPRT locus) and animal carcinogenesis [C37]. DDREFs in excess of 2 were seen in many cellular systems; for most of the studies of cancer in animals, the experimental end point nearest to cancer in humans "yields [DDREF] estimates on the order of 2 to 6, with most values in the range 4–5" [C37]. Table 8 summarizes the estimates that have been made of DDREFs and related quantities.

60. For high-LET radiations, such as neutrons and alpha particles, no such reduction factor is indicated, because in general the dose response for tumour induction and hereditary effects following exposure to these sorts of radiation is linear, with no variation in effect with dose fractionation [I11, U5]. The reason for this may be connected with the fact that, at a tissue level, a low dose rate results in most cells being non-irradiated. For example, a dose of 1 mGy from exposure to alpha particles would result in 99.7% of cells being non-irradiated and in fewer than 1 in $10^6$ cells being hit more than once [U5]. This would lead one to expect that, at relatively low tissue doses, cancer risk would be proportional to the number of cells traversed, and therefore to dose. When a single high-LET particle strikes the cell nucleus, it delivers a large dose (for example 370 mGy on average for an alpha particle), so that even when the tissue dose is low, at a cellular level those cell nuclei that are hit receive a high dose.

61. There are no epidemiological studies that permit a direct internal comparison—to facilitate calculation of DDREF—between *(a)* exposures that are high dose and high dose rate, and *(b)* those that are highly fractionated or protracted. A second-best alternative is to compare risk estimates from the available high-dose and high-dose-rate studies with those from fractionated or protracted dose studies. In performing comparisons, the Committee has restricted its attention to studies where there is good quality organ dosimetry, good follow-up and good case ascertainment. Tables 9–12 show results for three specific classes of tumour—lung cancer, breast cancer and leukaemia—from various studies involving low-LET exposure. In particular, tables 9, 10 and 12 show results of comparing risks in various medically exposed groups with subsets of the atomic bombing survivor data for cancer incidence [P4, T1] and mortality [P1] matched for sex, age at exposure and years of follow-up. These comparisons are taken from the paper of Little [L20], and further details on the methodology are given there.

62. Table 9 shows that, in general, lung cancer ERRs in the medically irradiated groups are substantially below those in similar subsets of the LSS data. This is true for all four of the medical studies considered. For three of the studies this discrepancy is highly statistically significant (2-sided $p < 0.001$). Of particular interest are the findings that highly fractionated exposures confer little risk for lung cancer as compared with an acute exposure, both in the Canadian tuberculosis (TB) fluoroscopy study [H7] and in the Massachusetts TB fluoroscopy study [D4]. However, caution should be exercised in interpreting the results, as there may be confounding by smoking habits in both studies. Smoking histories were available in the TB medical records in the Canadian study [H7] and in the Massachusetts study [D4], and these showed no confounding with dose. However, the patients' subsequent smoking habits may have changed because of their respiratory illness and could have affected the lung cancer outcomes. Nevertheless, the Massachusetts study [D4] obtained smoking information from the patients many years after they had been hospitalized for TB, thus it is unlikely that changes in smoking habits would have been a factor.

63. Table 10 shows that for breast cancer the picture is very different. Although the ERR for the survivors of the atomic bombings is higher than that for the medical studies in two instances, it is lower than the corresponding ERR for another two medical studies, although nowhere is this difference statistically significant. Table 11 extends the analysis of dose-rate effects for breast cancer by reproducing the results of a recent meta-analysis of breast cancer [P3]. (The benign breast disease study considered by Preston et al. [P3] is excluded from the comparisons given here because the central value of age at exposure used for adjustments, 25 years, is considerably different from the value, 50 years, used in most of the other studies, making meaningful comparisons of ERR difficult.) As can be seen, breast cancer risks in the three high-dose and high-dose-rate studies are not consistently different from those in the two low-dose-rate studies, irrespective of whether EARs or

ERRs are considered. However, when Preston et al. [P3] compared the high-dose-rate thymic irradiation study of infants with the low-dose-rate haemangioma study of infants, the differences in the EARs were of the order of sixfold.

64. Little and Boice [L5] previously compared breast cancer incidence rates in the LSS and the Massachusetts multiple fluoroscopy study. They found that the ratio of the ERR per unit dose for the Japan study to that of the Massachusetts study was 2.1 (95% CI: 1.05, 5.0). However, this occurred primarily because of the lower underlying rates of breast cancer in Japan. When EARs were compared, the Japan/Massachusetts ratio of EARs was 0.73 (95% CI: 0.4, 1.4), indicating good comparability. These findings do not necessarily contradict the findings of Preston et al. [P3], who used the same Massachusetts fluoroscopy data but a version of the LSS incidence data with an extra six years of follow-up, i.e. to the end of 1993. Although Preston et al. used the same Massachusetts TB data, they analysed them differently. They used breast cancer rates from the Connecticut cancer registry to estimate the underlying (zero dose) rates, in contrast to Little and Boice [L5], who used a parametric model to estimate the term for underlying rates. In addition, Preston et al. [P3] discarded all person-years before the age of 20 and all person-years within 10 years of exposure. While this last assumption would make little difference to the Japanese cohort, for whom follow-up only started in 1958 (over 12 years after the bombings), it might make more difference to the Massachusetts data.

65. Table 12 shows that, in general, leukaemia risks follow the pattern for lung cancer, so that ERRs for the medically irradiated groups are substantially below those for similar subsets of the LSS data. This is true for all six medical studies considered. For three of the studies this discrepancy is statistically significant (2-sided $p < 0.05$).

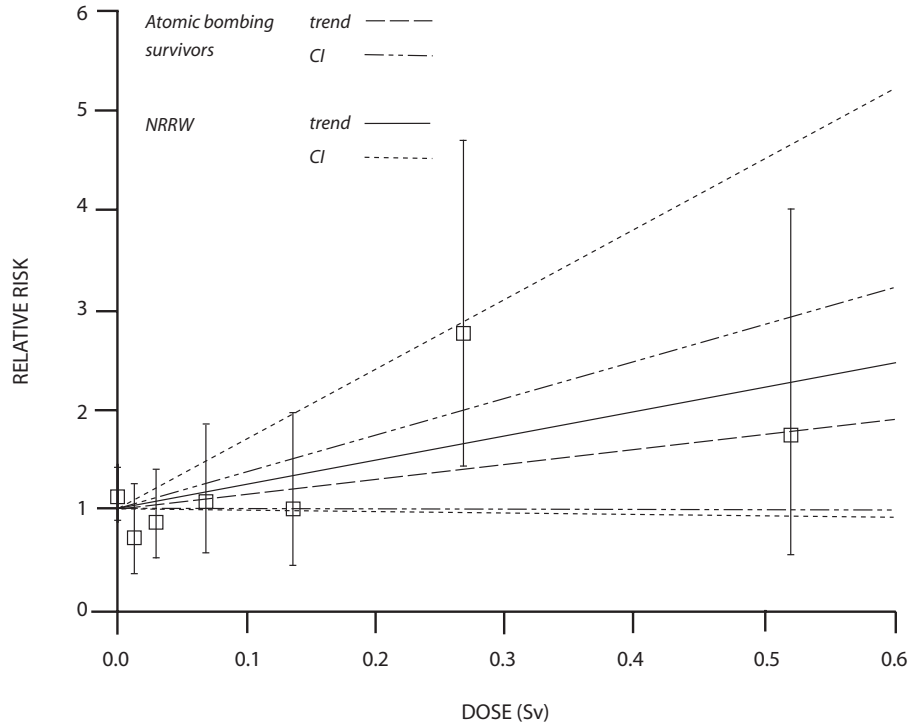
66. Thus the risks of cancer induction at certain sites (e.g. leukaemia, lung) for particular groups undergoing radiotherapy are much less than would be expected from the risks observed in the LSS. It has been generally assumed that the reason for this is cell sterilization, the effect of which is to remove cells that might otherwise develop into cancer. However, cancer risks are not lower in all radiotherapy groups (e.g. [G23, T25, V8]), which implies that in these cases the effects of cell killing (known to take place at the very high local cumulative doses in many radiotherapy regimes [T25, V8]) are being countered by cell repopulation within the irradiated areas. A model recently developed by Sachs and Brenner [S84] proposed a simple and radiobiologically plausible mechanism for repopulation of cells after radiation exposure that explains why this might happen, at least for solid tumours. This has been generalized to leukaemia, where it is also necessary to consider the role played by cell migration from blood to bone marrow and vice versa [L91, S85].

67. As noted in section I.H above, it is not clear in general how radiation-induced cancer risks should be transferred between populations. Caution should therefore be exercised when making quantitative inferences about the effects of dose rate, or any other factor, on the basis of comparisons of the excess cancer risks in different populations. This is especially so when, as is the case for breast and lung cancer in the Japanese, North American and Western European populations considered here, there are substantial differences in the underlying risks. Another complication in comparing radiation risks across studies is that the radiation energy spectrum involved varies. For the survivors of the atomic bombings, the dose was predominantly from high-energy (>1 MeV) gamma radiation, with a small contribution (1–2%) from high-energy (>1 MeV) neutrons [L28, R12, R20]. Most of the gamma-ray energy from the two atomic bombs was in the range 2–5 MeV [R12, R20]. In most of the medical studies considered here, the photon energy was 300 kVp or less. Higher-energy gamma rays are known to be less biologically effective [N8, S31]. For example, the relatively high-energy gamma rays produced by the atomic devices used in Hiroshima and Nagasaki would be less biologically effective, by a factor of about 3, than photons with an energy of 250 kVp [S31].

68. Direct estimation of cancer risks in human populations arising from exposure to radiation at moderate and low dose rates is possible for only a few exposed populations [U2, U4]. Among the most useful estimations are those from the various studies of nuclear workers [C3, C41, M12]. Table 13 (adapted from reference [M12]) gives a summary of ERRs from the major published studies on workers to date. Table 13 shows that the ratio of the leukaemia ERR estimate for the second analysis of the National Registry for Radiation Workers (NRRW) of the United Kingdom of Great Britain and Northern Ireland [M12] to that for the current LSS mortality data on the survivors of the atomic bombings [P9, P10] is 1.60 (90% CI: <0, 5.27) (see figure V). The corresponding ratio for solid cancers excluding lung cancer is 0.67 (90% CI: <0, 2.74) (see figure VI). (Lung cancers are excluded because of possible confounding by cigarette smoking.) The three-country study of the International Agency for Research on Cancer (IARC) [C3] yields similar values, with slightly narrower confidence intervals. The IARC 15-country study [C41] yields similar values for leukaemia, although for solid cancers there are (statistically non-significant) indications of higher RRs than from the LSS: the ratio of RRs is 3.93 (95% CI: <0, 8.62). These values imply that the ERRs from the LSS do not markedly underestimate risks in the nuclear worker studies. There is no strong evidence for a DDREF greater than 1, although the substantial uncertainties are certainly consistent with a DDREF of 2 (or indeed ∞). As well as the statistical uncertainties, there are uncertainties relating to the fact that dose in the worker studies was measured with film badges, which, because of anisotropy in the radiation fields to which the workers were exposed, may not accurately represent whole body dose, and of course take no account of the contribution from internal emitters. Another factor that must be

**Figure V. Trends with dose in relative risk (and 90% CI) for leukaemia excluding chronic lymphocytic leukaemia in the NRRW [M12] and among the survivors of the atomic bombings in Japan [P10]**

The results for the atomic bombing survivors are based on the linear component of a linear–quadratic dose response (adapted from Muirhead et al. [M12]). The points represent estimated RRs for certain dose intervals, and the regression line is based on a fit to these data



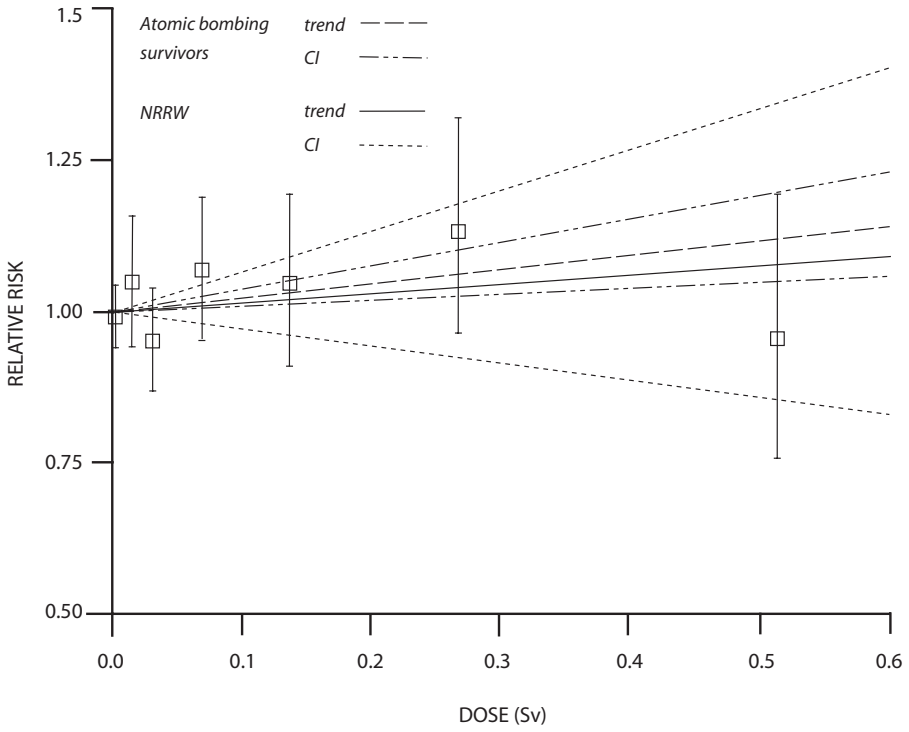

considered in comparing the worker studies and the LSS data is the radiation energy spectrum. As noted above, most of the gamma-ray energy from the two atomic bombings was in the range 2–5 MeV [R12, R20]. There is considerable variation in the radiation energy spectrum among the nuclear workforces. Even at the Sellafield site there was substantial variation in radiation energy, with some workers exposed to high-energy gamma radiation, with an energy of up to 7 MeV, although for the majority of workers most of the dose was delivered by photons with an energy in the range 0.1–1 MeV [K28]. As noted above, higher-energy gamma rays are known to be less biologically effective [N8, S31]. For example, the relatively high-energy gamma rays produced by the atomic devices used in Hiroshima and Nagasaki would be less biologically effective by a factor of about 2 than photons with an energy of 0.5 MeV [S31].

69. As an alternative to deriving values for DDREF by comparing cancer risks in groups exposed at high dose rates (such as the survivors of the atomic bombings) with those in groups exposed at lower dose rates, attempts have been made at assessing the curvature in the dose–response relationship for cancer derived from the LSS data in order to assess cancer risks at low doses [C35, L37, P1, P11, V5]. Most of these attempts use various versions of the LSS data on cancer mortality.

70. Pierce and colleagues [P11, V5] and Little and Muirhead [L37] fitted linear–quadratic and linear models to the LSS data and derived estimates of a quantity called the low-dose extrapolation factor (LDEF), which is the amount by which the low-dose (linear) slope of the linear–quadratic model is overestimated by the slope of the linear model, and so is somewhat analogous to DDREF. Pierce and Vaeth [P11] analysed the LSS Report 11 mortality data and derived values for LDEF of about 1.8 (95% CI: 1.0, 6.0) for leukaemia and about 1.2 (95% CI: <1, 3.4) for solid cancers. Vaeth et al. [V5] analysed a preliminary version of the older cancer incidence data [P4, T1] and derived values for LDEF of about 2.5 (95% CI: 1.3, 8.4) for leukaemia and about 1 (95% CI: <1, 1.4) for solid cancers. Little and Muirhead [L37] analysed the older version of the cancer incidence data [P4, T1] and derived values for LDEF of 2.47 (95% CI: 1.24, >1000) for leukaemia and 1.06 (95% CI: <1, 1.62) for solid cancers. When attention was restricted to the 0–2 Gy dose range, Little and Muirhead derived values for LDEF of 1.73 (95% CI: <1, 147.67) for leukaemia and 1.21 (95% CI: <1, 2.45) for solid cancers. The value of 2 for DDREF recommended by the ICRP is consistent with these values [I11]. For solid cancers, values of DDREF much greater than 2 would not be consistent with the LSS data. Moreover, a value for DDREF of 1 would also be consistent with these data.

**Figure VI. Trends with dose in relative risk (and 90% CI) for all malignant neoplasms other than leukaemia and lung cancer in the NRRW [M12] and among the survivors of the atomic bombings in Japan [P9]**

The results for the atomic bombing survivors are based on a linear dose response, without adjustment for dose rate (adapted from Muirhead et al. [M12]). The points represent estimated RRs for certain dose intervals, and the regression line is based on a fit to these data




### K. Thresholds and other departures from linear–quadratic curvature

71. It has been customary to model the dose–response function, $F(D)$, in fits to biological data [U5] and epidemiological data [U2, U4] by the linear–quadratic expression:

$$F(D) = \alpha \cdot D + \beta \cdot D^2 \quad (1)$$

It should be noted that this is a model for cancer induction whose parameters bear no relation to the $\alpha$ and $\beta$ values commonly used in radiotherapy to describe cell killing by fractionated radiotherapy. While the linear–quadratic dose response (with upward curvature) that is found for leukaemia is perhaps the most often employed departure from linearity in analyses of the shape of the dose–response curve for cancer in radiation-exposed groups [C35, P1, P11, S3], there are various other possible shapes for the dose–response curve. Some use has been made of exponential adjustments to the linear–quadratic term in the dose–response function, described by:

$$F(D) = [\alpha \cdot D + \beta \cdot D^2] \cdot \exp(\gamma \cdot D) \quad (2)$$

72. This form has been employed in fits to biological data [U5] and epidemiological data [B5, L29, L30, L31, S32, T21, W2]. In particular, there is evidence of cell sterilization effects in the dose response for non-melanoma skin cancer among the survivors of the atomic bombings [L30] and for leukaemia in a pooled analysis of the survivors and two medically exposed cohorts [L31]. The $\alpha \cdot D + \beta \cdot D^2$ component represents the effect of (carcinogenic) mutation induction, while the $\exp(\gamma \cdot D)$ term represents the effect of cell sterilization. In general, the cell sterilization coefficient is <0. Variant forms of the cell sterilization term, $\exp(\gamma \cdot D)$, incorporating higher powers of dose, $D$, i.e. $\exp(\gamma \cdot D^k)$ for $k>1$, are sometimes employed [L30, U5].

73. Evidence has been presented for possible hormetic or beneficial effects of low doses of ionizing radiation, whether in respect to cancer [D23, H29, M2] or other end points [M25], although these interpretations of the data have been challenged [U5]. For the class of deterministic effects defined by the ICRP [I11], it is assumed that there is a threshold dose below which there is no effect, so that, generalizing the above, the dose–response function could take the form:

$$F(D) = [\alpha \cdot [D - D_t] + \beta \cdot [D - D_t]^2] \cdot \exp(\gamma \cdot [D - D_t]) \cdot 1_{D>D_t} \quad (3)$$

74. This form of dose response assumes that the radiation-induced excess risk will be zero up until dose $D_t$, after

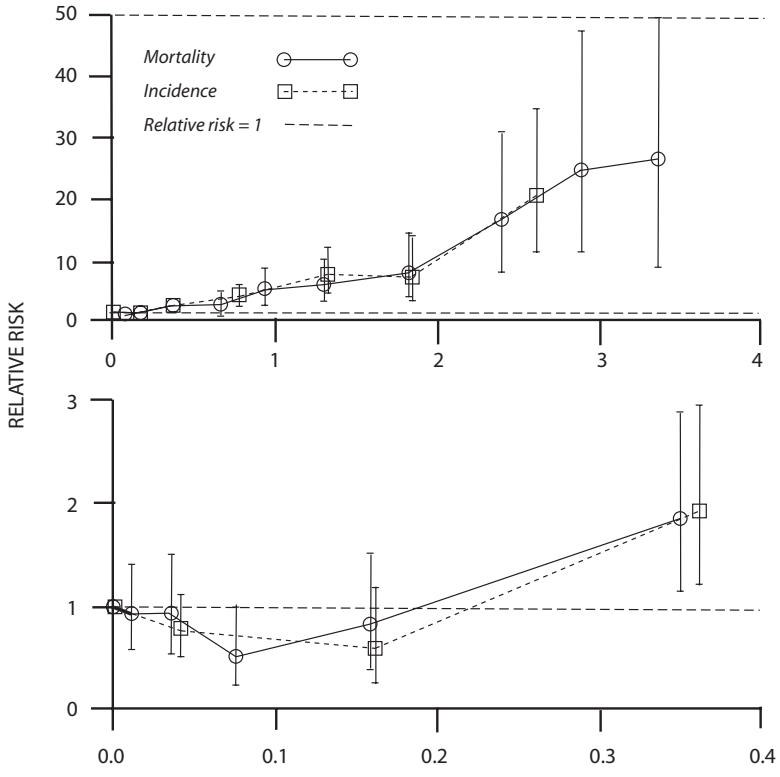
which it smoothly varies. Such a form of dose response has also been employed in analyses of brain damage and small head size among those exposed in utero to the atomic bombings at Hiroshima and Nagasaki [O3, O4]. There are a number of cancers, such as rectal cancer and non-Hodgkin's lymphoma, which have generally only been observed in excess following relatively high therapeutic doses of radiation [U2, U4]. It is possible that this reflects variations in susceptibility to radiation-induced cancer and indeed significant differences in the shape of the dose–response curve for different cancers.

75. Little and Muirhead [L29, L33, L34] fitted linear–threshold and linear–quadratic–threshold models to the LSS incidence data (for solid cancers and leukaemia), adjusting also for measurement error. There was no evidence of threshold departures from linearity in the solid cancer data, with fairly tight upper bounds (≈0.2 Sv) on the magnitude of a possible threshold. Pierce and Preston [P12] also fitted linear–threshold models to the LSS solid cancer incidence data, with an extra seven years of follow-up (to the end of 1994). Perhaps because of the extra years of follow-up data, Pierce and Preston [P12] observed a somewhat tighter upper bound of about 0.06 Sv on the possible threshold when fitting a linear–threshold model. However, Little and Muirhead [L29, L33] found evidence at borderline levels of statistical significance ($p$ = 0.04–0.05) for departures from linear–quadratic curvature for leukaemia incidence. In fits to the LSS Report 12 mortality data, Little and Muirhead [L35] found no evidence for threshold departures from linear–quadratic curvature ($p$ = 0.16) for leukaemia, and as with the incidence data there was no evidence for threshold departures from linearity for solid cancers, with fairly tight upper bounds (≈0.15 Sv) on the magnitude of a possible threshold. As Little and Muirhead [L35] document, the LSS leukaemia mortality and incidence data are fairly similar (see figure VII) (most leukaemia cases were fatal in the 1950s and 1960s). Little and Muirhead [L34, L35] concluded that the most likely explanation of the difference in findings between the leukaemia incidence and mortality data is the finer disaggregation of dose groups in the publicly available version of the mortality data compared with the incidence data (14 versus 10).

76. Similar models have also been fitted to the LSS incidence data by Hoel and Li [H30] and by Baker and Hoel [B21]. Hoel and Li [H30] did not adjust for measurement

**Figure VII. Relative risk for leukaemia mortality and incidence, derived from data on survivors of the atomic bombings in Japan, as a function of the average true bone marrow dose, with 95% CI (shielded kerma dose < 4 Gy and colon dose < 4 Sv)**

Upper panel: all data; lower panel: low-dose region of upper panel. (Reproduced from Little and Muirhead [L34, L35])



error, which may invalidate the results of their analysis, as discussed by Little [L36] and as elaborated below. Baker and Hoel [B21] fitted a variety of dose–response models, one of which allowed for a dose-dependent RBE for neutrons. The findings of Baker and Hoel [B21] were generally similar to those of Little and Muirhead [L29, L33, L34] and of Pierce and Preston [P12], the main difference being that when using the variable RBE model there was evidence for a threshold for solid cancers. As pointed out by Little [L36], there are certain methodological difficulties associated with the use of threshold models, since the asymptotic ($\chi^2$) distribution of the deviance difference statistic employed for significance tests is not guaranteed, owing to the lack of sufficient smoothness in the likelihood function [S33]. This problem is circumvented by the likelihood-averaging (regression calibration) techniques used by Little and Muirhead [L29, L33, L34, L35] and by Baker and Hoel [B21] to take account of measurement error, at least when the GSD for dose is assumed to be non-zero. $C^2$ smoothness of the likelihood is a sufficient condition that guarantees asymptotic properties of maximum-likelihood estimates [S33]. However, it is not a necessary condition, and in practice maximum-likelihood parameter estimates and uncertainties obtained without likelihood smoothing in this data set, for example those obtained using 0% GSD errors, are reasonably similar to those obtained with non-zero errors [L29].

77. One way in which epidemiological evidence for a threshold can be assessed is by examination of the lowest dose at which a statistically significant positive dose response can be detected. Pierce et al. [P1] used this approach on the LSS mortality data. It suffers from the defect alluded to above, i.e. that one is to some extent estimating the dose threshold $D_t$ from the data, and the lack of sufficient smoothness in the likelihood as a function of this parameter means that the asymptotic ($\chi^2$) distribution of associated deviance–difference statistics is not guaranteed. More refined versions of the tests performed by Pierce et al. [P1] have also been proposed [L89, P45].

78. These problems notwithstanding, this report now briefly reviews the evidence for the lowest dose at which excess cancer risk has been observed, for the most part restricting attention to the LSS data. Simple linear RR models were fitted to the LSS mortality and solid cancer incidence data [P10, P48], in which the number of cancer cases or deaths in stratum *s* and dose group *d* (with average organ dose *D*) is given by $PY_{sd} \cdot \lambda_s \cdot (1 + \alpha \cdot D)$, where $PY_{sd}$ is the number of person-years of follow-up (adjusting the cancer incidence data for migration out of the two cities). The $\lambda_s$ are stratum-specific underlying cancer rates; in all the analyses the stratification is defined by city, sex, attained age and age at exposure. These data are summarized in table 14 for various cancer sites using the latest LSS DS02 cancer mortality and solid cancer incidence data [P10, P48]. The table shows that for all solid cancers a statistically significant (2-sided $p = 0.05$) positive trend occurs over the 0–0.2 Sv dose range in the cancer mortality data, and in the 0–0.25 Sv dose range in the incidence data. For subsites of solid cancer, the lowest dose ranges for which there exist statistically significant positive dose trends are generally higher, although for colon cancer and female breast cancer the dose response also attains statistical significance over 0–0.25 Sv. There might appear to be contradiction with the previous findings of Pierce and Preston [P12], who derived an apparently statistically significant solid cancer dose response down to about 0.1 Sv in a previous follow-up of the incidence data, using the previous (DS86) dosimetry. The technique used by Pierce and Preston relied on fitting an RR model with semi-parametric dose response (RR constant within each dose interval), and with parametric adjustments for sex and age at exposure, over the full dose range. That done, Pierce and Preston smoothed the resulting RRs using a weighted moving average, taking account of the (Wald, likelihood-based) standard errors to compute uncertainty bounds. This should be contrasted with the somewhat simpler approach adopted here, in which the data set is progressively truncated, by omitting survivors who received more than a certain dose, and then simple linear RR models are fitted to the truncated data sets. In the method used here, not taking into account the variability by sex and age at exposure somewhat inflates the uncertainty in ERR coefficients, and this probably accounts for the discrepancy between these two assessments.

79. Direct epidemiological evidence exists of excess cancer risk in a number of groups exposed at low doses or low dose rates, as reviewed in a recent ICRP task group report [I25]. In particular, excess cancer risk is associated with radiation doses of the order of a few tens of milligrays from X-ray pelvimetry in the Oxford Survey of Childhood Cancers (OSCC) and in various other groups exposed in utero [H56, M16, S11]. However, these in utero studies are controversial [I33, M48], in particular because: *(a)* there is no specificity in risk; risks for all childhood cancers are increased by about 40%, implying a possible bias; *(b)* there is apparent inconsistency with the largely negative findings for the atomic bombing survivors exposed in utero [D14]; *(c)* risks are not appreciably higher in studies of data on twins [I26, M57, R46], despite the presumably much higher prevalence of pelvimetry in this group; *(d)* risks associated with pelvimetry are elevated in case-control studies, but not generally in otherwise similar cohort studies [C42, D45]; and *(e)* risk is equally elevated for tumours such as Wilm's tumour and neuroblastoma of early embryonal origin; this is implausible given that most of the radiation dose is delivered in the third trimester [B42]. The ICRP [I33] has carefully reviewed all these studies, in particular the OSCC, where it has noted a number of methodological problems, in particular possible selection and recall biases that may operate. Doll and Wakeford [D37] and Wakeford and Little [W23] also carefully reviewed the literature and concluded that most of the criticisms of these studies could be addressed, in particular the five stated above. Doll and Wakeford [D37] concluded that "there is strong evidence that low dose irradiation of the foetus in utero … causes an increased risk of cancer in childhood." However, the ICRP was more cautious and concluded that

"although the arguments fall short of being definitive because of the combination of biological and statistical uncertainties involved, they raise a serious question of whether the great consistency in elevated RRs, including embryonal tumours and lymphomas, may be due to biases in the OSCC study rather than a causal association" [I33]. Wakeford and Little estimated the ERR coefficient for childhood (<15 years of age) cancer obtained from the OSCC to be around 50 $Gy^{-1}$, leading to a risk coefficient for total incidence of about 8% $Gy^{-1}$; however, the statistical, dosimetric and modelling uncertainties in these risk estimates are considerable [W23].

80. Increased breast cancer risk has been observed among young women exposed to high cumulative doses from multiple thoracic fluoroscopic X-ray exposures, delivered in fractions that were, on average, of the order of 10 mGy [B3, H9, L5]. Increased breast cancer risk has also been observed in a study of patients given multiple X-rays as part of the diagnosis of scoliosis; doses in this study were due to conventional X-rays rather than fluoroscopic X-ray exposures [D17]. A typical chest fluoroscopic exposure given in the period between 1930 and 1950 would last about 15 s, and patients would receive 0.01–0.10 Gy [L5]. These fluoroscopic exposures were not low-dose-rate exposures (see section I.J above), although as the fluoroscopic exposures would be every two weeks for three to five years, the wide temporal separation of such fractionated low-dose exposure should theoretically result in a linear dose–response relationship directly applicable to the estimation of low-dose effects [N16, U5], as discussed in section I.J above. Excess (absolute) breast cancer risks per unit of total dose in these groups are comparable to those among survivors of the atomic bombings [L5, P3]. However, there is no comparable excess risk of lung cancer among fluoroscopy patients, even though lung doses were comparable to breast doses [D4, D6, H7]. This difference between the findings for breast and lung cancer among fluoroscopy patients suggests that there may be variation in results among cancer sites in terms of fractionation effects. However, it should be kept in mind that exposure to tobacco smoke is by far the dominant risk factor for lung cancer. It is possible that among TB patients who underwent lengthy courses of lung collapse therapy associated with high cumulative radiation dose from fluoroscopic examinations, below-average exposure to tobacco smoke might mask a radiation-related increase in lung cancer risk. As discussed in section I.J, attempts were made to control for smoking in some of the analyses, but these were based on fairly crude measures such as "ever/never" smoking [D4, H7], so that residual confounding cannot be ruled out. Nonetheless, the mean doses for smokers and non-smokers, for both men and women, were remarkably similar, and there was no difference in the percentage of smokers by lung dose over six categories of dose up to and greater than 3 Sv [H7].

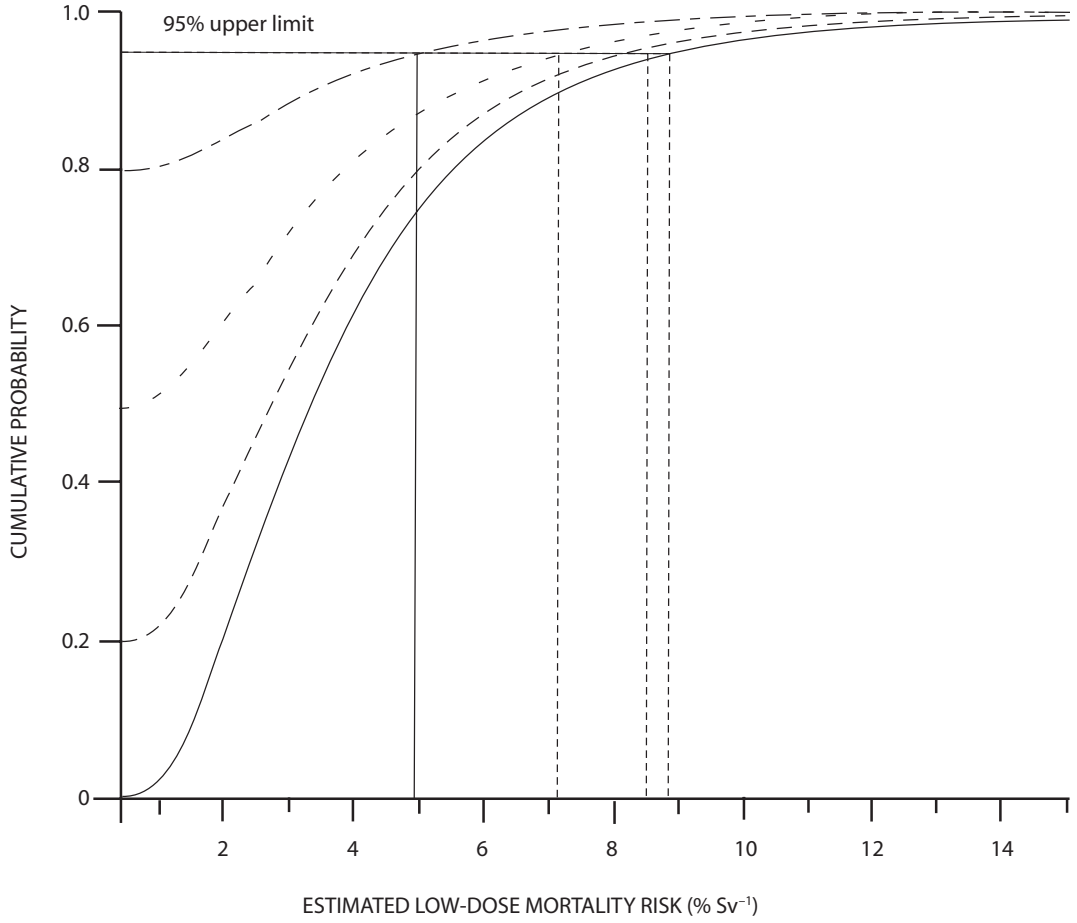
81. As discussed above, there are a number of studies of occupationally exposed persons, who generally receive low doses of ionizing radiation at low dose rates [C3, C36, C41, M12]. For example, in the IARC 15-country study [C41], average cumulative doses were 19.4 mSv, and fewer than 5% of workers received cumulative doses exceeding 100 mSv. As noted above, risks observed in these studies are generally consistent with those seen in the LSS, as well as being consistent with much lower risks.

82. Recently the ICRP has carefully reviewed the issue of possible thresholds and their effect on risk estimates ([I25], but see also [L99]). A survey of the epidemiological data indicates that, as discussed above, there are a number of groups exposed to low doses and dose rates that exhibit excess risk compatible with extrapolations from risks observed at high doses and dose rates (such as in the LSS [I25]). They present an illustrative exercise in quantitative uncertainty analysis, in which the various uncertain components of estimated cancer risk associated with low-dose, low-LET radiation exposure are combined. Attention is paid to the resulting uncertainty distribution for ERR per unit dose, with and without allowing for the uncertain possibility of a universal low-dose threshold below which there would be no radiation-related risk. Illustrative calculations demonstrate that assuming various subjective probabilities of a low-dose threshold of between 20% and 80% makes very little difference to the upper 95% confidence limit of cancer risk. Even when a low-dose threshold is assumed with 80% subjective probability, the upper 95% confidence limit of cancer risk is about 5% $Sv^{-1}$, compared with the 95% upper confidence limit of about 9% $Sv^{-1}$ if no low-dose threshold is assumed [L99] (see figure VIII). In the example used, which considers risk from all cancers combined, including leukaemia but not non-melanoma skin cancer, the major contributors to uncertainty in the overall risk factor are: statistical variation in the estimated ERR at 1 Gy for the population of survivors of the atomic bombings; subjective uncertainty with respect to the DDREF to be applied at low doses and dose rates; and the postulated uncertainty concerning the existence of a universal threshold at some dose above that for which the calculation was being made. The ICRP concluded that, unless the existence of a threshold was assumed to be virtually certain, the effect of introducing the uncertain possibility of a threshold was equivalent to that of an uncertain increase in the value of DDREF, i.e. a variation on the result obtained by ignoring the possibility of a threshold [I25].

### L. Effect of age at exposure, latency and time since exposure

83. When estimating population cancer risks from epidemiological data, one of the principal uncertainties is due to the fact that few radiation-exposed cohorts have been followed up to the end of life of all study subjects. For example, 55 years after the atomic bombings of Hiroshima and Nagasaki, 45% of the survivors were still alive [P10]. In attempting to estimate lifetime population cancer risks, it is therefore important to predict how risks might vary as a

**Figure VIII. Effect on the probability distribution of excess lifetime risk per unit dose of assuming the possible existence of a low-dose threshold, with probability $p = 0.2$, 0.5 or 0.8 (reproduced from Land [L99])**




function of time after radiation exposure, in particular for that group of people for whom the uncertainties in projecting risk to the end of life are most uncertain, namely those who were exposed in childhood.

84. Analyses of solid cancers in the LSS and other exposed groups have found that the radiation-induced excess risk can be approximately described by a constant RR model [I11, U2]. The time-constant ERR model assumes that if a population is irradiated, then, after some latent period, there is an increase in the cancer rate, the excess rate being proportional to the underlying cancer rate in a non-irradiated population. For leukaemia, this model provides an unsatisfactory fit to observations, and consequently, for a group of similar malignancies, a number of other models have been used, including one in which the excess cancer rate resulting from exposure is assumed to be constant rather than proportional to the underlying rate, i.e. the time-constant EAR model [U6].

85. For solid cancers there is a large body of evidence that ERRs diminish with increasing age at exposure [L51, L52, U2]. In particular, this pattern of risk is observed in the LSS data for both solid cancer incidence and mortality, for many solid cancer sites and for all solid cancers as a whole [P1, P10, P48, T1] (see also figure X in section II below), and in a variety of other groups (e.g. radiotherapy patients) [L51, L52]. The pattern of variation of EARs with age at exposure is generally the reverse of this. For constant attained age the EAR for solid cancers or solid cancer mortality increases with increasing age at exposure, as seen in the LSS [P10, P48] (see also figure X).

86. For leukaemia, ERRs also generally diminish with increasing age at exposure [L51, U2]. In particular, this pattern of risk is observed in the LSS data for both solid cancer incidence and mortality [P1, P4, P10], as well as in a variety of other groups (e.g. radiotherapy patients) [L51, L52, U2]. The pattern of variation of EARs with age at exposure is generally the reverse of this. EAR increases with increasing age at exposure, whether for constant attained age or constant time since exposure, in both the incidence and the mortality data sets of the LSS [P4, P10]. Patterns of variation of risk by leukaemia subtypes are not so well understood, in part because of a lack of statistical power. In a combined analysis of three cohorts—the LSS cohort (using incidence data) [P4], the United Kingdom ankylosing spondylitis patients [W2] and a group of women treated

for cervical cancer [B5]—different patterns of variation of risk were seen for the three main radiogenic subtypes [L31]. For acute myeloid leukaemia (AML) and chronic myeloid leukaemia (CML), the ERR was described by negative powers of years since exposure (–0.9 and –2.7, respectively), implying no extra variation with age at exposure. However, for acute lymphoblastic leukaemia (ALL), the ERR was described by a negative power (–6.3) of attained age, implying a reduction of risk with increasing age at exposure [L31].

87. To some extent related to these issues is that of the "latency period". This may be defined as the minimum period following exposure after which an excess risk is detectable, but is often taken to be the minimum period following exposure after which a statistically significant excess risk is detected. As such, it will obviously depend on the magnitude of the dose administered and on other factors, e.g. the magnitude of the ERR and the underlying cancer rate. For this reason, the latency period may not be a very useful quantity. Bearing this out, certain groups exposed to radiation due to the Chernobyl accident [K52] and other (medically exposed) cohorts [L98] provide evidence of shorter latency periods when exposures are higher. Excess solid cancer mortality is statistically significant for the LSS cohort already in the period 5–10 years after exposure [P10]. For example, for the period 1950–1952, the ERR per unit colon dose (with 35% GSD errors), calculated using a stratified linear RR model, is 0.41 (90% CI: –0.01, 0.99) $Sv^{-1}$; for 1950–1955, the ERR is 0.38 (90% CI: 0.07, 0.75) $Sv^{-1}$; and for 1950–1960, the ERR is 0.24 (90% CI: 0.05, 0.45) $Sv^{-1}$. In other words, there is evidence of excess risk within 10 years of exposure, and a suggestion of an excess (i.e. not quite statistically significant) within 7 years. An excess of thyroid cancer about 5 years after the Chernobyl accident has been observed among residents of heavily contaminated areas of the Ukraine [S90]. Given that thyroid doses due to the Chernobyl accident averaged 1 Gy or more to some groups (e.g. the 1986 evacuees in Belarus and Ukraine [C50, U2]) compared with the much lower doses (e.g. about 0.2 Sv) in the LSS [P48], the apparent discrepancy in latency period is easily explained. Latency periods of much longer than 10 years are statistically inconsistent with the LSS breast cancer data [L78]. For solid cancers, excess risk is manifest between 5 and 10 years after exposure in a number of therapeutically irradiated groups [L51, W8]. However, BEIR VII [C37] presents evidence from various studies that indicate shorter latency periods for solid cancers, and it assumes a latency period of 5 years for solid cancers when estimating cancer risks for the United States population.

88. Excess leukaemia risks within 5 years of exposure have been observed in the ankylosing spondylitis cohort in the United Kingdom [D53], and there are suggestions of excess leukaemia risks in Hiroshima and Nagasaki within 5 years of the bombings, albeit based on an open city sample that includes some people not resident in the cities at the time of the bombings and with no estimates of dose [F18].

89. For those exposed in childhood, there is evidence that solid cancer ERRs may eventually decrease with increasing time after exposure [L16, L53, L90], although this has not been seen in all such groups [S7]. For those exposed in adulthood, risks are more approximately constant over time [L51], although again exceptions have been seen [W8]. As will be seen later (in table 45), the optimal generalized RR models for solid cancers, fitted to the latest LSS mortality data [P10], are ones assuming that—as a function of dose, $D$, age at exposure, $e$, and years since exposure, $t$—the $ERR = \alpha \cdot D \cdot t^{1.0} \cdot [t + e]^{-2.6}$, or that the $ERR = (\alpha \cdot D + \beta \cdot D^2) \cdot t^{1.0} \cdot [t + e]^{-2.6}$. This implies in either case that the ERR increases up until approximately $0.6 \cdot e$ years after exposure, after which it decreases. In particular, this means that the RR decreases sooner for those exposed in childhood than for those exposed in adulthood, which is consistent with observations from the LSS and studies of other irradiated groups.

90. Solid cancer EARs generally show marked increases over time for all ages at exposure. For example, this pattern is observed in the latest LSS mortality data [P10] (see table 45 and figure X), and also for many solid cancer sites in the incidence data [P48] (see tables 47–58). As can be seen from table 45, the optimal generalized EAR models for solid cancers, fitted to the latest LSS mortality data [P10], are ones assuming that—as a function of dose, $D$, age at exposure, $e$, and years since exposure, $t$—the $EAR = \alpha \cdot D \cdot t^{0.7} \cdot [t + e]^{2.4}$, or that the $EAR = (\alpha \cdot D + \beta \cdot D^2) \cdot t^{0.7} \cdot [t + e]^{2.3}$.

91. The ERRs for leukaemia generally peak very shortly after exposure, consistent with the short latency period for this cancer, and then decrease with increasing time after exposure. This pattern is observed in the LSS incidence and mortality data [L29, P4, P10], in the United Kingdom ankyosing spondylitis mortality data [W2], in the international cervical cancer case-control study [B5] and in a variety of other groups (generally radiotherapy patients) [L51, L52, U2]. Patterns of variation of risk over time by leukaemia subtype are not so well understood, in part because of a lack of statistical power. The combined analysis of the three (LSS, United Kingdom ankylosing spondylitis and international cervical cancer) cohorts discussed above documented different patterns of variation of risk over time for the three main radiogenic subtypes (AML, CML and ALL) [L31]. For AML and CML, the ERR was described by a negative power of years since exposure, with a more strongly negative exponent (–2.7) for CML than for AML (–0.9). For ALL, the ERR was described by a negative power (–6.3) of attained age, implying a very marked reduction of risk with increasing time after exposure [L31]. As can be seen from table 46, the optimal generalized RR models for leukaemia, fitted to the latest LSS mortality data [P10], are ones assuming that—as a function of dose, $D$, age at exposure, $e$, and years since exposure, $t$—the $ERR = \alpha \cdot D^2 \cdot [t + e]^{-1.6}$, or that the $ERR = (\alpha \cdot D + \beta \cdot D^2) \cdot [t + e]^{-1.6}$. This implies in either case that the ERR decreases with increasing time after exposure. In interpreting this it should be noted that the first 5.1 years of follow-up are

missing in the LSS data set [P4, P10], so that the early rapid increase in leukaemia ERR is probably missing.

92. The pattern of variation of leukaemia EAR is generally similar, with a pronounced decrease in EAR with increasing time after exposure. This pattern is observed in the LSS incidence and mortality data [P4, P10], at least for all leukaemia subtypes together. Patterns of variation of EAR over time by leukaemia subtype are more complex. In the LSS incidence data there are indications that the EAR for AML increases over time in the group with the oldest (>40) age at exposure, although the EAR decreases with time in groups with younger ages at exposure [P4]. As can be seen from table 46, the optimal generalized EAR models for leukaemia, fitted to the latest LSS mortality data [P10], are ones assuming that—as a function of dose, $D$, and years since exposure, $t$—the $EAR = \alpha \cdot D^2 \cdot t^{-0.7}$, or that the $EAR = (\alpha \cdot D + \beta \cdot D^2) \cdot t^{-0.6}$. This implies in either case that the EAR decreases with increasing time after exposure, but as mentioned above, the problems that result from the missing first 5.1 years of follow-up in the LSS data set [P4, P10] should be noted.

# II. NEW OR UPDATED STUDIES

## A. Survivors of the atomic bombings in Japan (LSS)

93. Since the UNSCEAR 2000 Report was issued, the solid cancer mortality experience of the LSS has been updated by another 10 years, to the end of the year 2000. There have been two substantial reports on LSS mortality, the first updating follow-up to the end of 1997 [P9] and the second taking follow-up to 2000 [P10]. The first report described an increase in the number of deaths due to solid cancers (in the group with a shielded kerma dose of under 4 Gy) from 8,040 in the year 1990 to 9,335 in the year 1997, an increase of 16% [P9]. The second report described an increase in the number of deaths due to solid cancers to 10,127 in the year 2000, a further increase of 8% over the previous follow-up [P10].

94. The major change made in the latest LSS mortality report [P10] is the use of the new set of dose estimates for the survivors of the atomic bombings, the DS02 dosimetry [R12]. This differs slightly from the DS86 system, for both neutron and gamma doses, generally by no more than 20% in the range up to 1500 m from the two hypocentres, where survivors received the highest doses [C13, R12]. Analyses of the LSS data for solid cancer and leukaemia mortality using the new dosimetry indicate that estimates of cancer risk might fall by about 8% as a result, with no appreciable change in the shape of the dose–response curve or in the age and time patterns of excess risk [P10]. A few highlights of the report can be summarized in selected figures from it. Of the total of 10,127 deaths due to solid cancers in the cohort (considering all survivors, including those with a shielded kerma dose of greater than 4 Gy), about 5% (479) would be attributable to radiation exposure [P10].

95. The excess risk of solid cancer appears to be linear in dose, even in the dose range 0–150 mSv. Figure IX plots the dose–response data for the ERR, giving the best-fitting linear dose–response slope and showing a smoothed non-parametric dose–response fit to the data points along with error bounds on the non-parametric curve. In view of the fact that the upper and lower confidence bounds around the smoothed curve are drawn at one standard error, most of the points and the fitted regression line would be within 95% bounds (which would be about twice the width). Hence there is no indication of upward curvature below 0.5 Gy. The dose response appears to be slightly steeper up until 0.2 Gy, as described previously by Pierce et al. [P1]. They commented that there might possibly be a differential bias in ascertainment of death among low-dose survivors compared with higher-dose survivors, which would account for this downward curvature in the dose response in this region.

**Figure IX. Solid cancer dose–response function (taken from Preston et al. [P10])**

The left panel presents dose-category-specific ERR estimates based on DS02 (circles) and DS86 (triangles) with locally weighted regressions. The right panel displays the DS02 dose response for a low dose range together with linear fits based on dose ranges of 0–1 Sv and 0–2 Sv and the linear–quadratic fit based on the 0–2 Sv range. These curves fit the data about equally well

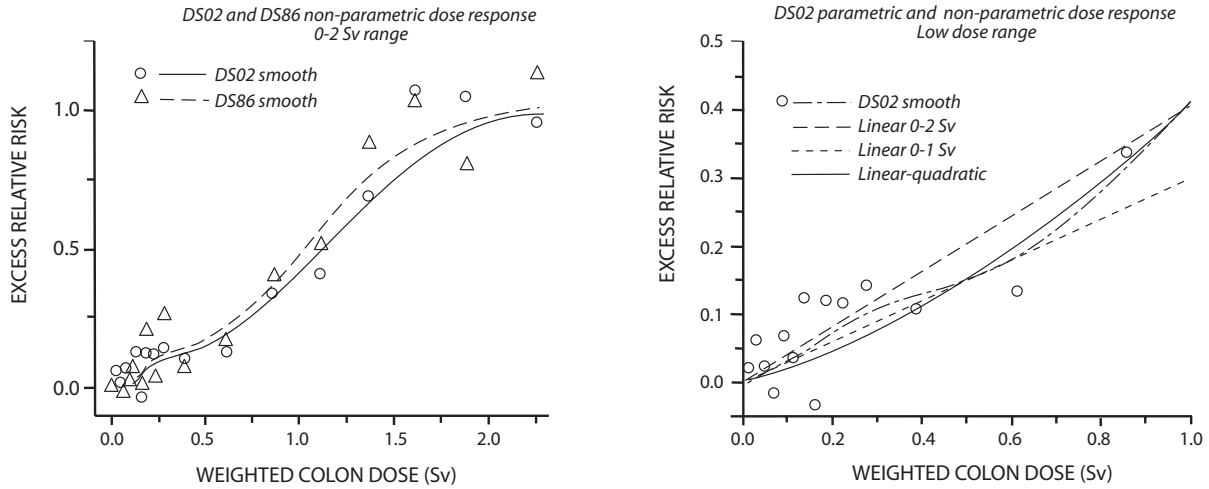
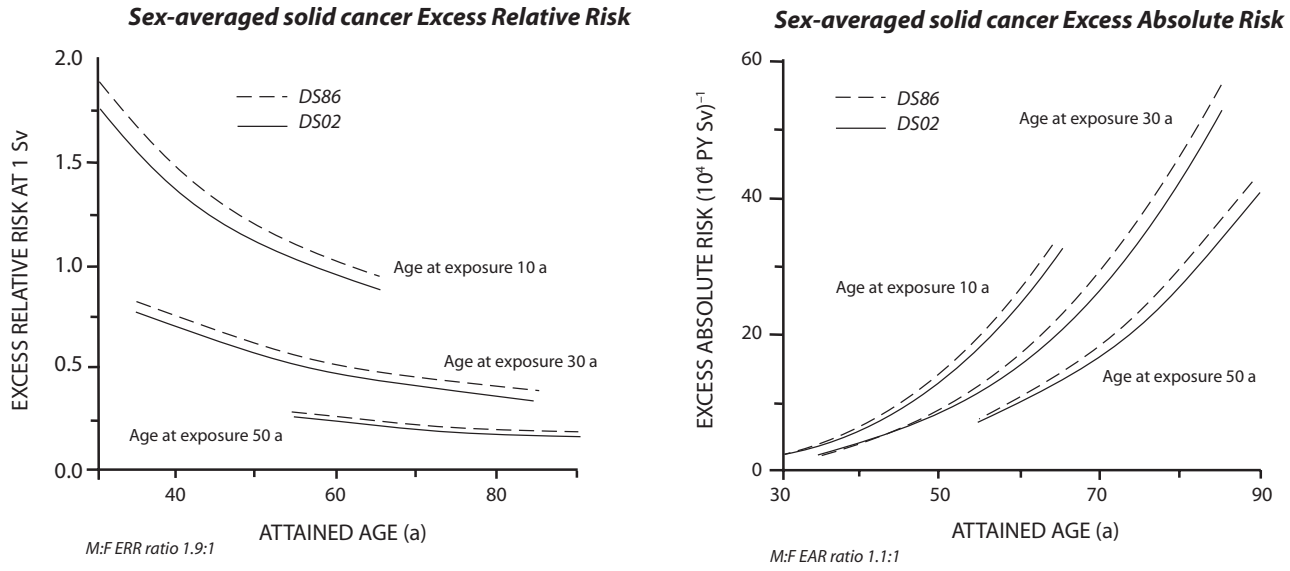


**Figure X. Primary descriptions of the excess risk of solid cancer (reproduced from Preston et al. [P10])**
The left panel presents fitted sex-averaged ERR estimates using both DS86 (dashed lines) and DS02 (solid lines) doses, for ages 10, 30 and 50 at exposure. The right panel presents fitted EAR estimates for the same dose groups




96. The extended follow-up continues to confirm that the ERR per unit dose is modified both by age at exposure and (more weakly) by attained age (i.e. age at observation). Figure X shows the marked trend of decreasing ERR for solid cancer with increasing age at exposure; this is highly statistically significant ($p < 0.001$) (see appendix D, table D1). After adjustment for age at exposure, there is evidence at borderline levels of statistical significance for a decline in the solid cancer ERR with increasing attained age ($p = 0.04$) (table D1). However, if EAR models are fitted instead, the EAR per unit dose increases with attained age and with age at exposure, both of these effects being highly statistically significant ($p < 0.001$ and $p = 0.002$, respectively) (table D1). After adjustment of EAR for attained age, however, EAR decreases with increasing age at exposure, as can be seen in figure X. For those exposed before age 20, the estimated number of radiation-related deaths has approximately doubled in each of the last three decades. The ERR and EAR estimates are greater for women than for men, and for ERR this difference is statistically significant ($p < 0.001$) (table D1). For EAR, without adjustment for time since exposure and age, there is also evidence of a difference in EAR between the sexes ($p = 0.003$) (table D1). However, after adjustment for time since exposure and attained age, the difference in EAR estimates between the sexes is no longer statistically significant ($p > 0.5$). This suggests that the greater estimate of ERR for women may occur because the underlying cancer rates in Japan are lower for women than men.

97. At present the analysis of cancer mortality using DS02 dose estimates has been conducted only for solid cancers and leukaemia [P10]. An evaluation for more detailed cancer end points was conducted in the previous follow-up, using DS86 dose estimates [P9]. Figure XI shows the best estimates of ERR for a number of solid tumour sites taken from this earlier report [P9]. The numerical values corresponding to these estimates and their confidence intervals are given in the respective tables of this annex for these tumour sites. It is notable that analyses showed that the risk estimates for nearly all the tumour types were generally compatible with the estimate for solid cancers as a whole, namely an ERR of 0.47 (90% CI: 0.37, 0.57) $Sv^{-1}$. The ERRs for breast cancer and lung cancer have somewhat higher values, while the ERRs for cancers of the uterus and pancreas have lower values, as shown in figure XI [P9]. Nevertheless, the variation in the ERRs among the 14 solid cancer sites depicted is statistically significant ($\chi^2_{13} = 28.8$, $p = 0.01$). The largest contribution to the $\chi^2$ heterogeneity statistic is from cancer of the uterus (6.0) followed by cancer of the pancreas (4.6).

98. The solid cancer incidence data have recently been reanalysed using the DS02 dosimetry [P48]. This extends the follow-up to 1998 from the previous 1994 follow-up of these data [P12], resulting in a total of 18,645 cases, 13,454 of which were among people within 10 km of the respective hypocentres at the time of bombing, for whom doses were estimated using the DS02 dose assessment methodology. (It should be noted that these numbers differ from those given in table 19 because survivors with doses of less than 0.005 Sv are omitted from all of tables 19–44.) By comparison, the previous follow-up had 11,455 cases among people within the 10 km range [P12]. Section IV of this annex presents evaluations of population cancer risks for a variety of populations using risk models derived from these latest mortality and incidence data sets [P10, P48].

### B. Mayak worker study

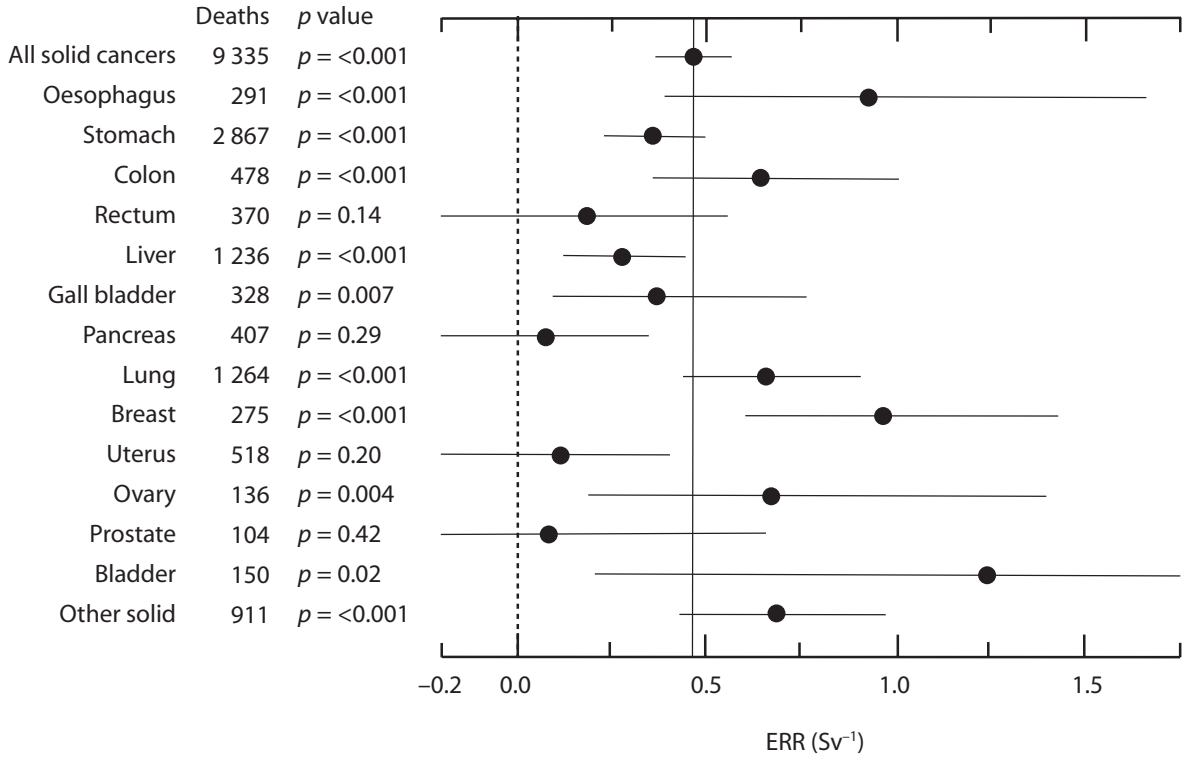
99. Major new reports are available concerning lung and liver cancer risks for workers at the Mayak nuclear complex in relation to both external radiation and plutonium exposure, and these reports are discussed in the sections below for the respective organ sites [G2, G12]. The research is especially important in that it is the only study that has a large enough number of persons with moderate to high plutonium exposures to be informative regarding the health effects of plutonium exposure. The dosimetry is being improved [K23, K24, R2], and the first overall assessment of cancer end points has appeared [S28], albeit only in relation to external dose. Internal doses have been calculated for only a few organs. Shilnikova et al. [S28] studied cancer mortality among all the approximately 21,500 people who worked at the Mayak nuclear complex between 1948 and 1972. This included workers in the nuclear reactor complex (4,396 workers), the radiochemical plant (7,892 workers), the plutonium production plant (6,545 workers) and two auxiliary plants (2,724 workers), the water treatment facility and the mechanical repair plant. The latter two groups had relatively low radiation exposures. The average cumulative external dose among those monitored for external radiation exposures was 0.8 Gy. About 24% of the cohort were women, and their mean cumulative dose was similar to that of the men. Workers in the radiochemical and plutonium production facilities had a potential for significant internal exposures from inhaled plutonium ($^{239}$Pu) aerosols as well as from external gamma radiation. Approximately one third of those potentially exposed to plutonium were monitored for plutonium exposure. Among those monitored, the mean body burden was 2.1 kBq, considerably higher than body burdens in other worker series in the United Kingdom or the United States.

100. The follow-up until 1997 of the workers has been of good quality: only 10% of the entire group have been lost from the follow-up, and the cause of death is documented for 97% of the deceased. The workers have been followed for an average of roughly 40 years. There were 7,067 deaths in all, including 1,730 due to solid cancers and 77 due to leukaemia (66 excluding chronic lymphocytic leukaemia (CLL)). The largest numbers of cancer deaths were due to cancer of the lung (569) and of the stomach (308). The deaths due to solid cancers included 668 deaths from cancers in the organs of primary plutonium deposition (569 lung, 67 liver and 32 skeletal cancers).

101. The dose–response analyses for external gamma radiation took into account exposures to plutonium, using measured values when available or an ordered score

**Figure XI. Estimates of the site-specific solid cancer ERR with 90% CIs and 1-sided *p*-values for testing the hypothesis of no dose response**

Except for sex-specific cancers (breast, ovary, uterus and prostate), the estimates are averaged over both sexes. All estimates and *p*-values are based on a model in which the effects of age at exposure and of attained age were fixed at the estimates for all solid cancers as a group. The dotted vertical line at 0 corresponds to no excess risk, while the solid vertical line indicates the sex-averaged risk for all solid cancers (reproduced from Preston et al. [P9])



judging the potential for plutonium exposure when measurements were not available. For total solid cancers, the ERR estimate for external exposure (adjusted for plutonium exposure) was 0.15 (90% CI: 0.09, 0.20) $Gy^{-1}$. However, it showed a downturn at higher doses (concave upward curve). The addition of a quadratic component to the fit produced an estimate for the linear component of the ERR of 0.30 (90% CI: 0.18, 0.43) $Gy^{-1}$, twice the simple linear estimate of 0.15 (90% CI: 0.09, 0.20) $Gy^{-1}$ [S28].

102. Even after adjusting for plutonium exposure, the external gamma risk estimate for lung, liver and skeletal cancers combined was greater than that for other cancers. This may be because plutonium deposition could only partially be adjusted for by using the surrogate exposure measure. The linear ERR estimates were 0.30 (90% CI: 0.18, 0.46) $Gy^{-1}$ for lung, liver and skeletal cancers, and 0.08 (90% CI: 0.03, 0.14) $Gy^{-1}$ for other solid cancers. For both groups of cancers, there were suggestions of concave upward curvature, such that the linear terms in linear–quadratic models of dose response were approximately twice those from the simple linear models [S28]. An evaluation of effect modifiers on radiation risk showed no difference by age or by time since exposure, but did show a significant decline in risk with older age at hire. The limited data available suggested that smoking was not a major confounding factor for the radiation effect in this study.

103. There was an approximately 40% excess mortality for leukaemia excluding CLL. The estimated ERR was 0.99 (90% CI: 0.45, 2.12) $Gy^{-1}$. There was a suggestion of concave upward curvature, but it was not statistically significant ($p = 0.1$). There was a strong temporal effect, such that the risk from doses received in the most recent 3–5 years was observed to be more than 10 times that from doses received more than 5 years earlier.

104. The risk estimates are somewhat lower than those from the LSS cohort, but the authors cautioned that any comparison should be regarded as tentative in view of the dosimetric uncertainties for the Mayak cohort. Lung doses due to plutonium are extremely high for this cohort, so high that in some cases fibroses developed. It appears that subjects receiving higher doses were more often autopsied than those receiving lower doses; therefore this group may have had better ascertainment of causes of death. Given these factors, it is difficult at present to compare the results of this study with others.

### C. Techa River study

105. The dosimetry and epidemiological procedures are being improved for the study of persons exposed to effluents of the Techa River in the Russian Federation [D8, D22, K5, K6]. Internal doses have been estimated from autopsy samples collected from 1951 onwards (i.e. from very close to the time of maximum exposure in the early 1950s), from in vivo beta measurements in teeth from 1959 onwards, and from a large number of whole-body-counter (WBC) measurements of $^{90}Sr$ based on bremsstrahlung from the decay of $^{90}Y$ [D22]. About half the original Techa River cohort has such individual measurements [D22]. Internal doses for this cohort were estimated by scaling $^{90}Sr$ intakes for a reference village (Muslyumova) by the average WBC-estimated $^{90}Sr$ skeletal body burdens in other settlements, and similarly for other shorter-lived radionuclides, giving what are fundamentally age-specific village-level internal dose estimates. External doses were computed on the basis of measurements made near the shoreline and in individual villages, and on the basis of estimates of radionuclide transport from the site of release [D22]. Estimates of annual village-level mean doses were computed on the basis of details on the distribution of distances of houses from the shoreline within each village. Dose estimates for cohort members were individualized by taking into account factors such as their residence history, length of follow-up and age. An updated dosimetry system, TRDS-2000 [D22], was developed several years ago. Internal doses from $^{90}Sr$, which accounts for most of the red bone marrow dose received by this cohort, do not change markedly using the TRDS-2000 dosimetry system [D22, K6]. There is much more change in the external dose estimates, which are generally lower using TRDS-2000 [D22]. While some questions have been raised about the external dose component of TRDS-2000 [J5, M22], dose estimates have been validated on a village level using physical measurements on bricks [J5]. A recent review of the system [B66] suggested that the basic methodology was sound, although the reviewers indicated that the values of risk estimates using the system should be considered preliminary.

106. The first reports on health effects using TRDS-2000 have appeared [K49, K50, O2], and the preliminary risk estimates provide evidence of increased solid cancer and leukaemia risks following protracted low-dose exposures. There are, however, likely to be changes to the risk estimates from this cohort associated with the fact that, as indicated above, the dose estimates are based on individualized village-level mean radionuclide intake and external exposure estimates. While genuine individual doses are clearly preferred, using the individualized dose estimates probably results in Berkson errors. In general, Berkson errors result in little, if any, bias in the dose–response estimates, but rather lead to a reduction in the statistical power to detect an effect if it exists.

107. The patterns of variation of risk for solid cancer in this cohort are unusual, with indications that ERR increases both with age at first exposure (2-sided $p = 0.08$) and with attained age (2-sided $p = 0.03$) [K50]. These patterns are not observed for leukaemia, although there is a suggestion of an increase in ERR with increasing age at first exposure (2-sided $p = 0.10$). Such patterns are the reverse of what is observed in the cancer mortality data for the survivors of the atomic bombings [P9, P10] and in many other radiation-exposed groups [U2]. The efforts currently under

way to provide increasingly individualized dose estimates and to improve mortality and morbidity ascertainment should make this cohort more informative regarding cancer risks at low dose rates.

108. A nested case-control study of leukaemia risk has been performed using incidence data for this cohort, based on the older TRDS96 dosimetry system [O13]. There are a somewhat larger number of cases (83) than from the recent mortality data [K50] (49 non-CLL, 12 CLL), although only 50 of these cases are of known cell type, and 20 of these 50 cases are CLL. The results confirmed an increase in risk with red bone marrow dose, for both internal and external exposure. No increase in risk was observed with age at the time of maximum releases.

### D. Semipalatinsk weapons test site fallout

109. To date there have been a number of publications about dosimetry [G4, S10] and health follow-up [G7, S9] in populations in Altai (Russian Federation) and Kazakhstan exposed to radioactive fallout from the nuclear weapons tests at Semipalatinsk, although only the recent report of Bauer et al. [B58] assesses health effects in relation to received dose. The cohort consists of inhabitants of 10 exposed villages near the Semipalatinsk test site (STS) and of six comparison villages some hundreds of kilometres distant from the STS. For both exposed and comparison groups, persons had to have been born before 1961 and to have been permanently resident in one of the villages. Dose reconstruction for the exposed subcohort is based on historical data for levels of radionuclides in food and the environment and on semi-empirical models for radionuclide accumulation and metabolism. Doses due to radionuclide ingestion and inhalation were estimated for the thyroid (due to $^{131}$I), the whole body (due to $^{137}$Cs) and bone marrow (due to $^{90}$Sr). Most internal dose was due to $^{131}$I. For the comparison group, settlement-specific dose estimates could not be obtained, so a per caput cumulative dose of 20 mSv due to fallout was assigned to all persons. Even within the exposed group the doses were estimated for subgroups according to their age at main exposure and settlement, so that, as constituted at present, the study is fundamentally an "ecological" one. The possibilities of bias in such studies are well known [G13, P15]. The extent of variation of dose within each settlement is not clear, although there is certainly substantial variation (by at least three orders of magnitude) of, for example, thyroid dose over time [G4]. Hence substantial "ecological bias" cannot be discounted.

110. Bauer et al. present two sets of analyses: those internal to the 10 exposed villages, and those for both exposed and comparison villages [B58]. Results are similar for both sets, although excess risks tend to be higher if the full cohort is used rather than only the exposed group. Because of deficiencies in the dosimetry for the comparison group, the Committee has concentrated on results internal to the exposed group. Bauer et al. observed elevated risks that were statistically significant for all solid cancers (ERR = 0.81 (95% CI: 0.46, 1.33) Sv$^{-1}$), stomach cancer (ERR = 0.95 (95% CI: 0.17, 3.49) Sv$^{-1}$) and lung cancer (ERR = 1.76 (95% CI: 0.48, 8.83) Sv$^{-1}$) [B58]. The ERR was statistically significantly increased with increasing age at exposure ($p < 0.0001$). Such patterns are the reverse of what is observed in the cancer mortality data of the survivors of the atomic bombings [P9, P10] and of many other radiation-exposed groups [U2]. Taken together with the generally higher ERR for solid cancers in this cohort compared with that observed in the atomic bombing survivor data, again the reverse of what might be expected following protracted exposure, this suggests that "ecological bias" may be operating preferentially in groups with older ages at exposure.

### E. International worker study

111. Following an earlier pooled analysis of data on radiation workers at selected sites in three countries [C3, I2], a larger international collaborative study has been conducted based on workforces from 15 countries working in any of 154 nuclear facilities, numbering 407,391 workers monitored for external photon (X and gamma) radiation with personal dosimeters [C41]. This study, which included most of the cohorts included in the earlier three-country study [C3, I2], has attracted considerable attention, including a substantial editorial by Wakeford [W37]. The study excluded 190,677 workers because they had not been employed in one or more of the facilities for at least one year, or because they had not been monitored for external exposure, or because they had potential for substantial exposure from internal emitters or neutrons (amounting to more than 10% of the effective dose). The study followed mortality in the cohort, and accumulated 5.2 million person-years of follow-up. The average individual effective dose was 19.4 mSv, with 90% of the workers receiving cumulative doses of less than 50 mSv and with fewer than 0.1% of the workers receiving doses of more than 500 mSv. There were 6,519 deaths from cancer excluding leukaemia, and 196 from leukaemia excluding CLL.

112. Cardis et al. estimate the ERR for cancers excluding leukaemia to be 0.97 (95% CI: 0.14, 1.97) Sv$^{-1}$, for all solid cancers to be 0.87 (95% CI: 0.03, 1.88) Sv$^{-1}$ and for leukaemia excluding CLL to be 1.93 (95% CI: <0, 8.47) Sv$^{-1}$ [C41]. As noted in table 13, while the difference from the LSS risks in a comparable group (male, age at exposure 20–60 years) is not statistically significant, there are indications that the solid cancer risks observed are 4 times higher than those in the LSS. As pointed out by Wakeford [W37], since the worker risks relate to exposure at low dose rates, a DDREF of 2 might be indicated [I11] (see section I.J above), so that the true discrepancy with LSS solid cancer risks may be about a factor of 8, but with very wide confidence limits. The ERR for solid cancer is strongly

influenced by that for lung cancer, 1.86 (95% CI: 0.26, 4.01) $Sv^{-1}$. The ERR for cancers excluding leukaemia, lung and pleural cancers is 0.59 (95% CI: –0.29, 1.70) $Sv^{-1}$ [C41]. However, smoking-related cancers other than lung cancer exhibit an ERR of 0.21 (95% CI: <0, 2.01) $Sv^{-1}$. Set against this, the ERR for non-malignant respiratory disease is 1.16 (95% CI: –0.53, 3.84) $Sv^{-1}$ and that associated with chronic obstructive bronchitis and emphysema is 2.12 (95% CI: –0.57, 7.46) $Sv^{-1}$, both of these groupings of diseases that are related to smoking. As Cardis et al. indicate, "Taken together, these findings indicate that a confounding effect by smoking may be partly, but not entirely, responsible for the estimated increased risk for mortality from all cancers other than leukaemia" [C41]. Therefore caution is suggested in interpreting the study results.

113. As noted by Wakeford [W37], the Canadian data have "a surprisingly large influence on the ERR for all cancers other than leukaemia". Indeed, although the Canadian data contribute 400 deaths from cancers other than leukaemia (6% of the total deaths from this cause), and notwithstanding the fact that the Canadian workers have an average individual effective dose (19.5 mSv) that is virtually the same as the full cohort (19.4 mSv), removing the Canadian cohort results from the estimation of solid cancer ERR produces a value of 0.58 (95% CI: –0.22, 1.55) $Sv^{-1}$, i.e. a reduction of 40% from the overall central estimate value. This estimate is still larger than the corresponding estimate from the LSS data, although it is no longer statistically significant [C41]. The fact that this study has such a large influence on the results, given the small size (in terms of relative numbers of deaths, person-years of follow-up, person-dose (that is to say, the sum of the cumulative dose per person over the cohort)) of the Canadian cohort, appears to reflect the low precision in the findings from the other cohorts. Figure 2 in the paper [C41] shows that the Canadian cohort has a solid cancer ERR of >6 $Sv^{-1}$ with a lower 97.5% centile confidence limit of >2 $Sv^{-1}$. A previously published study of Canadian nuclear workers [Z6] gave a lower risk estimate for solid cancers (ERR = 2.80 (95% CI: –0.038, 7.13) $Sv^{-1}$), of only borderline statistical significance ($p$ = 0.054). Detailed analyses have been conducted aimed at understanding the apparent differences in risk estimates for the Canadian nuclear worker cohort between Zablotska et al. [Z6] and the 15-country study [C41]. These analyses show that the difference is related to the exclusion of Ontario Hydro workers from analyses of solid cancers in the latter study, owing to the lack of information on socio-economic status (SES) for this group of workers. Several studies of radiation workers (e.g. [C3, M12]) have shown that both solid cancer risk and occupational radiation dose are related to SES, and hence SES is a confounding factor. All other differences between references [Z6] and [C41] in analytical approaches, dosimetric quantities and definition of study populations had very little impact on the results [E12]. In the Canadian National Dose Registry, which includes a large number of other personnel (e.g. medical and dental radiographers) not included in the 15-country study, the ERR for cancers other than leukaemia among males was also large, 2.5 (90% CI: 1.1, 4.2) $Sv^{-1}$ [S8], as was that for mortality from all cancers among males, 3.0 (90% CI: 1.1, 4.9) $Sv^{-1}$ [A8]. However, whereas many non-cancer causes of death (including infectious and parasitic diseases, and accidents) were correlated with dose in analyses of the Canadian National Dose Registry, suggesting the possibility of bias in vital status ascertainment, this was not the case for the Canadian component of the 15-country nuclear worker study [E12]. The ERR for Canadian workers in the latter study appears to be unusually high and the lower confidence bound does not include the combined estimate. Reviews of historical dose records have raised possible concerns about the completeness of records in one Canadian facility (Atomic Energy of Canada Limited) that may have biased the Canadian ERR. This is currently being evaluated. It should be stressed that there are substantial uncertainties in the risk estimates derived from the 15-country study. Consequently, not too much should be made of the apparent discrepancies with risks observed in other studies, such as the LSS.

### F. United States medical radiologic technologists

114. The cohort of 146,022 United States "radiologic technologists", of whom 106,884 (73.2%) are female, was drawn from those certified by the American Registry of Radiologic Technologists (ARRT) during 1926–1982 [M10, M31, S29]. The vital status at the end of 1997 of 99.3% of the technologists was established and includes 12,624 deaths [M31]. A study of cancer incidence based on individuals who responded to two questionnaire surveys in the periods 1983–1989 and 1995–1998 (or who died between the first and second surveys) identified 2,651 cancer cases [S29] among the respondent subcohort of 90,305 persons. Individual dose reconstructions are being conducted but are not yet available, so year of entry to the ARRT is used as a crude surrogate for dose, since exposure levels were considerably higher in earlier years. About 1.6% of the cohort was first certified before 1940, 3.9% in 1940–1949, 13.1% in 1950–1959, 28.1% in 1960–1969, 48.3% in 1970–1979 and 5.1% in 1980 or later [M31]. About half had worked as radiologic technologists for 10 or more years [M31, S29]. As with most working populations, the rates of death from all cancers were lower than expected in the general population, for both sexes [D3, M31]. No specific cancer type showed an overall excess risk.

115. Mortality from all cancers combined, and separately from breast cancer, lung cancer and leukaemia excluding CLL, was examined in more detail among those who had completed the initial questionnaire survey, which permitted control for other disease risk factors [M31]. The results showed that the cumulative number of years of work as a radiologic technologist was not associated with the risk of any of these cancer categories, nor was there any association between year of first certification as a radiologic technologist and lung cancer or leukaemia excluding CLL

[M31]. Mortality risks of all cancers combined showed a modest but statistically significant increase (2-sided $p$ = 0.04) with earliest calendar year first employed, as also did breast cancer mortality (2-sided $p$ = 0.002). In addition, the number of years worked before 1950, when exposures were likely to have been higher, was positively associated with both breast cancer risk (2-sided $p$ = 0.018) and risk of leukaemia excluding CLL (2-sided $p$ = 0.05) [M31].

116. There are substantial methodological concerns with these related data sets. The year of first entry into the profession (entry to the ARRT) is largely confounded by year of birth. Substantial birth cohort effects would be expected, for example effects associated with changes in reproductive patterns over this period, although some of these lifestyle factors (age at first childbirth, age at menopause, family history of breast cancer) were adjusted for in the breast cancer mortality study [M10]. There being as yet no radiation dose estimates for this cohort, the putative radiation effect is implicitly derived from comparisons of persons entering the ARRT prior to 1940 with those entering later, and so may be difficult to separate out from the effect of year of birth. In addition, because there are relatively few persons in the older age groups among those entering the profession later (for example after 1960), there will be little overlap in these older age groups with those entering before 1940, so that age-specific adjustment (for example by comparison of cancer rates at similar ages in the post-1960 versus pre-1940 birth cohorts) is not possible. Cancer incidence rates were estimated from a combination of death certificates, questionnaire responses and medical records from physicians and hospitals [S29]. These were compared with Surveillance, Epidemiology and End Results (SEER) population-based incidence rates. As these incidence rates were calculated for various metropolitan regions that may not reflect the geographical distribution of the ARRT cohort, but in any case have much more uniform (and higher quality) ascertainment of cases, it is possible that biases would be introduced in the calculation of standardized incidence rates (SIRs).

### G. Chinese radiologists and technologists

117. Wang et al. [W3] have updated their study of cancer incidence among medical X-ray workers in China to include the years 1950–1995. An important aspect of the new update is that group doses are now available, which should permit risk estimates to be calculated, although these have yet to be taken into account in the analyses of cancer risk [W3]. The study group consisted of 27,011 medical diagnostic workers, including both radiologists and technicians, employed between 1950 and 1980 in 24 provinces of China. A control group consisted of 25,782 workers from other medical specialties who did not use X-ray equipment in their work. Eighty per cent of X-ray workers and 69% of controls were males. Seventy per cent of the diagnosed cancers had histological confirmation; most of the other diagnoses were made by X-ray examination.

118. Since there was no systematic individual dose monitoring before 1985, a retrospective dose reconstruction was performed [Z1] by measuring exposures to a dose phantom at 608 X-ray machines and 1,632 workplaces with simulated historical working conditions. In addition, 3,805 X-ray workers were randomly chosen to be interviewed concerning details of their occupational exposure histories. To assess the validity of their dose reconstruction, stable chromosome analysis was performed for 96 workers using G banding and fluorescence in situ hybridization (FISH) techniques [W4]. A correlation between the biodosimetry and physical dose estimates was found, although the physical dose estimates were consistently about 50% higher. The estimated mean cumulative doses for those who began practising radiology prior to 1960, in 1960–1969 and in 1970–1980 were 758, 279 and 83 mGy, respectively.

119. An excess of total cancers (RR = 1.19; 95% CI: 1.1, 1.3, $n$ = 836) was found. There was also a significant excess of leukaemia among X-ray workers, with 44 cases versus 25 in the control group (RR = 2.17; approximate 95% CI: 1.6, 2.9) [W3]. The RR for leukaemia was greatest among those employed as X-ray workers before age 20 and declined progressively for those first employed at older ages. The RR for leukaemia was greater (RR = 2.4) for those employed before 1970 than for those first employed in 1970–1980 (RR = 1.7). The excess leukaemia incidence rate in the irradiated group was not attributable to a deficit in the control group, as the leukaemia rate in the control group was at least as high as in the general population.

120. Significant excess risks were also reported for female breast cancer (RR = 1.34, $n$ = 46), non-melanoma skin cancer (RR = 4.05, $n$ = 18), oesophageal cancer (RR = 2.65, $n$ = 39), liver cancer (RR = 1.20, $n$ = 155), lung cancer (RR = 1.20, $n$ = 151) and bladder cancer (RR = 1.84, $n$ = 21). Age at exposure appeared to be an effect modifier for thyroid and lung cancer, as those first employed at the youngest ages had nominally higher RRs. The RRs for total solid cancers and for cancers of the liver, skin, bladder and thyroid were somewhat higher in the earlier cohort (first employed before 1970) of X-ray workers. However, cancers of the stomach were very much higher in the younger cohort (first employed in 1970–1980). The reported statistical significance of the results in this study, however, should be treated cautiously, as it appears that calculations were performed without taking into account the variance contributed by the control group. The inconsistent trends in risk in the later compared with the earlier groups imply some problems with this study, perhaps in relation to the comparison group.

### H. Studies of aircrew

121. Because aircrew receive elevated doses, which can range up to 6 mSv per year, with a substantial neutron component (representing 25–50% of the absorbed dose) [B22,

G15], there has been much interest in studies of this group. To date there have been various, generally small, studies of aircrew, whether pilots or flight attendants. The largest studies to date are three large pan-European studies, the first of flight attendants [Z4], the second and third of male cockpit crew [B23, L48]. The two studies of male cockpit crew differ principally in that the first [B23] used length of employment as a relatively crude analogue for exposure, whereas the second [L48] used total flying time and radiation dose, although these measures were only available for a subset of the full cohort (excluding cohorts from Greece and the United Kingdom for which insufficient information was available). Radiation dose was estimated on the basis of "block hours", a measure of time spent on the aircraft (including time on the runway), the type of aircraft a pilot was licensed to fly in a particular year, and a job–exposure matrix based on typical routes of each national airline for each type of aircraft in a specific year and at typical flight altitudes [L48]. The first study, of flight attendants, found a statistically non-significant increase in mortality from melanoma (standardized mortality ratio (SMR) = 1.93; 95% CI: 0.70, 4.44) among male crew, but no suggestion of increased risk among female staff (SMR = 0.36; 95% CI: 0.04, 1.37) [Z4]. The second study, of male cockpit crew, found a statistically significant increase in mortality from melanoma (SMR = 1.78; 95% CI: 1.15, 2.67) [B23]. No consistent association between employment period or duration and cancer mortality was observed, whether for melanoma or any other end point, in either study [B23, Z4]. In the third study, none of the SMRs were significantly elevated, nor were there any trends of mortality with dose for any cancer site [L48]. If anything, there were indications of a negative trend in the risk of all cancers combined with increasing radiation dose ($p$ = 0.101), so that, for example, the RR associated with doses of greater than 25 mSv was 0.74 (95% CI: 0.51, 1.06) [L48]. In some of the studies of groups nested within this cohort, the dosimetry based on hours spent in certain types of flight (i.e. low-altitude, intermediate-distance, long-distance) has been evaluated [P21]. There is in general no assessment of solar exposure or constitutional factors, a serious problem in evaluating skin cancer risk. The aircrew studies have recently been reviewed, and evidence has been found of consistent excess risk of melanoma, non-melanoma skin cancer and breast cancer [S35]. However, as with the three large studies discussed above, there is generally no relation with duration of employment. In the absence of individual information on radiation dose and solar exposure in most of the studies, as well as reproductive histories, it would be difficult to ascribe the excess risks observed in these studies to ionizing radiation exposure [S35].

### I. Patients treated with radiation

122. Patients treated with radiation are providing opportunities to learn about the mechanisms of carcinogenesis as well as providing opportunities to estimate risks of a second cancer following both high and low doses [A37, B67, C51, I34, T49, T50, V6]. Radiation doses to specific organs can be estimated with precision, scatter doses to organs outside the treatment beams are low, the numbers of exposed patients are large, and the relatively high survival rates of children and young adults provide opportunities to study the patterns of risk expression over long periods of time. Large-scale international studies of patients treated with radiation exhibit risk estimates that are generally lower than those from the studies of the survivors of the atomic bombings in Japan; these lower risks have been attributed in large part to cell killing and fractionation effects [L20, L23].

123. A new study of cervical cancer patients showed an increased rate of leukaemia, other than CLL, that occurs within a few years after treatment [K57]. This study of over 16,000 women treated with radiation in the United States and followed within the SEER cancer registration system also found no evidence that CLL was increased at any time after exposure, similar to the absence of excess risk reported in previous studies of leukaemia after cervical cancer [B5, K1]. Also consistent with previous studies [B8, B11], radiotherapy for cervical cancer has contributed to the increased risk among long-term survivors for subsequent primary cancers of the stomach, rectum, urinary bladder, and bone and joints.

124. Recent studies of patients receiving radiation treatment for Hodgkin's disease (HD) continue to provide new information on risks for second cancers. The risks of breast cancer are elevated in a dose-dependent manner following radiotherapy, and ovarian ablation associated with radiotherapy and chemotherapy substantially reduces the risk [T25, V8]. A family history of breast cancer does not appear to influence radiation risk [H59]. Estimates of cumulative absolute breast cancer risk have been developed to assist physicians in counselling patients [T51]. Lung cancer incidence rates have also been found to be elevated in long-term survivors of HD, even after very high therapeutic doses, although estimates of excess risk per unit dose are much lower than reported in lower-dose studies [T3]. Cigarette smoking and high lung dose enhanced the risk of lung cancer in a near-multiplicative fashion [G23]. Leukaemia is also a potential consequence of treatments for HD, although the risk from chemotherapy was generally much greater than that associated with radiotherapy [S46, T7].

125. Children and young adults treated for cancer are surviving much longer than in years past; this allows time for increasing numbers of late effects to be detected [G32, M58]. High-dose radiotherapy for childhood cancer increases the risk of thyroid cancer, but a downturn in risk is observed above about 30 Gy, attributable in all likelihood to cell killing [S88], consistent with previous studies [T5]. Significant increases in the incidence rate of second tumours that occur in the brain are associated with treatment for cancer, with children showing higher risks than adults [I20, N14, N20, W35]. Treatment for childhood HD can result in higher risks of breast cancer occurring in later life [G29, V8]. Treatment for retinoblastoma results in

increased rates of sarcoma and other malignancies, which suggests a possible interaction with an underlying genetic susceptibility [K43, W11]. Long-term survivors of childhood cancer are showing increased risks of second cancers that are now persisting late into life; continued follow-up and study has been recommended to quantify risks and learn about patterns of risk expression over long periods of time [G30, M59, N21, S47].

### J. Worker and public exposure to uranium

126. Many workers employed during the early years of uranium processing, manufacturing and milling potentially inhaled or ingested relatively large amounts of uranium but with minimal exposure to radon gas. Because of recent concern about the possible health effects of exposure to depleted uranium, studies of uranium workers (excluding underground miners) have been carefully evaluated in various meta-analyses [H60, I35, T32]. Fourteen epidemiological studies were conducted of more than 120,000 workers at uranium processing, enrichment, metal fabrication and milling facilities [T32]. These studies, overall, did not find the rate of any cancer to be significantly increased. The total risk for all cancers taken together was close to that expected; that is, 7,442 cancers were observed compared with 8,178 expected (SMR = 0.91) [T32]. There was reasonable consistency among the findings from the 14 epidemiological studies of workers employed throughout the world [T32]. Although there were weaknesses in these studies because of limited dosimetry, the absence of time response analyses and the inherent difficulties associated with accounting for the healthy worker effect, the results were consistent with a large-scale case-control study of 787 lung cancer cases among workers at four uranium processing operations, which found no association with estimated lung dose [D43]. A recent study of workers in the early days of nuclear energy development incorporating comprehensive dosimetry for internal emitters also revealed no statistical evidence for increased cancer risks, although the numbers were not especially large [B68, B69]. In contrast to the negative findings from studies of uranium workers other than miners, studies of underground uranium and other hard rock miners have revealed consistent and substantial increases in lung cancer attributable to radon and its decay products [C36, L8].

127. The primary occupational exposures in uranium mills were to uranium, silica and vanadium. A recent study of Colorado Plateau millers was conducted by the National Institute of Occupational Safety and Health (NIOSH) of 1,484 men who worked at one of seven uranium mills on or after 1 January 1940 [P25]. Increased numbers of deaths were found for non-malignant respiratory diseases, lung cancer, lymphoma and kidney disease. The authors were unable to show conclusively whether these deaths resulted from working in the mills, because increased risk was not associated with length of employment.

128. The extraction of uranium from ore produces solid and liquid wastes, called tailings. The wastes contain the radionuclides present in the ore, including thorium, radium and other decay products. Tailings ponds, runoff collection ponds, ore transport and mills (extraction facilities) present the potential environmental exposure pathways to humans [N22]. Concerns surrounding mill activities include possible increased exposure to ionizing radiation from uranium and its decay products, possible contamination of groundwater and vegetation, and possible increased levels of indoor radon. Descriptive correlation studies, however, find no excess cancers among populations residing near uranium milling, mining or processing facilities [B29, B30, B31, M60]. Studies of populations with increased levels of uranium and other radionuclides in drinking water also have not found associations with any cancers or overt kidney disease [A25, A26, K56, K58, K59].

129. There has been much controversy surrounding the use of depleted uranium, especially on the battlefield. This topic has been comprehensively reviewed by the Royal Society [T32, T52] (see also [H60, I35]). The Royal Society concluded that doses from depleted uranium are unlikely to be high, even in the most unfavourable (battlefield) conditions, so that lung cancer risks are unlikely to be more than doubled [T32]. There is potential non-radiological risk associated with exposure to depleted uranium, in particular associated with its nephrotoxicity, although there is little or no evidence of this in practice [T52].

130. There appear to be several possible reasons why uranium is not conclusively found to cause cancer in humans and why it is not considered a human carcinogen [I35]: uranium is not very radioactive (having such a long half-life of billions of years, $^{238}U$ decays very slowly), and its chemical properties are often such that any inhaled or ingested uranium is excreted rather quickly from the body [H60]. Some compounds of uranium are relatively insoluble and can be retained in the body. Nonetheless, there is little or no epidemiological evidence for an association between uranium and any cancer.

# III. SITE-SPECIFIC CANCERS

131. Table 15 summarizes the principal features of cohort and case-control epidemiological studies of the carcinogenic effects of exposure to low-LET radiation. Table 16 provides a similar summary of the studies for high-LET exposure. The sections below on specific cancer sites consider these studies in greater detail. table 17 summarizes the strengths and weaknesses of cohort and case-control studies for low-LET exposure, and table 18 provides a similar summary of the strengths and weaknesses of studies for high-LET exposure. Most of these studies were considered in the UNSCEAR 2000 Report [U2].

132. As much as possible in tables 19–44, estimates of cancer risk per unit dose (in $Gy^{-1}$ or $Sv^{-1}$) are those given in the original publications, but for publications that did not calculate risk estimates, the methods described in Section I.C of Annex A of the UNSCEAR 1994 Report [U4] 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 based on age- and sex-specific rates in the reference population (typically the general population), $D$ denotes the average dose and $PY$ denotes the number of person-years of follow-up, then the ERR at 1 Sv is estimated by $(O - E)/(E \cdot D)$, and the EAR per unit dose and per unit time at risk is estimated by $(O - E)/(PY \cdot D)$. Instances where this approach has been implemented are indicated by a footnote in tables 19–44. It should be noted that the results based on this methodology might differ from those based on a dose–response analysis if those data were available. A particular problem with this approach occurs when exposed populations are explicitly or implicitly selected for good health (e.g. working populations or higher-social-status groups, respectively) and the expected values are derived from the general population. In such cases, the risk estimates will tend to be biased in a downward direction and therefore the true risks may be masked. Risk estimation that used the general population statistics to derive the expected values is therefore indicated by a footnote.

133. Risk estimates have been made from the LSS mortality and incidence data in tables 19–44, wherever possible using the latest DS02 dosimetry and follow-up (i.e. 1950–2000 for the mortality data [P10] and 1958–1998 for the solid cancer incidence data [P48]). For site-specific solid cancers, mortality risks were estimated using the previous (DS86) dosimetry and the 1950–1997 follow-up [P9]. For a few cancers (e.g. non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma and leukaemia), older incidence [P4] and mortality [P1] data are employed. In calculating summary ERR and EAR measures, the following simple linear models were fitted to each data set in which the expected disease rate (i.e. numbers of cases or deaths per person-year of follow-up) in the stratum with age $a$, city $c$ and sex $s$ is given by:

$$h_0(a,c,s) \cdot [1 + \alpha \cdot D] \tag{4}$$

when assessing ERR, and by:

$$h_0(a,c,s) + \alpha \cdot D \tag{5}$$

when assessing EAR. In both cases, in general $h_0(a,c,s)$ has the form:

$$h_0(a,c,s) = \exp[\kappa_0 + \kappa_1 \cdot s + \kappa_2 \cdot c + \kappa_3 \cdot s \cdot c + \kappa_4 \cdot \ln[a] + \kappa_5 \cdot \ln[a]^2 + \kappa_6 \cdot s \cdot \ln[a] + \kappa_7 \cdot s \cdot \ln[a]^2] \tag{6}$$

When fitting to the mortality and incidence data for bone and salivary cancers and for melanoma, because of the small number of cases and deaths for these end points, slightly simplified versions of the model for underlying rates, $h_0(a,c,s)$, were assumed, in which $\kappa_1 = \kappa_2 = \kappa_3 = \kappa_6 = \kappa_7 = 0$, i.e. in which $h_0(a,c,s) = \exp[\kappa_0 + \kappa_4 \cdot 1n[a] + \kappa_5 \cdot 1n[a]^2]$. The same was done for thyroid cancer mortality data. For bone cancer the models fitted were of purely quadratic form, so that the bone cancer rate for the ERR model (4) is, given by $h_0(a,c,s) \cdot [1 + \alpha \cdot D^2]$ and for the EAR model (5) is given by $h_0(a,c,s) + \alpha \cdot D^2$. The tables also provide 90% profile-likelihood confidence intervals [M21] on the fitted ERR and EAR (the parameter $\alpha$). It should be noted that in deriving these simple summary measures (ERR and EAR), there is no implication that the corresponding models (4) and (5) fit the various data sets well. As discussed in Section I.L, in general the sex, age at exposure and time since exposure substantially modify both ERR and EAR for most of the data presented.

134. In fitting to the latest mortality and incidence data [P10, P48], as also to the previous (pre-DS02) mortality data [P9], the doses used were adjusted truncated doses, calculated using the methodology described by Pierce et al. [P2]. In particular, the adjustment factors used in this process were derived from the previous (DS86) dosimetry [P2]. Prior to models being fitted to the latest incidence data [P48], as also to the previous (pre-DS02) mortality data [P9], the respective data sets were collapsed over strata defined by age, sex, attained age, age at exposure and years

of follow-up. In other words, person-years and cases or deaths were summed over these strata, and doses in each stratum were replaced by person-year weighted averages over the stratum. To estimate the "expected" LSS cases or deaths for these two data sets [P9, P48], in these tables the RR model (4) was fitted, and the sum

$$\sum h_0(a,c,s)$$

evaluated, corresponding to the cases predicted at zero dose. In all tables this sum, and also the sums of cases or deaths and person-years of follow-up, are over those survivors with respective organ doses of greater than 0.005 Sv. Throughout tables 19–44, the LSS cohort is assigned to the category of "external low-LET exposures". Of the dose received by survivors, 1–2% is due to neutrons, most of the rest being due to high-energy (mostly 2–5 MeV) gamma radiation [R12]. Even after application of a neutron RBE of 10 (as is done in most of the analysis presented here), the dose in this cohort results predominantly from external low–LET exposures. Similar simplifications are made for various other studies. It should be noted that, while the above procedures were used to estimate risks for the LSS given in tables 19–44, results given in the main text are in general based on the published reports [P2, P9, P10, P48] wherever possible. These may be slightly different. Many of the slight differences relate to the 0.005 Sv cut-off used in the tables, which because of the grouped nature of the publicly available data file will result in groups that do not always correspond precisely to the set of survivors with this dose. It should also be noted that, for solid cancers (table 19), the Techa River cohort [K50] is assigned to the category of "external low-LET exposures", since 75% of the stomach dose is thought to be from this source (with most of the rest from $^{137}$Cs). For leukaemia (table 44), the Techa cohort it is assigned to the category of "internal low-LET exposures", since 92% of the bone marrow dose is thought to be from internal beta emitters [K50].

## A. Total solid cancers

135. The solid cancer mortality experience of the LSS of survivors of the atomic bombings up until the end of 2000 has been reported [P10]. This represents an additional three years (1998–2000) of follow-up since the previous report [P9]. There are 10,127 deaths from solid cancer and 296 deaths from leukaemia. If attention is restricted to survivors who received a shielded kerma dose of less than 4 Gy, there are 10,071 solid cancer deaths and 284 leukaemia deaths. Preston et al. [P10] estimate that about 479 (~5%) of the 10,127 solid cancer deaths would be attributable to radiation exposure. Among survivors with (DS02 or DS86) colon doses of greater than 5 mSv, about 8% of solid cancer deaths would be attributable to exposure, a figure very similar to that of the previous follow-up [P9]. In general, although risk estimates are somewhat lower than before, for both solid cancers and leukaemia the patterns of the distribution of excess risk by age and time are very similar to those of the previous follow-up [P9]. A striking feature of the solid cancer data is that, in a lower-dose (less than 2 Sv) group, there is statistically significant upward curvature [P10]. This is not an artefact of the new dosimetry: the same finding had been observed in the previous follow-up of the LSS mortality data, using the DS86 dosimetry [W20]. As noted in the previous report [P9], the solid cancer radiation risks are highest among those exposed as children, and as before there is a steep decline in ERR with increasing time after exposure in this group (figure X).

136. As noted in table 19, both the ERR and the EAR for total solid cancers are somewhat higher (by about a factor of 2) for women than for men.

## B. Salivary gland cancer

### 1. General background

137. Cancers of the salivary gland are rare. Annual age-standardized world rates are fewer than 1.5 and 1.3 cases per $10^5$ persons for men and women, respectively, in the vast majority of tumour registries represented in Parkin et al. [P19]. Rates tend to be slightly higher in developed countries. Among the highest rates are in parts of Australia, where annual age-standardized rates of 1.9 per $10^5$ persons are recorded for men, and in parts of Canada, where rates of 3.8 per $10^5$ persons are recorded for women [P19]. Rates are somewhat lower for developing countries. For example, in Martinique, age-standardized rates of 0.4 and 0.2 per $10^5$ persons are recorded for men and women, respectively [P19]. Benign tumour rates are 2–3 times higher, with tumours appearing at somewhat younger ages [B48]. Apart from ionizing radiation, causes of salivary gland cancer are not clear. There have been suggestions of associations with the use of hair dyes or mouthwash and with certain occupational factors, but few suggestions of associations with dietary factors, tobacco or alcohol use [B27].

### 2. Summary of UNSCEAR 2000

138. Salivary gland cancer was not considered in the UNSCEAR 2000 Report [U2].

### 3. New or updated studies

*(a) External low-LET exposures*

139. A number of early studies, mostly based on small numbers of cases, have suggested an association between salivary gland tumours and radiation exposure at young ages [H41, J6, M54, M55, S53, S71, S72]. These published results were the basis for: *(a)* a meta-analysis that resulted

in estimates of 0.26 ± 0.06 excess malignant tumours and 0.44 ± 0.11 excess benign tumours following childhood exposures of $10^4$ PY Gy [L82]; and *(b)* estimation of the probability of causation for radiation-related salivary gland cancer following childhood exposure [N11]. Concurrently and more recently, Hildreth et al. [H26] estimated an RR of 5.5 for benign salivary gland tumours associated with therapeutic X-ray treatment in infancy for enlarged thymus. Preston-Martin et al. [P7] compared reported histories of dental X-ray examinations in patients with benign and malignant parotid gland tumours and matched controls, estimating RRs of 5.6 and 1.5 for malignant and benign tumours, respectively, associated with exposures of greater than 0.5 Gy. No dose–response analyses were presented in either study. In a study of occupational exposures and mortality due to salivary gland cancer among African-American and white workers in the United States, Wilson et al. [W34] found a positive trend ($p = 0.08$) among white workers with probability of exposure to ionizing radiation, as measured by a job–exposure matrix.

140. Results from an incidence and pathology study of benign and malignant salivary gland neoplasms in the LSS population are presented in table 20 [L83, S73]. Information from the LSS Tumor Registry was supplemented by additional case findings, with pathology review, from autopsy, from biopsy and from surgical specimens maintained at the Radiation Effects Research Foundation and elsewhere. The incidence of malignant tumours (ERR = 3.5 (90% CI: 1.5, 7.5) $Gy^{-1}$; based on 31 cases with estimates of radiation exposure) and of benign tumours (ERR = 0.7 (90% CI: 0.1, 1.7) $Gy^{-1}$; based on 64 cases) both increased significantly with radiation dose, and no modifying effects of exposure age, attained age, sex or time since exposure were observed. Remarkably, most of the evidence for a malignant tumour dose response pertained to mucoepidermoid carcinoma (ERR = 8.3 (90% CI: 2.6, 29.6) $Gy^{-1}$; based on 11 cases), and most of the evidence for a benign tumour response pertained to Warthin's tumour (ERR = 3.1 (90% CI: 0.6, 10.3) $Gy^{-1}$; based on 12 cases). Both of these tumours occur only in the parotid glands. Dose response for residual malignant tumours was of only suggestive significance (ERR = 1.4 (90% CI: 0, 4.7) $Gy^{-1}$; based on 20 cases; $p = 0.11$), while that for residual benign tumours (ERR = 0.3 (90% CI: –0.1, 1.2) $Gy^{-1}$; based on 52 cases; $p = 0.29$) was positive but not statistically significant.

141. Schneider et al. [S74] studied radiation dose response for incidence of salivary gland tumours in a cohort of 2,945 persons medically irradiated as children between 1939 and 1962, mainly for treatment of enlarged tonsils and adenoids. Twenty-two patients developed malignant salivary gland tumours that were verified by pathology after surgery, including 9 cases of mucoepidermoid carcinoma, and 66 developed benign salivary tumours (including only 2 cases of Warthin's tumour). The incidence of malignant tumours was not significantly associated with radiation dose (ERR = –0.06 (95% CI: undetermined, 4.0) $Gy^{-1}$), even though 22 cases were observed versus 0.39 expected according to age- and sex-specific population rates. Conversely, the incidence of benign tumours was significantly associated with dose (ERR = 19.6 (95% CI: 0.16, undetermined) $Gy^{-1}$). The very large numbers of malignant and benign tumours observed relative to the expectation based on population rates were partly ascribed by the authors to notification and screening programmes for the study population. These began in 1974 and resulted in a threefold increase in the numbers of cases diagnosed after 1974. In a group irradiated in childhood for treatment of tinea capitis, there was no statistically significant elevation in the RR for salivary gland tumours (6 tumours among those irradiated versus 2 tumours in the control group (RR = 1.8; 95% CI: 0.4, 8.9)) [S68].

142. In comparing the results from the LSS and from medically irradiated populations discussed in the previous two paragraphs, it is illuminating to consider the distribution of dose within the two populations. As generally for the LSS cohort [P9, P10, R20], the distribution of salivary gland doses among the exposed population is highly skewed, and the mean doses and inter-quartile ranges for different types of tumour differ markedly from those of the population as a whole. By contrast, in the medically irradiated population, doses are much higher than in the LSS population, and they are more closely and more symmetrically concentrated around the mean value. Thus, as stated by Schneider et al. [S74], the LSS results are not directly comparable to theirs, and extrapolation of their results to lower doses may not be justified. One possible explanation offered for the difference, that the LSS doses are partially due to neutrons, seems less tenable in view of the reduced role assigned to neutrons in the most recent refinement of that dose reconstruction system [P10]. There remains a possibility, however, that the small neutron component might be of some importance, since the gamma-ray estimates are influenced by the choice of the RBE for neutrons [W20].

143. Salivary gland tumours have been studied for a number of nuclear worker cohorts. In particular, a statistically significant excess risk (2 cases versus 0.19 expected) has been observed in a group of workers at the Lawrence Livermore National Laboratory in the United States [W39]. There is no analysis of dose response in relation to salivary gland tumour risk. However, in three other United Kingdom cohorts, there were no statistically significant elevations in risk (2 cases versus 2.23 expected [M4], 1 case versus 2.97 expected [M5] and 2 cases versus 0.38 expected [M6]).

### 4. Summary

144. The available evidence indicates that the salivary gland is susceptible to the induction of cancer by ionizing radiation; the evidence for this comes almost entirely from studies of external low-LET exposure. There is little evidence for the modifying effects of sex, age at exposure or time since exposure.

## C. Oesophageal cancer

### 1. General background

145. Rates of oesophageal cancer vary widely by country and ethnic group [M32], with low rates in many countries but extremely high rates among Chinese and certain Central Asian groups, and intermediate rates in black populations [M32]. For example, age-standardized world rates of 183.8 and 123.1 cases per $10^5$ persons for men and women, respectively, have been observed in parts of China [P19], whereas the rates are fewer than 10 cases per $10^5$ persons [P19] in many European countries. Since oesophageal cancer is generally fatal, mortality rate is a good surrogate for incidence rate. The major known risk factors for oesophageal cancer are heavy alcohol consumption, tobacco use and chewing of betel nut [M32]. Other possible risk factors, but where the weight of evidence is less strong, are consumption of pickled foods and nutritional deficiency [M32].

### 2. Summary of UNSCEAR 2000

146. The UNSCEAR 2000 Report stated that the LSS data did 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. Cancer incidence data from the LSS, which began 12 years after exposure, do not show a significant excess risk of oesophageal cancer [T1]. The LSS mortality data also showed a higher ERR for this cancer in females than in males, although not significantly so.

147. The United Kingdom ankylosing spondylitis study was the only study of medically exposed populations to report a significant risk of radiation-associated oesophageal cancer [W8]. Regarding internal low-LET exposures, little epidemiological information was available. The data from patients treated with $^{131}$I for adult hyperthyroidism [R3] showed no increased risk of this cancer, but the doses received by the oesophagus were small.

148. Oesophageal cancer data were available from several worker studies following high-LET exposures. In a study of three groups of workers exposed to plutonium in three United Kingdom nuclear industry workforces, no clear excess of oesophageal cancer was seen (23 observed versus 21.3 expected deaths), nor was any excess seen among workers monitored for exposures to uranium, polonium, actinium and other radionuclides (apart from tritium) (9 observed versus 16.1 expected deaths), although doses to the oesophagus were probably small [C40].

### 3. New or updated studies

#### *(a) External low-LET exposures*

149. The updated LSS [P9] identified 171 oesophageal cancer deaths among those with at least 5 mSv of exposure. Since the underlying mortality rates of oesophageal cancer are considerably higher for males than females, the estimates of ERR were lower among males (0.55 $Sv^{-1}$) than females (1.40 $Sv^{-1}$) (table 21).

150. Several studies of workers exposed to external radiation have reported data on the risks of oesophageal cancer (table 21). Although these were reported before 2000, in some cases, they were not discussed in the UNSCEAR 2000 Report, so the Committee considers them here. Of these, three studies reported data based on "internal dose"–response comparisons. The NRRW [M12] reported a dose–response association non-significant in the negative direction that was based on 120 cases of oesophageal cancer in informative strata (strata defined by age group, sex, interval of follow-up, etc., with at least one cancer death and at least two dose groups with persons contributing to the follow-up) and a mean dose of 0.03 Sv. A smaller United States study of workers at Los Alamos National Laboratory [W6] reported a marginally positive dose response ($p < 0.1$) but a deficit compared with the United States population (22 observed and 27.4 expected cases). A study of oesophageal cancer incidence among workers in the Canadian National Dose Registry [S8] reported a null dose–response association based on 22 observed cancers, and an update of the segment of the Registry concerning nuclear power industry workers also produced a null result [Z6]. Other studies of workers (workers at Oak Ridge National Laboratory in the United States [F2], radiation workers at Électricité de France [R54], Japanese nuclear workers [I14], and radiologic technologists in Japan and the United States [M31, Y5]) reported deficits in oesophageal cancer mortality rates based on comparisons with reference general populations. Only the study of Chinese medical X-ray workers reported an excess of oesophageal cancer among both early workers (mean dose 0.55 Sv) and more recent workers (0.08 Sv) [W3]. It is notable that the workers in this study had higher radiation exposures than those in the other studies, and hence there was a greater potential to observe excess cases. In a United Kingdom study of Springfields uranium workers [M5], no excess of oesophageal cancer was seen (25 observed versus 34.54 expected cases) (table 21).

151. A United States study of women treated with radiation for primary breast cancer documented RRs of 2.83 (95% CI: 1.35, 5.92) and 2.17 (95% CI: 1.67, 4.02) for squamous cell oesophageal cancer occurring between 5 and 9 years and at 10 or more years, respectively, following radiation therapy [Z11]. This increase was mainly due to tumours located in the upper and middle thirds of the oesophagus. No assessment of radiation doses has been carried out for this cohort.

*(b) Internal low-LET exposures*

152. The only new data on internal exposures and oesophageal cancer are those from the study of persons exposed to weapons test fallout in the Semipalatinsk area of Kazakhstan [B58], which reported a highly statistically significant trend of increasing risk with dose in women ($p$ = 0.003), although not for men ($p$ = 0.46). The aggregate ERR based on an internal analysis was 2.37 (95% CI: 1.47, 3.63) $Sv^{-1}$; however, when analysis was restricted to the exposed group, based on individual dose estimates, the trend estimate was much reduced and no longer statistically significant: 0.18 (95% CI: –0.09, 0.66) $Sv^{-1}$. As noted in section II.D, "ecological bias" may operate in this study, so these findings should be treated with caution.

#### 4. Summary

153. The new or updated data are broadly supportive of the conclusions in the UNSCEAR 2000 Report. There is an association of radiation exposure and oesophageal cancer in the LSS, although since oesophageal cancer is relatively rare, there was insufficient statistical power to detect an excess in the several low-dose occupational exposure studies. There are insufficient data to characterize the shape of the dose–response curve or to establish a dose-rate effectiveness factor. Virtually no human data are available on the magnitude of effects following exposure to high-LET radiation.

### D. Stomach cancer

#### 1. General background

154. Stomach cancer is the fourth most common malignancy worldwide and appears to be the second leading cause of cancer mortality [N10, S59]. Rates are higher among men than women and show a sharp increase with age. The incidence rate of stomach cancer varies considerably with geographical location and among different ethnic groups within the same locality [S59]. Approximately 60% of all stomach cancers occur in developing countries. The highest rates are found in Eastern Asia, the Andean regions of South America, and Eastern Europe, while low rates are found in North America, Northern Europe and most countries in Africa and South-East Asia [P19, S59]. For example, annual age-standardized world rates of 145.0 and 34.5 cases per $10^5$ persons for men and women, respectively, have been observed in parts of China [P19], whereas in many European countries the rates are fewer than 30 cases per $10^5$ persons [P19]. Studies of migrants suggest that environmental factors may be largely responsible for the variation in rates [N10]. Of particular interest is the fact that the Japanese people have had much higher rates of stomach cancer than people in Western countries. In most countries, including Japan, stomach cancer incidence and mortality rates have declined markedly over the past 50 years [N10, S59]. These changes are likely to reflect changes in diet, including increased consumption of fresh vegetables and fruits and decreased salt intake (which case-control studies have shown to be linked to reduced stomach cancer risks [K36]). Dietary factors are important, and infection with *Helicobacter pylori* [S69], especially with certain genetic or physiological cofactors, has been associated with elevated risks of stomach cancer [C18, K36].

#### 2. Summary of UNSCEAR 2000

155. The Committee reported in 2000 that the dose response seen in the LSS incidence data up to 1987 was consistent with linearity, and that the ERR per unit dose was higher for females than for males, decreased with increasing age at exposure, and did not vary significantly with the time since exposure [T1]. The findings for mortality rates up to 1990 were very similar [P1].

156. The major studies of patients whose stomachs were irradiated with moderately high doses—particularly the studies of patients treated for cervical cancer [B8], ankylosing spondylitis [W8] and peptic ulcer [G6]—produced estimates for EAR per unit dose that were appreciably lower than those from the LSS, but the ERR estimates of these studies and of the LSS were statistically compatible.

157. The Committee also reported in 2000 that there was a suggestive excess of stomach cancer among Mayak workers with external doses exceeding 3 Gy [Z3]. However, studies of workers exposed to lower doses have not provided evidence of a dose–response relationship for stomach cancer [C3].

158. The Swedish study of patients treated with $^{131}I$ for hyperthyroidism reported increased incidence [H6] and mortality rates [H24] from stomach cancer, with some indication of a dose–response trend. In general, however, the epidemiological data were too sparse to quantify a dose or dose-rate effectiveness factor or to characterize risks from internal low-LET or high-LET exposures.

159. Studies of persons exposed to $^{224}Ra$ [N2, W15] and the diagnostic contrast medium Thorotrast [A5, V3, V4] provide little evidence of elevated risks of stomach cancer. A study of 11 cohorts of underground miners found excess mortality rates from stomach cancer in comparison with national and local rates, but no evidence of an increase in mortality rates with increasing cumulative radon exposure [D10]. Because doses to the stomach from radon are estimated to be very low, it seems likely that the excess is due to other factors, such as other exposures in mining environments or smoking.

### 3. New or updated studies

#### *(a) External low-LET exposures*

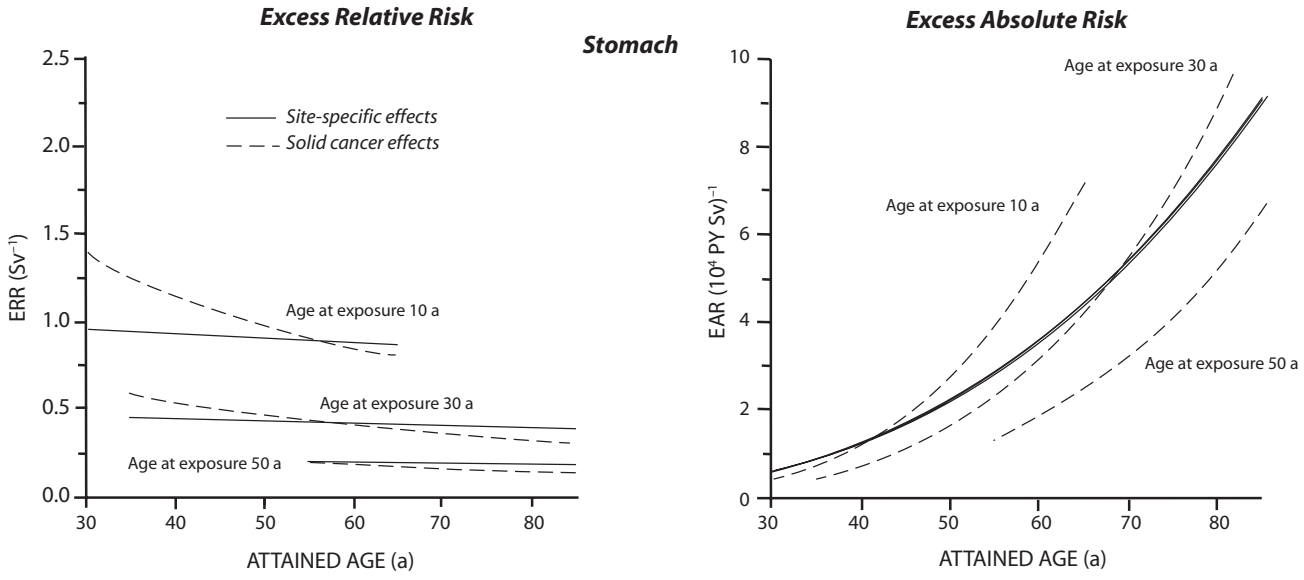
160. A summary of results from both old and new studies is shown in table 22. In the updated mortality assessment of the LSS up to 1997, 1,685 stomach cancer deaths occurred among those people who received doses of at least 5 mSv. Of these deaths, it was estimated that about 100 were attributable to the radiation exposure [P9]. The ERR was greater for females (0.65 $Sv^{-1}$) than for males (0.20 $Sv^{-1}$), as was the EAR (3.3 $(10^4$ PY $Sv)^{-1}$ and 2.1 $(10^4$ PY $Sv)^{-1}$, respectively). For the ERR, the patterns of variation of radiation effects with age at exposure and attained age were not significantly different from those for solid tumours as a whole. Specifically, the ERR per unit dose declined substantially with increasing age at exposure but declined very little with increasing attained age, as shown in figure XII. For the EAR, there was no significant increase or decrease with age at exposure, a pattern that differed from that for all solid cancers combined (figure XII). The EAR showed a steep increase with attained age, similar to that for all solid cancers as a group. The difference in the patterns for the ERR and EAR with age at exposure is related to the decline in underlying rates with birth cohort, a variable that is confounded with age at exposure.

161. An update of the United States peptic ulcer study [C4] reported as its main result an ERR of 0.06 (95% CI: 0.02, 0.10) $Gy^{-1}$ based on persons with 10 or more years of follow-up. However, among patients treated with 1–10 Gy, the ERR per unit dose was somewhat higher: 0.20 (95% CI: 0.0, 0.73) $Gy^{-1}$. This estimate should be treated with caution, however, as the numbers of deaths were relatively small (47 stomach cancer deaths among 1941 patients, or for 1–10 Gy, 11 deaths among 309 patients), the mean dose in that group was high (14.8 Gy overall, 8.9 Gy among the 1–10 Gy group), and the patients were being treated for a stomach condition that may cause hyperplasia or other cellular responses that potentially could alter carcinogenic susceptibility. The irradiated patients were predominantly male (78%), and a quarter had a history of stomach surgery. The *H. pylori* status of the patients was not known. The ERR per unit dose estimates in the lower-dose group are compatible with those based on male survivors of the atomic bombings; the EAR was not evaluated.

162. Several studies of occupational radiation exposure have reported data on stomach cancer incidence or mortality. Most studies, including the IARC [C3], NRRW [M12] and Canadian National Dose Registry [A8] studies, provide little evidence of a dose–response relationship for stomach cancer, but this may be due to the low doses and limited statistical power. A recent study of United States nuclear power industry workers [H44] indicated a large but non-significant ERR per unit dose based on 16 deaths. In a study of Japanese nuclear industry workers [I14], the risk of stomach cancer was not elevated in comparison with the general population, but the dose response based on 428 deaths was statistically significant; however, the finding was no longer significant when a Bonferroni

**Figure XII. Patterns of stomach cancer mortality with age and time among the survivors of the atomic bombings in Japan (reproduced from Preston et al. [P9])**

The dark curves are fitted age–time patterns in the ERR (left panel) and EAR (right panel). The light dashed curves are the patterns obtained when the age and age-at-exposure effects are constrained to equal those for all other solid cancer. The curves are sex-averaged estimates of the risk at 1 Sv for people exposed at ages 10, 30 and 50, with attained ages corresponding to the follow-up period



procedure was applied to take account of the multiple statistical tests that were performed. The authors note the possibility of confounding by dietary and socio-economic factors. Although not reported in the UNSCEAR 2000 Report [U2], the 1997 study of Artalejo et al. [A32] reported a slight deficit of stomach cancer mortality among workers for the Spanish Nuclear Energy Board. The SMR was 0.81 (95% CI: 0.49, 1.26) but was based on only 19 cancer deaths, of which 7 were among the 27% of the cohort who had been miners and may have been exposed to alpha radiation [A32].

163. Two relevant studies of occupational exposure in medicine have recently been reported, in the United States [M10, S29] and in China [W3]; in neither study have individual dose estimates been derived, so their utility for quantitatively understanding radiation risks is questionable. The Chinese study of medical X-ray workers showed no excess among those employed before 1970, when exposures were high (estimated mean cumulative dose of 0.55 Gy), but an excess was reported among those first employed during 1970–1980 (estimated mean cumulative dose of 0.08 Gy) [W3]. Among United States radiologic technologists, both males and females had lower stomach cancer incidence [S29] and mortality [M10] rates than the general population. Rogel et al. [R54] reported a deficit (at borderline levels of statistical significance) of stomach cancer mortality compared with French national rates among radiation workers of Électricité de France (3 observed versus 7.2 expected deaths; SMR = 0.41; 90% CI: 0.11, 1.07).

*(b) Internal low-LET exposures*

164. The only new data on internal exposures and stomach cancer are those from the study of persons exposed to weapons test fallout in the Semipalatinsk area of Kazakhstan [B58], which reported a highly statistically significant trend of increasing risk with dose in women ($p$ = 0.0016), although not for men ($p$ = 0.36). The aggregate ERR based on an internal analysis was 1.68 (95% CI: 0.83, 2.99) $Sv^{-1}$; however, when analysis was restricted to the exposed group, based on individual dose estimates, the trend estimate was somewhat lower at 0.95 (95% CI: 0.17, 3.49) $Sv^{-1}$. As noted in section II.D, "ecological bias" may operate in this study, so these findings should be treated with caution.

*(c) Internal high-LET exposures*

165. Travis et al. [T30] studied patients injected with Thorotrast during radiographic procedures in Denmark, Sweden and the United States. The stomach cancer incidence rate in a group of Thorotrast-exposed patients in Denmark and Sweden was significantly elevated compared with a control group, but there was no evidence of a trend of increasing stomach cancer incidence with a surrogate measure of cumulative radiation dose. Stomach cancer was not evaluated with respect to the mortality rate data that were available for the United States.

166. Auvinen et al. [A36] studied cancer epidemiology in relation to radon, uranium and other radionuclides in drinking water in a cohort of persons who used water from wells drilled into bedrock in Finland. Activity concentrations of $^{226}$Ra, radon and uranium were assessed by radiometric analysis of samples from each well. There was no relationship seen between stomach cancer incidence and levels of any of the three radionuclides. If anything, there was an inverse relationship: the hazard ratio in the group exposed to 130–299 Bq/L radon relative to the group exposed to less than 130 Bq/L was 0.54 (95% CI: 0.25, 1.18), and the hazard ratio in the group exposed to 300–15,000 Bq/L radon relative to that exposed to less than 130 Bq/L was 0.48 (95% CI: 0.25, 0.94). Similar inverse relationships between exposure and stomach cancer risk were observed for $^{226}$Ra and uranium.

### 4. Transfer of risk estimates across populations

167. Although the appropriate way to generalize or "transfer" risk estimates from one population to another is a general issue, it is especially important when there is a major discrepancy between the underlying cancer rates in the two populations. Stomach cancer is a prime example of such a situation. For example, lifetime risk estimates for stomach cancer based on transfer of absolute risks as presented in the UNSCEAR 2000 Report for the United States and the United Kingdom were several times higher than those based on transfer of RRs. The UNSCEAR 2000 Report observed that the attributable risk estimates in the studies conducted in Western populations were appreciably lower on average than those in the LSS, suggesting that using the ERR model may be a better way to "transfer" stomach cancer risk than using the EAR model. Updated data from the peptic ulcer study [C4] confirm that ERR estimates are very similar to those based on survivors of the atomic bombings. However, although RRs appear to be more comparable than absolute risks, other differences in the study populations may confound this comparison, particularly the much higher doses in some medical studies.

### 5. Summary

168. Updated data from the LSS [P9] and the peptic ulcer study [C4] continue to provide evidence of a positive dose response. Within the LSS, the ERR decreases with increasing age at exposure, but the EAR does not. Past studies of cervical cancer patients [B8] also provide evidence of excess stomach cancer risk from radiation exposure. Most studies of nuclear workers do not show an association of excess stomach cancer with low-dose protracted exposure, but this may be due to the limited statistical power of these studies. Weak associations are suggested by new studies of United States [H44] and Japanese [I14] nuclear power workers.

## E. Cancer of the small intestine, including the duodenum

### 1. General background

169. Cancer of the small intestine is only slightly less rare than cancer of the salivary gland, with annual age-standardized world rates of less than 4.0 and 2.0 cases per $10^5$ persons for men and women, respectively, in the tumour registries represented in Parkin et al. [P19]. The cancer can be induced in experimental animals by high-dose irradiation of exteriorized intestinal loops [O11], and the small intestine therefore is an organ susceptible to radiogenic cancer. However, the small intestine appears to have characteristics involving selective retention of template DNA strands and providing protection of the stem cell genome in intestinal crypts, which render it highly resistant to carcinogenesis at low to moderate levels of exposure to radiation and other environmental carcinogens [C31, P41]. A second line of defence, in which mutated stem cells are eliminated by radiation-induced apoptosis in the stem cell zone of intestinal crypts, may also come into effect [P42]. There are well known hereditary risk factors, in particular familial adenomatous polyposis (FAP), and certain other chronic diseases, in particular Crohn's disease [S57].

### 2. Summary of UNSCEAR 2000

170. Cancer of the small intestine was not considered in the UNSCEAR 2000 Report [U2].

#### *(a) External low-LET exposures*

171. In an international cancer registry study of second primary cancer incidence in a group of very-long-term survivors of cervical cancer [K1], the incidence of second cancers was evaluated in a group of 86,000 cervical cancer patients reported to 13 population-based cancer registries in five countries. Of these patients, 49,800 had received radiotherapy, with typical average organ doses of between 10 and 20 Gy to the small intestine; 16,700 had not been given radiotherapy; and 19,700 had missing treatment data. For the small intestine, 22 cases of second cancer were observed among radiotherapy patients, versus 12.3 expected from population rates (ratio of observed to expected (O/E) = 1.8; 90% CI: 1.3, 2.6), and 2 cases versus 2.7 expected were seen among women who had not been given radiotherapy [K1]. Among the radiotherapy patients, virtually the same O/E ratios were obtained for the period within 9 years after cervical cancer diagnosis (O = 9, E = 4.9, O/E = 1.8; 90% CI: 0.96, 3.2) as after 9 years (O = 13, E = 7.5, O/E = 1.7; 90% CI: 1.03, 2.8). In the parallel case-control study [B8], there is no evidence of increased risk. The RR is 1.0 (90% CI: 0.3, 2.9) among the 22 cases, despite the very high doses received (estimated to be several hundred grays on average). There is no evidence of a dose response ($p$ = 0.47 for trend among all survivors, or 10-year survivors); if anything, there are indications of a negative trend with dose. An earlier study by Smith and Doll [S75] of 2,068 women treated with radiation for benign gynaecological disorders found 3 deaths from cancer of the small intestine versus 0.4 expected. Cancer of the small intestine was not discussed in the most recently published follow-up study of this irradiated group [D7].

172. Despite the experimental evidence for induction by radiation of cancer of the small intestine, the weak epidemiological evidence, in particular the lack of any trend with dose in the international cervical cancer case-control study [B8], and the lack of the expected increase in risk with time in the cohort study, indicates that the small intestine is not susceptible to radiogenic cancer induction, even at high doses. It is possible that the very high doses in the cervical cancer study resulted in cell sterilization, which might partially explain the negative trend in the case-control study, although the trend was not statistically significant.

### 3. Summary

173. The available evidence indicates that cancer of the small intestine is not strongly inducible by ionizing radiation. However, the available evidence comes almost entirely from studies of external low-LET exposure at relatively high doses, and it is possible that cell sterilization may partially account for the largely negative findings.

## F. Colon cancer

### 1. General background

174. The colon resembles the small intestine in that stem cells deep in the intestinal crypts produce a continuous flow of new and relatively short-lived crypt cells that migrate towards the top of the crypt. However, survival and repair of DNA damage in the crucial stem cells is the rule rather than apoptosis and replacement (regeneration) as in the small intestine. This is perhaps because the latter strategy would be more error-prone in the colonic environment, which includes a much higher concentration of genotoxic molecules [P41]. In any case, cancer of the colon is much more frequent than cancer of the small intestine, and ionizing radiation exposure is an established risk factor. Underlying rates tend to be higher in developed countries (whether in North America, Europe, Oceania or Japan), with age-standardized world rates lying generally between 20 and 40 cases per $10^5$ PY, whereas rates are generally lower—fewer than 5 cases per $10^5$ PY—in Africa and Southern Asia [P19]. As with cancers of the small intestine, there are well established hereditary risk factors, in particular familial adenomatous polyposis (FAP) [S58]. There are also well-known dietary risk factors, in particular

high-fat and low-fibre diets and diets deficient in fruit and vegetables, and also risk factors associated with certain other chronic diseases, in particular ulcerative colitis and Crohn's disease [S58].

## 2. Summary of UNSCEAR 2000

175. The UNSCEAR 2000 Report stated that the LSS found a dose response consistent with linearity for both colon cancer incidence [T1] and mortality [P1]. However, the cervical cancer [B8] and peptic ulcer [G6] studies with colon doses of several grays showed little evidence of elevated risk, possibly owing to a cell-killing effect. There was no clear pattern in the variation of ERR per unit dose by sex, age at exposure or time since exposure among the survivors of the atomic bombings. However, the EAR per unit dose for mortality increased with time since exposure. Changes over time in underlying rates in Japan make it difficult to determine how to transfer risks across populations.

176. The LSS Tumor Registry incidence analysis for 1958–1987 [T1] gave an estimated ERR of 0.72 (95% CI: 0.29, 1.28) $Sv^{-1}$ ($p < 0.001$), with no significant variation between the sexes. The ERR per unit dose declined with increasing age at exposure and with attained age, but the decrease with attained age was statistically significant while that with age at exposure was not. The estimated ERR at age 50, after exposure at age 30, was 1.88 (90% CI: 0.69, 3.86) $Sv^{-1}$. The EAR per unit dose increases with time in the LSS mortality study [P1]. Nakatsuka et al. [N12] analysed colon cancer incidence for 1950–1980, obtaining results similar to those of Thompson et al. [T1] when the data were restricted to the period 1959–1980, but with a significant decrease in ERR per unit dose with age at exposure. An interesting finding was that very similar linear dose–response coefficients were obtained for cancers located in the caecum and ascending colon (ERR = 0.80 $Sv^{-1}$; 90% CI: 0.07, 1.96; $p = 0.06$ for trend), transverse and descending colon (ERR = 1.09 (90% CI: 0.17, 2.59) $Sv^{-1}$; $p = 0.04$) and sigmoid colon (ERR = 0.96 (90% CI: 0.33, 1.87) $Sv^{-1}$; $p = 0.003$).

177. Indications of radiation-related colon cancer risk were obtained from studies of patients irradiated for treatment of benign pelvic disease, including 267 patients followed for an average of 16 years, in which 4 intestinal cancer deaths were observed versus 1 expected [B49]. More convincing evidence came from a follow-up of patients treated for metropathia haemorrhagica [S75], which found no excess rates of mortality due to colon cancer within 5 years after treatment, but observed 21 colon cancer deaths versus 13.5 expected 5 or more years after treatment. The most recent follow-up of this series [D7] found 2 colon cancer deaths versus 1.7 expected within 5 years after treatment, and 45 versus 31.2 expected 5 or more years after treatment (O/E = 1.44; 90% CI: 1.1, 1.8). The estimated average colon dose was 3.2 Gy, with an 80% mid-range of 2.4–3.7. In other studies, only 32 colon cancers were observed compared with 29 expected among 1,893 women treated with radium implants or X-rays for benign gynaecological disorders [W30], and an incomplete follow-up of women treated with radium for benign uterine haemorrhage found no excess rates of mortality due to colon cancer [D41].

178. The UNSCEAR 2000 Report [U2] concluded that there was strong evidence of an effect on colon cancer risk due to ionizing radiation exposure that was consistent with a linear dose response. The effects of sex, age at exposure and time since exposure on the ERR per unit dose are not clear. The UNSCEAR 2000 Report [U2] considered the evidence for colon cancer risk by radiation type and concluded that there was little precision in the low-dose studies of external exposure to low-LET radiation and of internal exposure to low-LET and high-LET radiation, which limits the conclusions that can be drawn with respect to these modes of exposure.

## 3. New or updated studies

179. This section considers several studies (table 23) published well before the UNSCEAR 2000 Report [U2], although these studies were not considered there.

### *(a) External low-LET exposures*

180. In the latest follow-up of the LSS cohort, colon cancer mortality rates during the period 1950–1997 increased with neutron-weighted (weight = 10) radiation dose ($p < 0.001$), with negligible difference between the sexes [P9]. The estimate for ERR per unit dose based on a linear model, for exposure at age 30 with no assumed variation with attained age, was 0.54 (90% CI: 0.13, 1.2) $Sv^{-1}$ for males and 0.49 (90% CI: 0.11, 1.1) $Sv^{-1}$ for females, with a 25% decrease per decade of age at exposure.

181. In their tumour registry study of benign gastrointestinal tumour incidence among survivors of the atomic bombings, Ron et al. [R35] observed 215 histologically confirmed cases of benign colon tumour diagnosed between 1958 and 1989. There was little evidence of a radiation dose response (ERR = 0.14 (95% CI: –0.20, 0.76) $Gy^{-1}$). However, 74% of the tumours were diagnosed between 1985 and 1989, presumably reflecting a more frequent use of colonoscopy. The dose response was positive for the period 1958–1984 (ERR = 0.64 (95% CI: –0.11, 2.46) $Gy^{-1}$), whereas that for the period 1985–1989 was negative (ERR = –0.20 (95% CI: undetermined, 0.47) $Gy^{-1}$.

182. In their reports of cancer mortality among ankylosing spondylitis patients, for whom the estimated average colon dose [W8] was 4.1 Gy, Court Brown and Doll [C32] and Smith and Doll [S32] tended to discount their consistent observation of excess colon cancer mortality, because of known associations between spondylitis and ulcerative colitis and between ulcerative colitis and colon cancer.

Smith and Doll [S32] observed 16 colon cancer deaths 9 or more years after treatment, as opposed to 10.4 expected, a non-significant excess. However, 12 deaths in contrast to 6.9 expected were seen within the first 8 years after treatment, of which 6 occurred within the first 2 years after treatment, when 2.5 would have been expected. The most recent follow-up [W8] estimated RRs of 1.30 (95% CI: 1.07, 1.55), or ERR = 0.08 (95% CI: 0.02, 0.14) $Gy^{-1}$, 5 or more years after treatment, with a significant decrease in RR over time following treatment.

183. With an estimated typical average organ dose of 24 Gy, the colon was one of the heavily irradiated sites in an international cancer registry study of the risk of second primary cancer occurring among very-long-term survivors of cervical cancer [K1], although as generally in this study, no organ dose estimates were used in the analysis. Among patients treated with radiation, 178 colon cancers were diagnosed within 9 years following cervical cancer diagnosis, as opposed to 162.7 expected (O/E = 1.09; 90% CI: 0.96, 1.2), and 296 were observed versus 267.7 expected 10 or more years after cervical cancer diagnosis (O/E = 1.12; 90% CI: 1.01, 1.2). Among the smaller number of cervical cancer patients not given radiotherapy, the findings were very similar: 39 observed versus 37.3 expected within 9 years after cervical cancer diagnosis (O/E = 1.05; 90% CI: 0.77, 1.32), and 56 observed versus 53.1 expected 10 or more years after diagnosis (O/E = 1.05; 90% CI: 0.82, 1.29). Thus this study suggests that, at very high colon doses, there is little or no excess risk of colon cancer. The parallel case-control study assessed 409 cases and 759 controls but reported no increase in risk (RR = 1.02; 90% CI: 0.7, 1.6), despite the fact that sizeable numbers of cases were exposed at very high doses (e.g. 44 cases received doses of greater than 40 Gy). There was no observed trend of risk with dose ($p$ = 0.22); if anything, the risk of colon cancer appeared to decrease with increasing dose [B8].

184. Although not considered in the UNSCEAR 2000 Report [U2], the study of Artalejo et al. [A32] reported a slight deficit of colon cancer mortality among workers for the Spanish Nuclear Energy Board; the SMR was 0.83 (95% CI: 0.33, 1.72) but was based on only 7 cancer deaths, of which 1 was among the 27% of the cohort who had been miners and may have been exposed to alpha radiation [A32]. Rogel et al. [R54] reported no significant differences in colon cancer mortality rates compared with French national rates among radiation workers of Électricité de France (8 observed versus 8.3 expected deaths; SMR = 0.97; 90% CI: 0.48, 1.75).

#### *(b) Internal low-LET exposures*

185. A study of 6,841 Swedish, French and Italian patients treated with a combination of conventional (external beam) radiotherapy and $^{131}$I for thyroid cancer documented a modest, but not statistically significant, increase in colorectal cancer incidence (SIR = 1.3; 95% CI: 0.9, 1.6; 69 cases) [R38]. However, there was a statistically significant trend of increasing colorectal cancer risk with administered quantity of $^{131}$I. Adjusted for external radiotherapy, the ERR per activity of $^{131}$I administered was 0.10 (95% CI: 0.08, 0.27) per gigabecquerel. There was a statistically significant trend also among those who received no external radiotherapy, for whom the ERR per activity of $^{131}$I administered was 0.15 (95% CI: 0.02, 0.38) per gigabecquerel [R38]. Unfortunately there was no breakdown of the values for colorectal cancers into those for colon and rectal cancers separately for this cohort, but it is likely that the vast majority of these cancers were colon cancers.

#### *(c) Internal high-LET exposures*

186. The International Thorotrast Study [T30] did not find any elevation in colon cancer mortality risk. There were 16 cases in both the Thorotrast-exposed and the comparison group in the Denmark–Sweden part of this study, resulting in an RR of 1.5 (95% CI: 0.7, 3.0) [T30]. There were 5 deaths in the Thorotrast-exposed group and none in the comparison group for the United States part of this study, resulting in an undefined RR with a lower 95% CI of 0.5 [T30]. No colon (or other organ) dose estimates have been made for this study, and no trend with administered Thorotrast volume was reported.

### 4. Summary

187. The available evidence continues to indicate that colon cancer is inducible by ionizing radiation, compatible with a linear dose response. The evidence for this comes almost entirely from studies of external low-LET exposure, in particular from the LSS mortality data on the survivors of the atomic bombings. The LSS data suggest that the ERR per unit dose decreases with increasing age at exposure.

## G. Rectal cancer

### 1. General background

188. Cancer of the rectum occurs about half as frequently as cancer of the colon. Risks tend to be higher in developed countries (whether in North America, Europe, Oceania or Japan), with age-standardized world rates generally lying between 5 and 25 cases per $10^5$ PY, whereas rates are generally lower—less than 5 cases per $10^5$ PY—in Africa and Southern Asia [P19]. Many of the risk factors for colon cancer apply also for rectal cancer. In particular, there are well-known hereditary risk factors (e.g. familial adenomatous polyposis (FAP)), dietary risk factors (high-fat and low-fibre diets, diets deficient in fruit and vegetables) and risk factors associated with certain other chronic diseases (e.g. ulcerative colitis and Crohn's disease) [S58].

## 2. Summary of UNSCEAR 2000

189. Rectal cancer was not considered in the UNSCEAR 2000 Report [U2]. The Committee has therefore considered a number of earlier studies, which are reported in table 24 and discussed in the text.

### *(a) External low-LET exposures*

190. Although statistical data on cancers of the colon and rectum are often presented together as "colorectal cancer", the radiation dose–response behaviours of the two cancers differ considerably. In the most recent analysis of cancer mortality among the survivors of the atomic bombings [P9], rectal cancer mortality was not associated with radiation dose among men. Based on 172 deaths during the period 1950–1997, a linear model estimate for ERR was –0.25 (90% CI: <–0.3, 0.15) $Gy^{-1}$ for exposure at age 30 in a model with no dependence upon attained age. However, it was positively and significantly associated with dose among women. Based on 198 deaths, the ERR was 0.75 (90% CI: 0.16, 1.6) $Gy^{-1}$, again for exposure at age 30. The tumour registry analysis covering the period 1958–1987 [T1] found no significant dose response based on 351 cases of colon cancer arising evenly between the two sexes, with no difference between the sexes, and no significant trends with age at exposure or attained age.

191. In sharp contrast to the data on the survivors of the atomic bombings, there was a highly significant excess of rectal cancer among cervical cancer patients treated with radiation [K1]: the typical average organ dose was 30–60 Gy, and 340 cases were observed versus 205.5 expected (O/E = 1.7; 90% CI: 1.5, 1.8); whereas, among patients not given radiotherapy, there were 58 cases versus 43.1 expected (O/E = 1.3; 90% CI: 1.1, 1.6). No excess was seen among the radiotherapy patients 1–9 years after cervical cancer diagnosis (66 observed versus 81.5 expected), but there were 274 observed versus 124 expected 10 or more years after diagnosis (O/E = 2.2; 90% CI: 2.0, 2.4) (90% intervals calculated from table 5 of reference [K1]). In the parallel case-control study, individual organ doses could not be estimated, because small changes in the position of the radium inserts would lead to large changes in rectal dose [B8]. Doses are likely to be very high, of the order of hundreds of grays. Nevertheless, rectal doses could be grouped into broad ranges, and using these there is a trend with dose of high statistical significance ($p$ = 0.002 for 10-year survivors) [B8].

192. Increased incidence of rectal cancer has been observed in two studies of prostate cancer patients given radiotherapy, based on data from the SEER cancer registry [B50, B51]. Brenner et al. [B50], using SEER data for the period 1973–1993, found an increase that was not statistically significant in rectal cancer risk more than 5 years after prostate cancer diagnosis for patients given radiotherapy (O/E = 73/77 = 0.95) compared with those receiving surgery only (O/E = 86/121 = 0.75). The RR at 5 years after diagnosis of prostate cancer patients given radiotherapy compared with those receiving only surgery was 1.35 (95% CI: –0.01, 1.86), but at 10 years after prostate cancer diagnosis, the RR became 2.05 (95% CI: 1.09, 3.92) [B50]. A more recent analysis by Baxter et al. [B51] used SEER registry data from the nine SEER registries that contributed data in or before 1991 to identify prostate cancer cases diagnosed during the period 1973–1994 who were alive 5 or more years after their diagnosis, who had not been diagnosed with a colorectal cancer during the first 5 years after prostate cancer diagnosis, and who had undergone radiotherapy or surgical treatment not limited to orchidectomy. Kaplan–Meier curves representing the time from prostate cancer diagnosis until development of colorectal cancer were compared between the patients undergoing surgery and those receiving radiotherapy. The observed hazard ratio for rectal cancer following radiation therapy compared with surgery only was 1.7 (95% CI: 1.4, 2.2). The corresponding hazard ratios for "potentially irradiated" colorectal sites (rectosigmoid junction, sigmoid colon and caecum) and non-irradiated sites (the rest of the colon) were 1.08 (95% CI: 0.92, 1.26) and 0.95 (95% CI: 0.78, 1.15), respectively. The radiation dose to the rectum would be highly non-uniform, but at the point of highest exposure would approximate that to the prostate gland [B52]. In a "conventional" 70 Gy prostate treatment plan of around 1990, perhaps 40% of the rectum received more than 60 Gy, and 80% more than 40 Gy [P43]. Currently, with a 75 Gy intensity-modulated radiation treatment (IMRT) plan, perhaps 20% of the rectum receives more than 60 Gy, and 50% more than 40 Gy [L84].

193. In a group of Scottish women treated with X-rays for metropathia haemorrhagica (uterine bleeding), 14 deaths from rectal cancer were observed compared with 12.36 expected (SMR = 1.13; 95% CI: 0.62, 1.90). The average doses to the rectum were high: 4.9 Gy. There was a suggestive, though not statistically significant, trend of increasing mortality with dose: the ERR is 0.04 (95% CI: –0.09, 0.16) $Gy^{-1}$. A group of United States women treated with intrauterine radium to control uterine bleeding also had generally high rectal doses: mean = 3.0 Gy. This group exhibited little or no excess rectal cancer risk (15 observed deaths, SMR = 1.0), and there was no trend of excess risk with time since exposure or with radiation dose: the ERR is 0.03 (95% CI: –0.14, 0.19) $Gy^{-1}$ (1-sided $p$ = 0.45). A group treated for ankylosing spondylitis probably also had fairly high rectal doses (mean colon dose = 2.58 Gy) [W8]. There was no evidence of excess risk of rectal cancer mortality: there were 62 deaths compared with 56.9 expected (SMR = 1.09; 95% CI: 0.83, 1.39). There was no trend of excess risk with time in this group, but no dose–response analysis has been reported [W8].

194. In a cohort of United Kingdom radiation workers, there was no suggestion of increased rectal cancer risk in comparison with the national population: there were 123 deaths compared with 155.58 expected (SMR = 0.79; 95% CI: 0.66, 0.94) [M12]. However, there was a trend (at borderline levels of statistical significance) of increasing rectal

cancer mortality with dose in this cohort: the ERR is 1.69 (95% CI: –0.12, 5.01) $Gy^{-1}$ (1-sided $p$ = 0.067) [M12]. There was no suggestion of excess cancer incidence rate in comparison with national rates in a group of Canadian radiation workers (145 cases observed compared with 199.0 expected, SIR = 0.73; 90% CI: 0.63, 0.84), but as for other end points in this study, there was a very strong trend of increasing rectal cancer incidence with external dose: the ERR is 13.8 (95% CI: 3.7, 33.6) $Sv^{-1}$ [S8]. As with the parallel analysis of the mortality data associated with this cohort [A8], concerns have been expressed about the reliability of record linkage, a possible source of bias [G16].

#### *(b) Internal high-LET exposures*

195. The International Thorotrast Study [T30] did not find any elevation in rectal cancer mortality risk. There were 8 cases in the Thorotrast-exposed group and 7 in the comparison groups in the Denmark–Sweden part of this study, resulting in an RR estimate of 1.8 (95% CI: 0.6, 5.3) [T30]. No rectal (or other organ) dose estimates have been made for this study, and no trend with administered Thorotrast volume was reported.

### 3. Summary

196. There is little or no information on radiation-related risk of rectal cancer at doses of less than about 1 Gy, but it is reasonably clear that there is a radiation-related excess risk for rectal doses of tens of grays. It is also clear that the small intestine, colon and rectum vary greatly in their carcinogenic responses to ionizing radiation. There are few data on risks in relation to anything other than external low-LET exposure.

## H. Liver cancer

### 1. General background

197. There is wide geographical variation in liver cancer incidence rates. The disease is very common in many parts of Asia and Africa, but is infrequent in Western Europe and the United States [P31]. For example, in parts of Thailand, annual age-standardized world rates are as high as 88.0 and 35.4 cases per $10^5$ persons for men and women, respectively, but in most of the United States, age-standardized world rates are fewer than 5 cases per $10^5$ persons [P19]. Overall, primary liver cancer is the fifth most common cancer worldwide [L72]. Accurate data on primary liver cancer are difficult to obtain. Mortality data are unreliable because the liver is one of the most frequent sites for metastatic cancer. Up to 50% of liver cancers reported on death certificates are metastatic rather than primary liver cancers, and tumour registries vary in their success in distinguishing primary and metastatic liver cancers.

198. The great majority of primary liver cancers in adults are hepatocellular carcinomas (HCCs); about 75–80% of HCCs are aetiologically associated with chronic infection with the hepatitis B virus (HBV) [L72]. Infection with the hepatitis C virus (HCV) is responsible for about 10–20% of viral-associated HCCs, and plays an important role in some countries, notably in Japan. Other aetiological factors include heavy alcohol consumption, liver cirrhosis, the presence of liver flukes and exposure to aflatoxins. HCC is 4–5 times more frequent in men than in women.

### 2. Summary of UNSCEAR 2000

199. The UNSCEAR 2000 Report [U2] had limited data on liver cancer from external exposures to low-LET radiation, but far more information was available on internal high-LET exposures from Thorotrast. None of the studies on medically or occupationally exposed populations suggested an association between radiation exposure and liver cancer once dose–response relationships were examined, although the difficulty in distinguishing primary from metastatic liver cancers may have obscured any association.

200. The UNSCEAR 2000 Report [U2] stated that the LSS provided the most convincing evidence for excess liver cancers following exposure to low-LET radiation. The LSS showed that liver cancer was the third largest cancer risk due to radiation, after stomach and lung cancer. A significant dose response was found for liver cancer, with an ERR of 0.52 $Sv^{-1}$ for males and 0.11 $Sv^{-1}$ for females. The relationship was strengthened by the analysis of incidence data based on histologically and clinically verified primary liver cancer cases, mostly HCCs [C25]. In the latter study, the dose response was linear and the ERR was estimated to be 0.81 $Sv^{-1}$ (liver dose). Males and females had a similar RR so that, given a threefold higher underlying incidence rate for males, the radiation-induced excess incidence rate was substantially higher for males. The excess risk peaked for those exposed in their early 20s, with essentially no excess risk for those exposed before age 10 or after age 45.

201. Studies of Thorotrast-exposed patients consistently showed increased risks of liver cancer due to exposure to alpha radiation, but in contrast to the LSS, the liver cancers associated with Thorotrast exposure were most commonly cholangiocarcinoma, followed by angiosarcoma and HCC. There was also an indication that Mayak workers exposed to plutonium had an excess of liver cancer, although the numbers were small and the doses were not well characterized [G2].

### 3. New or updated studies

#### *(a) External low-LET exposures*

202. Epidemiological data on liver cancer associated with external exposure to low-LET radiation continue to be

limited. The data available up to the 1990s were presented in table 9 of the UNSCEAR 2000 Report [U2].

203. Liver cancers following external radiation exposure were primarily HCCs in the LSS [S70], but in the Thorotrast studies they have consisted mainly of angiosarcomas and cholangiocarcinomas [D36, T30]. The high prevalence of HBV or HCV infections found in Japan may act as confounding factors for the radiation effects in the LSS [F13]. HCC arises from liver parenchymal cells, while intrahepatic cholangiocarcinomas arise from epithelial cells of the bile duct. It is also likely that the differing histological distributions, with a predominance of cholangiocarcinomas, reflect the fact that for Thorotrast patients, areas of the liver containing bile ducts, from which cholangiocarcinomas arise, receive a daily dose of alpha particle radiation about 15 times higher than that received by hepatic cord tissue [D35].

204. In the latest LSS report on cancer mortality [P9], there were 1236 deaths from liver cancer, the leading cause of cancer death after cancers of the stomach and lung. A significant dose response is found for liver cancer, with an ERR of 0.39 $Sv^{-1}$ for males and 0.35 $Sv^{-1}$ for females, both exposed at age 30 years. Data on risk stratified by sex and specific age categories, or by specific latency periods, were not presented.

205. A detailed study of HBV and HCV infections in the LSS showed that both types of viral infection conferred a large risk for HCC: odds ratio (OR) = 5.5 (95% CI: 2.6, 12) and OR = 6.2 (95% CI: 2.8, 14), respectively. Even with the strong main effect of HCV infection, among those without cirrhosis there was a statistically significant interaction with radiation dose such that HCV-infected subjects were at a 58-fold (95% CI: 2.0, ∞; $p = 0.017$) higher risk of HCC for a sievert of radiation dose [S70]; such an interaction was not found for patients with cirrhosis. Regardless of the presence of cirrhosis, there was little evidence of an interaction between HBV infection and radiation exposure for HCC.

206. Also compatible with an interaction between radiation and hepatitis infection are data relating clearance of HBV and radiation exposure [F13]. The presence of both hepatitis B surface antigen (HBsAg) (indicating current infection) and of anti-hepatitis-B core antibody (a marker for both cured and current infections) increased with radiation dose, whereas that of anti-hepatitis-B surface antibody (indicating cured infection) did not. Although these data suggest that radiation exposure may reduce the likelihood of clearing a subsequent HBV infection, the authors urged further study.

207. Although not considered in the UNSCEAR 2000 Report [U2], the study of Artalejo et al. [A32] reported a slight excess of mortality from liver cancer among workers for the Spanish Nuclear Energy Board; the SMR was 1.51 (95% CI: 0.86, 2.46), but this was based on only 16 cancer deaths, of which 4 were among the 27% of the cohort who had been miners and may have been exposed to alpha radiation [A32]. Rogel et al. [R54] reported a statistically non-significant deficit of mortality due to liver cancer compared with French national mortality rates among radiation workers of Électricité de France (3 observed versus 5.0 expected deaths; SMR = 0.60; 90% CI: 0.16, 1.54).

### *(b) Internal low-LET exposures*

208. Epidemiological data with regard to liver cancer and internal low-LET exposures continue to be rare. As summarized in the UNSCEAR 2000 Report, in the United States thyrotoxicosis study, 21,000 hyperthyroid patients treated with $^{131}I$ were followed up for 45 years; 39 liver cancer deaths were observed, with an SMR of 0.87 [R3, U2]. The doses received by the liver were not estimated but were presumably very low. An increasing, albeit not statistically significant ($p = 0.78$), trend in liver cancer mortality with dose was observed in the study of persons exposed to weapons test fallout in the Semipalatinsk area of Kazakhstan [B58]. The aggregate ERR based on an internal analysis was 0.45 (95% CI: –0.18, 1.71) $Sv^{-1}$; however, when analysis was restricted to the exposed group, based on individual dose estimates, the trend estimate was negative, –0.08 (95% CI: –0.41, 1.00) $Sv^{-1}$. As noted in section II.D, "ecological bias" may operate in this study, so these findings should be treated with caution.

### *(c) Internal high-LET exposures*

209. As noted previously [U2], $^{232}Th$ is a primordial, alpha-emitting radionuclide with a physical half-life of more than 10 billion years. Thorotrast—colloidal ($^{232}Th$) thorium dioxide—was used widely as an intravascular contrast agent for angiography in Europe, the United States and Japan from the late 1920s to 1955. Thorotrast aggregates injected intravascularly tend to be incorporated into the tissues of the reticuloendothelial system, mainly the liver, bone marrow and lymph nodes. Deposition results in continuous alpha particle irradiation throughout life at a 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 [C34]. 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 [K41, M46], but a re-evaluation of liver organ mass has indicated that the annual dose is 0.40 Gy [K42]. 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 [I19]. Patients from the late 1920s to 1955 who were administered Thorotrast have been followed in Germany, Portugal, Denmark, Sweden, Japan and the United States. The results of studies conducted in Germany [V3, V4, V7], Portugal [D15], Denmark [A5, A28, A29] and Japan [M14, M19, M47] were reviewed in detail in the UNSCEAR 2000 Report [U2], and are summarized in table 25.

210. Results describing cancer incidence in the Swedish Thorotrast study were recently published [N1], and were incorporated in a later combined analysis of the Danish, Swedish and United States patients [T30]. The combined cohort consisted of 3,042 patients who had been injected during cerebral angiography with either Thorotrast ($n$ = 1,650) or a non-radioactive agent ($n$ = 1,392) and who survived two or more years. SIRs for Thorotrast-exposed ($n$ = 1,204) and 1,180 comparison patients (Denmark and Sweden) were estimated, and RRs, adjusted for population, age and sex, were calculated with multivariate statistical models. For United States patients ($n$ = 446 exposed, 212 not exposed), comparable procedures were used to estimate SMR and RR. In Denmark and Sweden, 136 primary liver cancers were diagnosed in the Thorotrast-exposed group and none in the comparison group (SIR = 108.9; $p < 0.05$; RR = ∞; 95% CI: 44.2, ∞). RRs were similar for all cancer sites for males (RR = 3.6; 95% CI: 2.8, 4.8) and females (RR = 3.3; 95% CI: 2.6, 4.2), but for liver cancer they were not presented separately for each sex. In the United States, 22 deaths due to primary liver cancer were reported among the Thorotrast-exposed patients and none in the comparison group (SMR = 22.5; 95% CI: 1.8, 464.3). The RR of primary liver cancers (Sweden and Denmark) increased with time after angiography ($p < 0.001$ for trend), and significant excesses (SIR = 4.0) persisted for 50 years. The actuarial risk for all liver cancers after 50 years of follow-up increased with the amount of Thorotrast injected (68.8% after >20 mL, 68.5% after 11–20 mL and 33.8% after 3–10 mL) ($p$ for non-homogeneity in dose category < 0.0001). Increasing cumulative radiation dose (expressed as volume of injected Thorotrast in millilitres × max[0, time since injection in years—5 years] × $10^2$) was associated with an increasing risk of primary liver cancer ($p$ trend = 0.001).

211. As summarized earlier [U2], liver cancer mortality was 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 [G2]. Liver cancer risks were elevated among workers with plutonium body burdens estimated to exceed 7.4 kBq, compared with workers with burdens of below 1.48 kBq (RR = 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 methodology for plutonium dosimetry, it was possible neither to quantify liver cancer risks from plutonium exposure in terms of organ dose, nor to make a reliable evaluation of the risk from external radiation in this cohort [G2].

#### 4. Summary

212. An association of liver cancer with radiation exposure has not been demonstrated in studies of groups of people medically or occupationally exposed to external or internal doses of low-LET radiation. However, the updated mortality data from the LSS of survivors of the atomic bombings continue to indicate a strong dose response ($p < 0.001$). Studies of Thorotrast-exposed patients consistently show increased risks of liver cancer that persist for 50 years due to alpha particle radiation exposure.

213. While the most frequent type of liver cancer associated with Thorotrast exposure is typically cholangiocarcinoma, followed by angiosarcoma and hepatocellular carcinoma, the excess risk associated with low-LET radiation exposure among the survivors of the atomic bombings is primarily expressed as HCC. Underlying rates of liver cancer are high in Japan, especially among males, and the high rates have been attributed to hepatitis viral infection, particularly infection with HCV. In transferring liver cancer risk estimates from one population to another, differences in the underlying liver cancer rates, as affected by the prevalence of hepatitis viral infection, should be considered. The significant interaction between radiation dose and HCV infection in the development of liver cancer among patients without cirrhosis merits further study.

### I. Pancreatic cancer

#### 1. General background

214. The pancreas consists of two separate functional entities—an endocrine portion that produces (most importantly) insulin and glucagon, and an exocrine organ that is an integral part of the digestive system, producing enzymes such as trypsin, chymotrypsin, amylase and lipase [A33]. Cancer of the pancreas can be considered virtually synonymous with exocrine adenocarcinoma of the pancreas, since endocrine neoplasms are relatively rare [A33]. Pancreatic cancer is one of the most rapidly fatal cancers, and its presentation and course are marked by severe pain. There is less than a 20% chance of surviving one year from diagnosis [A21, A33]. However, pancreatic cancer is relatively rare, with annual age-standardized world rates generally fewer than 10 cases per $10^5$ persons for both men and women [P19]. There is relatively small variation in incidence rates between countries, or between men and women, with age-standardized world rates ranging from about 1 case per $10^5$ persons in parts of Africa and Asia to about 15 cases per $10^5$ persons among some male United States black populations [P19]. Pancreatic cancer incidence and mortality rates increased in the United States between 1920 and 1965 [K51], but rates have been largely stable since then [A21]. The most consistent risk factor for pancreatic cancer is smoking, but diet, and in particular dietary fat, coffee and alcohol consumption, has also been indicated as a risk factor [A33].

#### 2. Summary of UNSCEAR 2000

215. Pancreatic cancer was not considered in the UNSCEAR 2000 Report [U2].

### 3. New or updated studies

#### *(a) External low-LET exposures*

216. As shown in table 26, there is no statistically significant excess pancreatic cancer mortality or incidence in the LSS [P9, P48]. For example, 163 deaths from pancreatic cancer were recorded in the LSS up to 1997 [P9]. Preston et al. [P9] report an ERR for pancreatic cancer in males of –0.11 (90% CI: <–0.3, 0.44) $Sv^{-1}$, and an ERR for females of –0.01 (90% CI: –0.28, 0.45) $Sv^{-1}$. The same is true for many other groups. In a case-control study of women receiving radiation treatment for cervical cancer, there was an OR for radiation exposure of 1.39 (90% CI: 0.7, 2.7), equivalent to an ERR of 0.21 (90% CI: –0.16, 0.89) $Gy^{-1}$ (table 26) [B8]. There was no statistically significant ($p = 0.37$) trend of OR with dose in this study [B8]. In a cohort of British radiologists, there was a statistically significant SMR among the "earliest entrance group" (those first registered in the period 1897–1920), when presumably doses would have been highest (5 deaths versus 1.29 expected, SMR = 3.88) (2-sided $p < 0.05$); there was no statistically significant excess among the radiologists registering after 1920 [B2]. The United States peptic ulcer study demonstrated a strong exposure-related increase in pancreatic cancer mortality; the ERR was 0.04 (95% CI: 0.0, 0.08) $Gy^{-1}$ [C4]. However, when attention was restricted to exposed patients only, there was no evidence of a positive trend: the ERR was –0.03 (95% CI: –0.10, 0.05) $Gy^{-1}$ [C4]. This lack of dose response is possibly a consequence of the high doses and generally narrow spread of doses received by the exposed group of patients [C4]. Inskip et al. analysed cancer mortality in a group of women treated with intrauterine $^{226}Ra$ capsules for uterine bleeding, and did not observe any statistically significant excess risk of pancreatic cancer with dose: the ERR was 0.14 (90% CI: –2.76, 28.84) $Gy^{-1}$ [I4]. A large and highly statistically significant trend of increasing pancreatic cancer incidence with radiation dose was observed in a Swedish group treated for haemangioma in infancy: the ERR was 25.1 (95% CI: 5.5, 57.7) $Gy^{-1}$ [L10]. However, this finding was based on only 9 tumours, and as the authors note, might well be due to chance. A study of benign breast disease among Swedish women observed a negative trend of pancreatic cancer mortality with dose, based on 30 deaths (14 in the exposed group, 16 in the unexposed group): the ERR was –0.37 (95% CI: <–0.37, 0.8) $Gy^{-1}$ [M3].

217. There was a trend of increasing pancreatic cancer mortality risk with cumulative film badge dose that approached conventional levels of statistical significance (1-sided $p = 0.07$) among workers at the Hanford site in the United States [G10]. The authors were inclined to treat the association as spurious, in view of the large number of end points studied and the lack of any prior basis for assuming a risk of pancreatic cancer [G10]. Combined analysis of the data on the Hanford, Oak Ridge National Laboratory and Rocky Flats weapons plant workforces in the United States did not indicate any statistically significant excess risk of pancreatic cancer mortality, and in particular no statistically significant trend in risk with dose [G8].

218. A large and (for males) statistically significant excess pancreatic cancer incidence has been seen in the Canadian National Dose Registry [S8]. The ERR for males was 9.2 (90% CI: 0.10, 36.8) $Sv^{-1}$, based on 58 cases; for males and females combined, the ERR was 6.9 (90% CI: <0, 27.1) $Sv^{-1}$, based on 76 cases. An increase of similar magnitude, although not statistically significant, was observed for males in the parallel mortality data, from which the ERR was 7.3 (90% CI: –4.4, 19.0) $Sv^{-1}$, based on 72 deaths [A8]. There was no suggestion of an increased risk for females from these data: the ERR was –0.2 (90% CI: –18.7, 18.3) $Sv^{-1}$, based on 15 deaths [A8]. As noted in section II.E above, similarly elevated ERRs per unit dose were found for many other cancer end points and for causes of death that included infectious diseases and accidental deaths, thus raising the question of bias in this study.

219. There was no statistically significant trend in pancreatic cancer mortality with cumulative film badge dose in a stratified cohort of United Kingdom radiation workers: the ERR was –0.003 (90% CI: –1.12, 2.31) $Sv^{-1}$, based on 129 deaths [M12].

220. There was a positive, but not statistically significant (1-sided $p = 0.115$), trend in pancreatic cancer mortality with radiation dose for the IARC three-country nuclear worker study [C3], based on 191 deaths from pancreatic cancer.

221. There was excess mortality due to pancreatic cancer at borderline levels of statistical significance compared with French national mortality rates among radiation workers of Électricité de France (11 observed versus 6.6 expected deaths; SMR =1.66; 90% CI: 0.93, 2.74) [R54].

#### *(b) Internal low-LET exposures*

222. There was no statistically significant excess of pancreatic cancer mortality in the United States thyrotoxicosis study, with 161 deaths versus 153.13 expected [R3]. There were no statistically significant trends in pancreatic cancer with administered $^{131}I$ in this study [R3].

#### *(c) Internal high-LET exposures*

223. There was a statistically significant increasing risk of pancreatic cancer mortality with increasing cumulative radon daughter exposure in a combined cohort of 11 groups of underground miners ($p < 0.05$); the ERR was 0.07% per working level month (WLM) (95% CI: 0.01, 0.12) [D10]. However, as there is little previous epidemiological basis for an association of pancreatic cancer with radon daughter exposure, and as this was the only one of 28 examined cancer sites to yield a statistically significant increased risk, the authors were inclined to view this as a chance finding [D10].

224. A statistically significant increase in pancreatic cancer mortality was observed among workers at a thorium processing plant (5 cancers observed, 1.21 expected; SMR = 4.13; 95% CI: 1.34, 9.63) [P37]. However, as with all studies involving occupational exposure to radiation, comparisons with cancer rates for the general population (which includes both workers and non-workers) may be misleading. Given the absence of information about risk in relation to cumulative exposure, it is difficult to interpret this finding.

225. Cancer incidences in a combined cohort of Danish, Swedish and United States patients given the diagnostic contrast medium Thorotrast have recently been published [T30]. The combined cohort consisted of 3,042 patients who had been injected during cerebral angiography with either Thorotrast ($n$ = 1,650) or a non-radioactive agent ($n$ =1,392) and who survived two or more years. A total of 14 pancreatic cancer cases were observed in the Thorotrast-exposed group, and 8 in the comparable control group. There were marginally statistically significant ($p$ = 0.07) trends of increasing pancreatic cancer incidence with time after injection of Thorotrast, and ($p$ = 0.05) with [injected Thorotrast volume] × [time since injection] [T30].

#### 4. Summary

226. There is little, if any, evidence for associations between pancreatic cancer and radiation dose, whether in relation to external or internal low-LET radiation, or to internal high-LET radiation.

### J. Cancers of the trachea, bronchus and lung

#### 1. General background

227. Lung cancer is both the most common malignant disease and the leading cause of cancer mortality worldwide. Rates tend to be higher in developed countries and lower in developing countries. For example, in parts of the United States, annual age-standardized world rates are as high as 107.0 and 40.8 cases per $10^5$ persons for men and women, respectively, but in most of Africa and South Asia, rates are fewer than 15 cases per $10^5$ persons [P19]. The wide range of geographical, temporal and sex differences in lung cancer mortality largely reflect variations in patterns of cigarette smoking, the main cause of the disease. Lung cancer incidence has increased rapidly since the beginning of the 20th century, but lung cancer mortality in males has begun to decline in several countries, including the United States, the United Kingdom and Finland. In most countries, lung cancer incidence rates are higher among people of lower socio-economic classes, probably because of differences in smoking prevalence. Lung cancer has also been linked with exposure to asbestos, with air pollution and with low consumption of vegetables and fruits [B34, S59].

228. Ionizing radiation has been linked with cancers of the trachea, bronchus and lung in numerous epidemiological studies. Dose–response relationships have been demonstrated for exposure to low-LET radiation, and also for exposure to inhaled high-LET alpha emitters, including radon (and its progeny) and plutonium.

#### 2. External low-LET exposures

##### *(a) Summary of UNSCEAR 2000*

229. Lung cancer has been strongly linked with radiation exposure in several studies, including those of the LSS cohort of survivors of the atomic bombings in Japan. Cancer incidence data from the LSS cohort for the period 1958–1987 indicated that the dose response was consistent with linearity, that the ERR ($Sv^{-1}$) for females was nearly four times that for males, and that there was little evidence that the ERR depended on either age at exposure or attained age [T1]. Results based on mortality data [P1] were similar, although the ratio of risk for females compared with that for males was not as striking. The analyses noted above did not take account of smoking habits. Efforts to do so [K35, P26, U2] suggested that the effect of the interaction of smoking and radiation was better described by an additive model than a multiplicative one, but could not definitively distinguish between the two models.

230. Lung cancer risk has been linked with radiation in studies of patients treated with radiation for ankylosing spondylitis and in patients receiving radiotherapy for Hodgkin's lymphoma. A noteworthy finding from the ankylosing spondylitis study was the decline in the RR 25 years after the first treatment [W8]. A limitation of this study is that data on smoking habits were not available. In a case-control study of lung cancer among Hodgkin's lymphoma patients, van Leeuwen et al. [V2] found a statistically significant supramultiplicative effect of radiation and smoking based on small numbers (30 cases, of whom 8 were either non-smokers or light smokers).

231. The UNSCEAR 2000 Report [U2] provided a detailed discussion of studies of lung cancer mortality among patients who received multiple fluoroscopies in the course of treatment for tuberculosis in Canada [H7] and the United States (Massachusetts) [D4]. The lung doses, mean age at exposure and follow-up were similar to those in the LSS cohort. Neither study found evidence of an association between lung cancer mortality and radiation dose. The Canadian study was large enough (25,000 subjects with lung doses in excess of 10 mSv) to demonstrate that estimates of the ERRs per unit dose were incompatible with those based on LSS data. These studies are important because, in contrast to the LSS cohort, in these cases the exposure was protracted. Howe [H7] explored several sources of potential bias, including dose measurement error, misclassification of lung cancer deaths as deaths from tuberculosis, smoking habits, differences in underlying rates, and

differences between patients with tuberculosis and healthy persons. No clear evidence of bias from any of these sources was found, but the possibility that the dose response might be different for patients with a lung disease (tuberculosis) cannot be excluded.

232. Studies of several cohorts with protracted exposures were reported and included a large international study of radiation workers [C3], studies of a selected group of early workers exposed at considerably higher doses at the Mayak nuclear plant in the former Soviet Union [K8, K17], and a study of natural radiation exposure in the Yangjiang area of China [T12, T14]. None of these studies indicated an elevated risk of lung cancer from low-dose, protracted exposure.

*(b) New or updated studies*

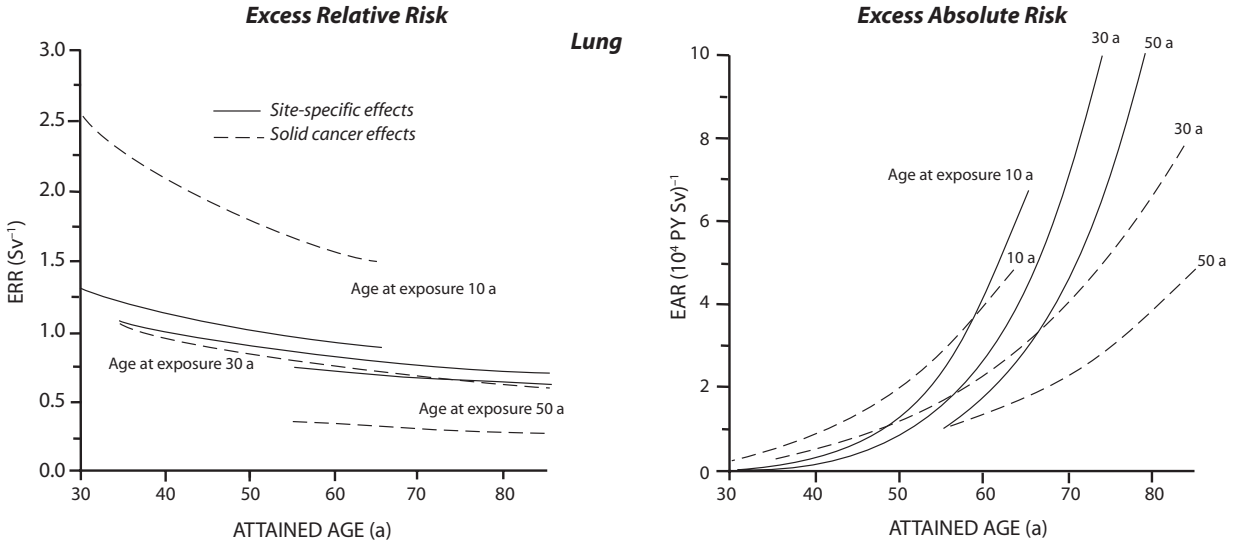
233. Risks of both lung cancer occurrence and mortality due to lung cancer have been strongly linked with radiation dose in the LSS cohort of survivors of the atomic bombings. On the basis of the most recent evaluation of mortality data from the LSS cohort [P9], the ERR per unit dose ($Sv^{-1}$) for females was about twice that for males, whereas the EARs per unit dose ($Sv^{-1}$) were similar for the two sexes. In contrast to many other solid cancers, for lung cancer there was only a very small decline in the ERR per unit dose with age at exposure, but the decline with attained age was comparable to that for all solid cancers as a group. By contrast, the EAR showed a pronounced increase with attained age (stronger than for most solid cancers) and a clear decline with age at exposure. As shown in figure XIII (from reference [P9]), the sex-averaged EAR for a person exposed at age 30 is about 2 $(10^4 \text{ PY Sv})^{-1}$ at attained age 60, but rises to about 7 $(10^4 \text{ PY Sv})^{-1}$ at attained age 70. Preston et al. [P9] note that underlying lung cancer mortality rates in the LSS cohort have increased with birth cohort, and that this may confound evaluation of the effects of age at exposure.

234. Pierce et al. [P17] evaluated the joint effects of smoking and radiation exposure on lung cancer incidence up to 1994 in a subset of about 45,000 members of the LSS cohort for whom data on both radiation doses and smoking habits were available. In analyses that took account of age at exposure, attained age, birth cohort and sex, they found that the effects of smoking and radiation exposure were significantly submultiplicative and consistent with an additive model. These investigators also found that adjustment for smoking reduced the ratio of the ERR per unit dose ($Sv^{-1}$) for females and males from 5.8 to 1.6; about 85% of the men and 16% of the women were smokers. In addition, after adjustment for smoking, there was evidence of a strong decline in the ERR per unit dose with increasing attained age, but no evidence of modification by age at exposure. Without adjustment, the decline with attained age was weaker and the ERR increased with age at exposure. Pierce et al. note that the ageing of the cohort and the higher smoking levels among more recent birth cohorts provide a stronger basis for evaluating the joint effects of smoking and radiation exposure than was possible in earlier analyses [K35, P26, U2].

235. Carr et al. [C4] evaluated risks of cancers of several exposed organs in patients (78% male) treated with radiation for peptic ulcer. This study updated a previous

**Figure XIII. Patterns of lung cancer mortality with age and time among the survivors of the atomic bombings in Japan (reproduced from Preston et al. [P9])**

The dark curves are fitted age-time patterns in the ERR (left panel) and EAR (right panel). The light dashed curves are the patterns obtained when the age and age-at-exposure effects are constrained to equal those for all other solid cancer. The curves are sex-averaged estimates of the risk at 1 Sv for people exposed at ages 10, 30 and 50, with attained ages corresponding to the follow-up period



analysis by Griem et al. [G6], and the number of lung cancer deaths increased from 99 to 125. Lung cancer mortality risk was significantly elevated compared with the risk among patients who were not treated with radiation, but there was no evidence of a dose response from analyses that were restricted to exposed subjects. Evaluation of the interaction of smoking and radiation exposure indicated that the data were compatible with a multiplicative interaction model.

236. Lung cancer risks were addressed in two recent case-control studies of Hodgkin's lymphoma patients and one such study of breast cancer patients. Swerdlow et al. [S60] conducted a case-control study that included 88 lung cancer cases and 176 matched control subjects with Hodgkin's lymphoma treated in the United Kingdom. No estimates of radiation doses were made, and data on smoking habits were available for only 39% of the subjects. There was no significant relation between risk and "radiation volume", used as a surrogate for radiation dose.

237. Travis et al. [T3] conducted an international population-based lung cancer case-control study that included 222 cases and 444 matched controls. Strengths of this study were the existence of dose estimates for the specific site of the lung tumour (or comparable location in matched controls), and of detailed data on both chemotherapy and tobacco use. The study showed a clear increase in risk with increasing dose after adjustment for chemotherapy and smoking habits, and suggested a multiplicative interaction of radiation exposure and smoking.

238. Gilbert et al. [G23] conducted additional analyses addressing the radiation effect on the basis of the 199 cases and 393 controls from the study by Travis et al. [T3] with adequate radiation dosimetric data and an additional 28 cases and 62 controls from a previous case-control study by van Leeuwen et al. [V2] (summarized in reference [U2]). There was little evidence of a departure from linearity or of modification in the ERR per unit dose ($Gy^{-1}$) with sex, time since exposure (after an initial 5-year latency period), age at Hodgkin's lymphoma diagnosis, or age at lung cancer diagnosis. There was evidence of a significant radiation dose response for all histopathological types of lung cancer evaluated (squamous cell, small cell, adenocarcinoma and large cell), and little evidence that the ERR per unit dose varied with type. The interaction of radiation exposure and smoking was consistent with a multiplicative relationship, but not with an additive one ($p < 0.001$). In contrast, the interaction of radiation exposure and chemotherapy was found to be well described by an additive relationship. The authors caution that the relevance of these findings for other populations may be limited owing to the very high doses (mean dose of 25 Gy) and the immunodeficiency inherent to Hodgkin's lymphoma and associated with chemotherapy.

239. Ford et al. [F15] conducted a case-control study (280 cases and 300 controls) of patients treated for breast cancer at the M.D. Anderson Cancer Center at the University of Texas in the United States. Their analyses suggest a supramultiplicative interaction between radiotherapy treatment and smoking. The study did not include quantitative information on either radiation exposure or smoking habits, and also did not consider possible modification of the risks by the length of period between breast and lung cancer diagnosis (latency), which was 0.5 to 10 years for 55% of the cases.

240. Zablotska and Neugut [Z8] conducted a cohort study using data from the SEER registry in the United States to investigate lung cancer incidence in groups of women treated for breast cancer with radiotherapy. After 10 years of follow-up, risk to the ipsilateral lung was significantly elevated for women treated after mastectomy (table 27), but not for women treated after lumpectomy, where doses to the lung are likely to have been much lower.

241. Several investigators have evaluated lung cancer mortality in a cohort of Russian workers at the Mayak nuclear facility. A difficulty in estimating the effects of the protracted external doses for this cohort is that many workers also received large doses from internal plutonium exposure, and only 40% of these workers were monitored for this exposure. Early analyses reviewed in reference [U2] showed little evidence of a relationship between lung cancer risks and external dose [K8, K17]. More recently, Kreisheimer et al. [K34] analysed data on 4,212 male workers in the main plants at the Mayak facility who were hired in the early period of operations (1948–1958) and for whom doses to the lung from exposure to plutonium could be estimated either because they had been monitored or because they had no potential for plutonium exposure. Using analyses that were adjusted for the lung dose due to plutonium, these authors found no significant association between lung cancer mortality and external dose.

242. Gilbert et al. [G12] evaluated lung cancer risk for a group of 21,790 Mayak workers, expanding the group evaluated in reference [K34] by adding females, persons hired in the period 1959–1972, auxiliary plant workers (with little potential for exposure) and workers potentially exposed to plutonium who were not monitored for this exposure. To adjust for plutonium exposure in the last group, a surrogate measure based on occupational histories was developed. These investigators found a highly significant dose response for external dose ($p < 0.001$). There was no evidence that the ERR per unit dose ($Gy^{-1}$) depended on sex, age at hire or attained age, although the power to address this was limited. An estimate for ERR per unit dose based only on workers whose doses due to plutonium could be estimated was 0.10 (<0, 0.29), similar to that obtained by Kreisheimer et al. [K34]. The authors note the possibility of bias due to inadequate adjustment for plutonium exposure, which might result from uncertainties in estimating doses due to plutonium as well as from using the surrogate measure. Parallel analyses of Mayak workers (external dose) and the LSS cohort indicated that both the level of risk and the patterns of risk for the ERR and EAR with sex and attained age were remarkably similar in the two cohorts.

243. Studies of nuclear workers exposed to low radiation doses generally provide little evidence of a dose response for lung cancer; this may be due to limited statistical power. In addition to the large international [C3, C41] and NRRW (United Kingdom) [M12] studies, recent studies of nuclear power industry workers in the United States [H44] and Japan [I14] showed no evidence either of excess risk in comparison with the general population or of dose response for lung cancer. Although the estimates of ERRs per unit dose ($Sv^{-1}$) for lung cancer [S8] and lung cancer mortality [A8] from the Canadian National Dose Registry were large, as noted in section II.E above, similarly elevated ERRs per unit dose ($Sv^{-1}$) were found for many other causes of death, which included infectious diseases and accidental deaths, thus raising the question of serious bias in this study.

244. Although not reported in the UNSCEAR 2000 Report [U2], the study of Artalejo et al. [A32] reported a slight deficit of lung cancer mortality among workers for the Spanish Nuclear Energy Board; the SMR was 0.98 (95% CI: 0.71, 1.31), based on 45 cancer deaths, of which 24 were among the 27% of the cohort who had been miners and may have been exposed to alpha radiation [A32]. Rogel et al. [R54] reported a statistically significant deficit of mortality due to lung cancer compared with French national mortality rates among radiation workers of Électricité de France (23 observed deaths versus 47.5 expected; SMR = 0.48; 90% CI: 0.33, 0.69); there was no statistically significant trend in respiratory cancer mortality with dose (ERR = 0.1 (90% CI: –7.5, 17.4) $Sv^{-1}$).

245. In a study of United States medical radiologic technologists, lung cancer mortality risk was not elevated compared with that of the general population, and there was no evidence of trends with either the length of radiation work or the year of first employment [M31]. The analyses were controlled for smoking habits as well as attained age, calendar year, race and sex. Lung cancer incidence was not elevated [S29]. Doses were not available for this study. A recent update of a study of cancer incidence among medical X-ray workers in China found elevated lung cancer risks in comparison with a control population of surgeons, physicians and otolaryngologists [W3]. However, the excess was largest for those workers who began their employment after 1970, when doses would have been smaller than in the earlier period. The authors note that their findings may be due to factors other than radiation exposure, such as smoking. The latest update of the mortality study of radiologists in the United Kingdom found excess lung cancer mortality among radiologists who had first registered before 1920 (based on 7 deaths), but no excess among those first registered in later years [B2].

### 3. Internal low-LET exposures

#### *(a) Summary of UNSCEAR 2000*

246. Studies of persons treated with $^{131}I$ were reviewed. Little evidence of excess risk was found, possibly because doses to the lung were low. Studies of cancer incidence near the Three Mile Island nuclear plant in the United States were also reviewed, with the conclusion that such studies were uninformative regarding radiation and lung cancer, and failed to provide convincing evidence that radionuclides released as a result of the accident contributed to lung cancer risk.

#### *(b) New or updated studies*

247. An increasing and highly statistically significant ($p$ = 0.0001) trend of lung cancer mortality with dose was observed in the study of persons exposed to weapons test fallout in the Semipalatinsk area of Kazakhstan [B58]. The aggregate ERR based on an internal analysis was 2.60 (95% CI: 1.38, 4.63) $Sv^{-1}$; when analysis was restricted to the exposed group, based on individual dose estimates, the trend estimate was somewhat reduced, 1.76 (95% CI: 0.48, 8.83) $Sv^{-1}$. As noted in section II.D, "ecological bias" may operate in this study, so these findings should be treated with caution.

### 4. Internal high-LET exposures (plutonium)

#### *(a) Summary of UNSCEAR 2000*

248. Studies of workers at the Mayak nuclear plant demonstrated clear evidence of a dose response for exposure to plutonium [K8, K17]. Studies of workers exposed to plutonium at the Sellafield plant in the United Kingdom [O1] and at Los Alamos National Laboratory in the United States [W6] failed to provide evidence of plutonium-related lung cancer risk, a finding that may be due to the relatively low doses and limited statistical power in these studies. The internal doses due to plutonium for workers in the United Kingdom and the United States were far lower than for workers at Mayak.

#### *(b) New or updated studies*

249. Three new analyses of data on workers at the Mayak nuclear plant quantify lung cancer mortality risk as a function of dose to the lung, and make use of improved internal dose estimates that became available in the year 2000. As noted above, Kreisheimer et al. [K34] evaluated lung cancer risks for a subcohort of Mayak workers whose plutonium doses could be estimated and who were hired in the period 1948–1958. In analyses that were adjusted for both external dose and smoking habits (i.e. yes or no), a linear dose–response relationship was found to describe the data well. Gilbert et al. [G12] evaluated a larger group of workers (see above), although the evaluation of the plutonium dose response was necessarily based on those workers whose plutonium doses could be estimated. These investigators confirmed the good fit of the linear model, and the estimated ERR per unit dose was similar to that obtained by Kreisheimer et al. They also fitted EAR models, and evaluated the modifying effects of sex, age at hire, attained age

and time since exposure on both the ERR and the EAR. The ERR per unit dose for females was about 4 times higher than that for males, whereas the EAR (expressed as excess deaths for $10^4$ PY Gy) for females was less than half that for males. The ERR per unit dose showed a strong decline with attained age, whereas the EAR increased with attained age until about age 65 and then decreased. Neither the ERR nor the EAR depended on age at hire. The ratio of coefficients for the effects of the internal dose due to plutonium and the external dose (i.e. the RBE) was estimated to be 33 (95% CI: 14, 98). Parallel analyses of Mayak workers, for whom plutonium dose estimates were adjusted by the quality factor of 20 recommended by the ICRP, and the LSS cohort indicated that the ERRs were reasonably similar in the two cohorts, although the decline with attained age was not observed in the LSS cohort. However, the pattern of the EAR with attained age was markedly different in the two cohorts. At younger ages (under 65 years), the EAR was higher for the Mayak workers, whereas at older ages, the EAR was higher for the LSS cohort. Comparisons were also made with risks observed for 11 cohorts of underground miners exposed to radon [C36]. The overall level of risk was compatible for the two types of exposure, and the decline in the ERR with attained age was very similar. After accounting for the effect of attained age, there was no evidence from the Mayak workers of the decline with time since exposure that was observed in the study of underground miners. However, this may have been because it was not possible to measure the pattern of lung dose accumulation due to plutonium in individual workers. Jacob et al. [J10] analysed the data using a two-stage "clonal expansion" model. In contrast to the other two analyses, the preferred model in this analysis was submultiplicative in the RRs due to smoking and to plutonium radiation dose, and resulted in a markedly lower estimate of the ERR per unit dose.

250. Wing et al. [W22] examined cancer risks in relation to work involving potential exposure to plutonium at the Hanford site in the United States. They used information on work location and job title to assess the likelihood of plutonium exposure. For most end points evaluated, including lung cancer, risks were significantly lower for workers judged to have potential plutonium exposure than for workers with no such potential. However, at ages 50 and above, the duration of employment in jobs with potential for plutonium exposure was found to be associated with mortality due to several other disease categories, with that due to lung cancer showing the largest increase. Because Wing et al. considered several alternative age cut-offs, this finding may be due to chance. Since workers with potential for exposure to plutonium were supposed to be monitored for this exposure, it is not clear whether the surrogate measure of plutonium exposure used was meaningful. No analyses of lung cancer risks in relation to plutonium monitoring data were reported, and no data on smoking habits were available.

251. Brown et al. [B35] conducted a case-control study for lung cancer among plutonium workers at the Rocky Flats plant in the United States. Annual doses to the lung due to plutonium, americium and uranium were estimated for the 180 cases and 720 matched controls included in this study, with most plutonium doses in the range 0–1 Sv. There was no evidence of increased risks from exposure to americium or uranium. Analyses of the cumulative dose due to plutonium using lag periods of 5, 10 and 15 years resulted in elevated (usually non-significantly) odds ratios for several dose categories, but did not show a consistent increase in risk with increasing dose. Because of concern regarding a differential healthy worker effect depending on duration of employment, analyses for three separate categories of employment duration were performed. Analyses restricted to those employed for 15–25 years produced a significant dose response, but analyses based on those employed for shorter or longer periods indicated no evidence of a dose response (the direction of the trend was negative). The results of trend tests were occasionally noted, but risk estimates per unit dose were not presented. Although Brown et al. allude to supplementary analyses that were adjusted for smoking, analyses presented in the paper were not so adjusted.

### 5. Internal high-LET exposures (Thorotrast and radium)

#### *(a) Summary of UNSCEAR 2000*

252. Studies of persons exposed to Thorotrast and $^{224}$Ra were summarized and found to provide little evidence of elevated risks of lung cancer. The statistical precision in these studies was limited by the small numbers of lung cancers.

#### *(b) New or updated studies*

253. Travis et al. [T30] studied patients injected with Thorotrast during radiographic procedures in Denmark, Sweden and the United States. The lung cancer incidence rate among Thorotrast-exposed patients in Denmark and Sweden was significantly elevated compared with incidence rates among the general population, but not in comparison with that in a control group. Lung cancer mortality rates in United States patients were non-significantly elevated in relation to both the general population and the control group. There was also no evidence of a trend of increasing lung cancer risk with a surrogate measure of cumulative radiation dose.

### 6. Internal high-LET exposures (radon)

#### *(a) Summary of UNSCEAR 2000*

254. The UNSCEAR 2000 Report [U2] summarized the results of various epidemiological studies of underground miners and of people exposed in residences, as well as many relevant biological data, and concluded that there was strong evidence for an association between lung cancer risk and exposure to radon daughters.

255. In particular, the results of a comprehensive analysis of miners conducted by the BEIR VI Committee [C36] were reviewed in the UNSCEAR 2000 Report [U2]. Summary data are given in table 28. The BEIR VI Committee re-examined the pooled data from 11 cohort studies of radon-exposed miners by Lubin et al. [L8], including updated data from China, the Czech Republic, France and the United States (Colorado Plateau) (see table 10 in reference [U2]). The BEIR VI models were based on a linear ERR model, but incorporated adjustments for effects of the time since exposure by differentially weighting exposures to radon received 5–14 years, 15–24 years and 25 or more years earlier. The models also allowed for variation in the exposure–response effects with attained age, with duration of exposure or with average radon concentration. The BEIR VI Committee derived two separate models, designated the "exposure–age–duration" model and the "exposure–age–concentration" model, but proffered no preference [C36]. The pooled data included nearly 1.2 million person-years of follow-up, from which there were 2,674 lung cancer deaths among workers with prior radon exposure, and 113 lung cancer deaths among workers without prior radon exposure. The large number of cases permitted detailed examination of many factors that may modify the risk of radon-induced lung cancer. The ERR per unit radon exposure ($WLM^{-1}$) decreased with increasing time since exposure and attained age, and with increasing average radon concentration (the exposure–age–concentration model) or with decreasing duration of exposure (the exposure–age–duration model). There was no variation in the ERR per unit radon exposure ($WLM^{-1}$) with age at first exposure; however, except for the cohort of Chinese tin miners, the range of ages at first exposure was limited, with mean age at first exposure more than 25 years in all cohorts. The joint effect of radon exposure and smoking on lung cancer risk was evaluated for six cohorts where information on smoking habits was available. The joint association for the RR was greater than additive and less than multiplicative, although the precise modelling of the joint effects was difficult to quantify definitively owing to the small number of miners who had never smoked and to the limited quantitative information on tobacco use. On the basis of differences in ERR per unit radon exposure ($WLM^{-1}$) in "ever-smoker" and "never-smoker", the BEIR VI Committee assigned a twofold greater ERR for never-smokers. Any modifying effects of exposure to other agents encountered in mines were not clear, although the ERR per unit radon exposure was lower after adjusting for arsenic exposure [L8]. Because of an absence of data, effects of radon exposure for females could not be evaluated.

*(b) New or updated studies*

256. Since the BEIR VI Report appeared, follow-ups of several of the miner cohorts have been extended and reanalysed, and new analyses have been conducted on related populations. A nested case-control study of lung cancer was selected from a cohort of non-smoking miners employed in the uranium mining industry of the Colorado Plateau region [G3]. Results for non-smokers were consistent with results from the Colorado Plateau and New Mexico cohort studies in the United States, and showed increased lung cancer risk with radon exposure (WLM), as well as evidence of a decreasing radon exposure–response relationship with increased exposure rate. Tomasek analysed the S (older, higher-exposed) and N (new, lower-exposed) cohorts of the Czech miner study [T33]. These data extend the follow-up of a subset of the Czech cohort included in the pooled analysis to the end of 1999. Results showed decreasing risk with time since exposure and with age at exposure, and a (non-significant) twofold greater ERR per unit radon exposure ($WLM^{-1}$) for non-smokers. Investigators added six years of follow-up to the French uranium miner cohort, identifying a total of 125 lung cancer deaths, nearly tripling the number of lung cancer deaths the cohort contributed to the pooled analysis [R39]. Results showed a decreasing ERR per unit exposure with time since exposure and with exposure rate, although the exposure-rate effect disappeared after 1956, when exposure assessment improved owing to more frequent and more comprehensive measurements. These results are difficult to interpret since the mean annual exposure among French miners was 23.9 WLM per year prior to 1956 and 1.5 WLM per year afterwards. A new, very large cohort study of miners of the Wismut uranium mining company in the former German Democratic Republic has recently been initiated [K37]. On the basis of year of initial employment, 60,000 subjects were selected from an estimated 400,000 total worker population covering three periods (1946–1954, 1955–1970 and 1971–1989), which represented the "wild" years (when radon exposures were high and reached 300 WLM per year), the "transition" years (when radiation protection procedures were introduced, radon measurements were started and exposures were reduced) and the "consolidation" years (when employment was stable and exposure levels were estimated as generally below 2 WLM per year), respectively. Cohort analyses have not yet been published, but given its size, this study should yield important new information.

257. Data used in the miner analyses were drawn from studies of a broad range of populations, including workers at uranium, tin, iron and fluorspar mines. For each study in this diverse group, the relationship between radon exposure and lung cancer mortality risk was consistent with linearity, and estimates of the ERR per unit radon exposure ($WLM^{-1}$) were statistically consistent with homogeneity of the radon effect [C36]. Nonetheless, concerns have been raised about the consequences of radiation exposures from sources other than radon, e.g. thoron ($^{220}Rn$ and its decay products) and gamma radiation, for lung cancer risks to uranium miners [D29]. However, the consistency of results from the pooled analyses and from a comparison of Czech tin and uranium miners [T34] suggests a limited impact from these other radiations on estimates for lung cancer risk due to radon exposure. If exposures to gamma radiation were a significant contributor to the total radiation exposure of uranium miners, then one might anticipate an

excess incidence of leukaemia, which to date has not been observed [D10, L54].

258. The presence of an inverse exposure-rate effect in the BEIR VI models has important implications for the extrapolation of risk from studies of miners to populations exposed in residences. This effect implies that, for equal total exposure, the risk is higher when the exposure is received over a longer rather than a shorter period of time. The inverse exposure-rate effect was seen, to varying degrees, in all of the miner studies, except for the French cohort, where miners often worked for many years at low exposure rates. However, a reanalysis of the data from the Beaverlodge uranium mine in Canada based on revised exposure estimates [H18] provided no evidence of an inverse exposure-rate effect. 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 and uncertainties in dose estimation were probably greatest. These greater exposure errors would bias the observed risks towards the null for these high exposure rates and potentially induce an inverse exposure-rate effect. However, adjustments by Lubin et al. [L8, L59] by calendar year of first exposure, calendar years of exposure, attained age and years since the last exposure did not markedly influence the effects. In a reanalysis of the Colorado cohort, Stram et al. directly adjusted for exposure uncertainties and found that the inverse exposure-rate effect remained, although it was smaller [S61]. It therefore seems unlikely that measurement error entirely explains the inverse exposure-rate effect.

259. Results of experimental studies using animals support the inverse exposure-rate effect, having shown that a longer duration of radon exposure at a lower rate induced more lung cancers than a shorter duration of exposure at a higher rate [C19, C20, M38, M42]. Regarding possible mechanisms, Moolgavkar et al. [M39, M40] suggested, on the basis of the two-stage initiation–progression model for carcinogenesis, that extended duration allows time for the proliferation of initiated cells and thus for higher excess incidence of disease. Brenner and Sachs postulated that the inverse exposure-rate effect is a consequence of the "bystander" effect, whereby irradiated cells send signals that can result in damage to nearby cells [B36, B40]. The model postulates that: *(a)* the bystander signalling emanates from cells whose nucleus is directly hit by an alpha particle, and additional hits do not increase bystander response; *(b)* at any given time, a subpopulation of target cells is hypersensitive in their response to the bystander signal; and *(c)* cells in the hypersensitive subpopulation are also hypersensitive to direct radiation damage, such that alpha particle traversal of a nucleus results in cell death [B40]. On the basis of the miner data, the model estimates that about 50 cells are signalled by the cell with the traversed nucleus [B40]. At low exposures, the bystander effect would be expected to dominate risk estimation; however, this effect has already been empirically incorporated into the BEIR VI models, and thus the BEIR VI extrapolations would not be expected to underestimate the risks of exposure to radon in residences [B40]. A contrasting view is given by Little, who believes that the inverse exposure-rate effect can be explained using a linear RR model with adjustment for attained age and age at first exposure, without the need to resort to a complex bystander effect [L47]. The bystander effect and other "non-targeted" effects are discussed at greater length in annex C of the UNSCEAR 2006 Report, "Non-targeted and delayed effects of exposure to ionizing radiation".

260. The biologically based, two-stage clonal expansion model has previously been applied in analysing data from the cohort study of Colorado Plateau uranium miners in the United States [L71] and experimental studies of radon exposure in rats [H45, K40]. Application of this model has now been extended to cohort studies of French [B60, H48], Czech [B60, H48] and Chinese [H47] miners. Precise interpretation of the results, however, remains problematic, owing to heterogeneity of parameter estimates across animal strains [K40] and among miner cohorts [H48], although this point is controversial [B60]. However, results generally suggest that radon exposure affects the initiation rate, but its dominating influence is on promotion (clonal expansion) [H49], while it does not affect the rate of transformation of initiated cells [H48]. Little et al. have raised concerns about these results, in particular with respect to the Colorado Plateau uranium miner data, as they found an improved fit to the data using a three-stage model compared with the two-stage model and an effect of radon exposure on the second-mutation rate [L41].

261. Since publication of the UNSCEAR 2000 Report [U2], several new epidemiological case-control studies of radon in residences and lung cancer have been reported, supplementing the already existing case-control studies (see table 29). While it remains important to assess lung cancer risk and radon concentration for a variety of populations that involve different lifestyles, smoking habits, occupations and other potential confounding factors, several consortia of investigators have reported results from the pooling of original data from China [L61], Europe [D24, D30] and North America [K38, K39]. These reports jointly represent the best available characterization to date of lung cancer risk and residential exposure to radon. These pooling projects were the result of extensive and ongoing planning workshops held between 1989 and 1995 and sponsored by the Office of Health and Environmental Research of the United States Department of Energy, and the Radiation Protection Programme, Commission of European Communities [D31, D32, D33, D34]. The goals of these meetings were: to minimize study heterogeneity by making the protocols for radon measurement and for collection of other data as consistent as possible across studies; to develop a common data format for the pooling of data; and to create a collaborative environment to facilitate analyses. Combined data for the studies of residential exposure included 12,282 lung cancer cases (China, 1,053; Europe, 7,148; North America, 3,662) and 21,486 controls (China, 1,997; Europe 14,208; North America, 5,281).

262. The importance of these pooling projects cannot be overemphasized. By the late 1980s, investigators had clearly identified elevated exposure to radon and radon progeny as a risk factor for lung cancer among underground miners [C34, I18, N13]. Surveys of radon concentrations in indoor air of residences, early epidemiological studies using surrogate markers of radon exposure and extrapolations using lung cancer risk models based on miner data suggested that the general population may carry a substantial burden of increased risk of lung cancer from radon exposures in dwellings [C34]. Owing to differences in environmental conditions between mines and dwellings, and in patterns of exposure between miners and the general population, there was substantial uncertainty about the application of models for estimating lung cancer risk based on miner data to general populations. The mean radon exposure of miners from the pooled data analysed by the BEIR VI Committee was 162 WLM [N2], which is 20–30 times the exposure from 25 years of residence in a typical dwelling. It should be recognized, however, that although mean exposures were higher for miners, 13.2% (353 out of 2,674) of the lung cancer deaths among exposed miners occurred among those exposed to less than 50 WLM. In comparison, long-term residence in dwellings with concentrations in the range 400–500 $Bq/m^3$ results in a radon exposure of about 50 WLM; the range reflects varying assumptions on residential conditions [D29, K39]. Thus cumulative exposures for some miners were comparable to cumulative exposures for long-term residents of dwellings with high radon concentrations. This overlap of the ranges of exposure for mines and dwellings helps to reduce the uncertainty associated with extrapolating beyond the ranges of observable data for miners. Nonetheless, owing to the potentially large number of individuals exposed to this known human carcinogen in the home, it was important to provide independent confirmatory information of the risk projections based on miner data by directly evaluating risks from epidemiological studies of radon exposure in dwellings. Lubin et al. [L62, L63] suggested, however, that epidemiological studies would have to overcome two substantial problems: *(a)* very low expected excess lung cancer risks from radon exposure, since the radon concentrations in the indoor air of most homes were low compared with those in mines; and *(b)* substantial uncertainties in estimating current and historical radon exposures for 20–30 years and more in the past, because some previous homes no longer exist or cannot be measured, and because of the natural temporal and spatial variability of radon concentrations in indoor air. As a result of these two limitations, Lubin et al. emphasized the need for sufficient statistical power to test for significant risk from radon exposure and to evaluate modifications in these effects by conducting studies with large sample sizes and by pooling original data from multiple studies [L62, L63]. The three current pooling studies effectively address these limitations.

263. Criteria for inclusion, as well as exposure assessment procedures, differed slightly for the three pooling projects. The pooling of Chinese studies included the two case-control studies conducted in China, which used air alpha track detectors accumulating exposure over 1 year, and collected comprehensive information on smoking habits and other personal characteristics [L61]. Exposure assessment focused on an "exposure time window" (ETW), defined as the period 5–30 years prior to disease occurrence for cases or prior to the year of interview for controls. For the Shenyang study [B37], investigators measured the radon concentration in air of one home only, either the current home if it was occupied for 5 or more years, or the previous home if it was occupied for 5 or more years. Because cases were ascertained in the period 1985–1987, before the importance of an ETW was fully appreciated, investigators recalculated exposures for the pooled analysis based on the 5–30 year ETW. The European study pooling included all 13 European studies that enrolled 150 or more cases and controls, ascertained detailed smoking histories and demographic and other information, and sought radon measurements in all homes occupied in the previous 15 years or more [D24, D30]. Exposure assessment relied mostly on radon concentrations measured using 1-year alpha track detectors, although two Swedish studies (nationwide [P18] and "never-smokers" [L65]) used 3-month detectors in winter, the Spanish study used 5-month detectors [B39], and the French [B41] and United Kingdom [D13] studies used 6-month detectors. The ETW was defined by the 30-year period 5–34 years prior to study enrolment. The North American pooling included all seven studies that enrolled 200 or more cases, and ascertained detailed smoking histories and demographic and other information [K38, K39]. It relied primarily on 1-year air alpha track detectors [K38, K39]. In the Winnipeg study, investigators based radon exposure assessment on two alpha track detectors placed consecutively for 6 months each [L64], while in the New Jersey study in the United States, the investigators surveyed the homes of 8% of subjects using a 4-day charcoal canister detector [S62]. However, data included in the North American analyses were limited to subjects whose exposure assessment was based, at least in part, on measurements using long-term alpha track detectors. The ETW was defined by the period 5–30 years prior to study enrolment. It should be noted that, except for the two Swedish studies, investigators who used detectors in place for less than 1 year either staggered measurements throughout the years or conducted seasonal adjustment. Thus the main influence on exposure assessment of using detectors in place for less than 1 year would be a slight increase in variability of assessed exposures, but no introduction of bias.

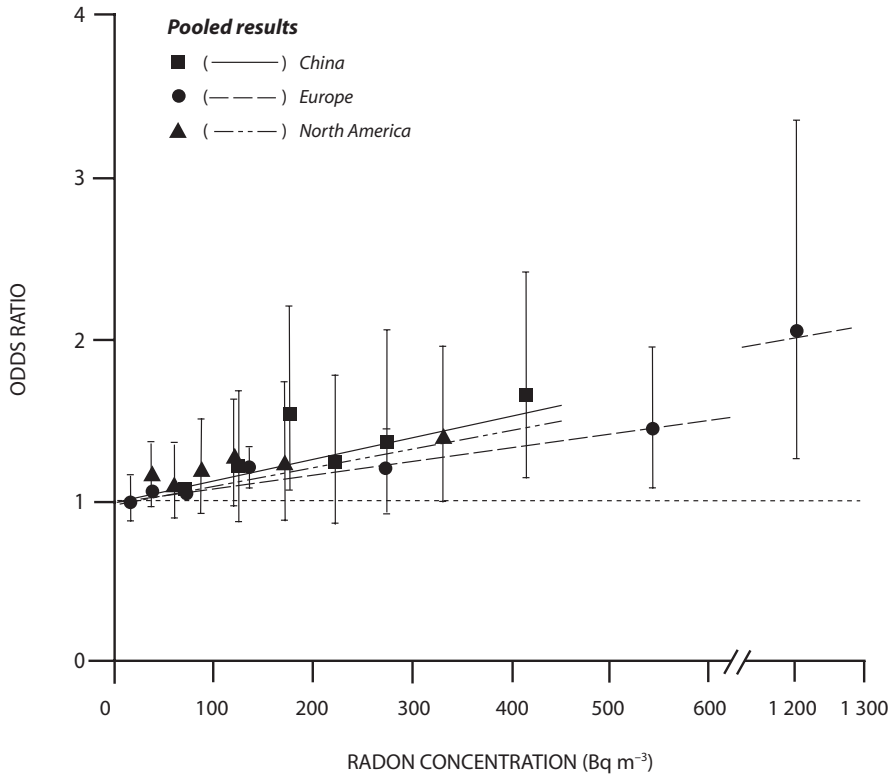
264. Table 29 summarizes mean radon concentrations in air of residences of both cases and controls, and values of excess odds ratios (EORs) for 100 $Bq/m^3$ based on a linear OR model. Although the range of estimates was wide, 19 studies estimated a positive trend with radon concentration, while three studies estimated a (non-significant) negative trend with concentration. The model for the summary ORs for each pooling was consistent with linearity and statistically significant (as shown in figure XIV). The estimated EORs were 0.13 (95% CI: 0.01, 0.36) for 100 $Bq/m^3$ for the Chinese pooling, 0.08 (0.03, 0.16) for the European

pooling and 0.11 (0.00, 0.28) for the North American pooling. Within each of the pooled analyses, the estimates of EOR were consistent with homogeneity of the radon effect across studies. The *p*-values for the test of the null hypothesis of homogeneity of the EORs for 100 Bq/m$^3$ were 0.29 (China), 0.94 (Europe) and 0.56 (North America). Each pooled analysis also evaluated variations in the EORs for 100 Bq/m$^3$, and found no significant variations on a multiplicative scale for the radon effect by sex, age or smoking status. For example, the EORs for 100 Bq/m$^3$ for males and females, respectively, were 0.16 and 0.08 for the Chinese pooling, 0.11 and 0.03 for the European pooling, and 0.03 and 0.19 for the North American pooling. For "ever-smokers" and "never-smokers", the EORs for 100 Bq/m$^3$ for males and females, respectively, were 0.13 and 0.13 for the Chinese pooling, 0.08 and 0.11 for the European pooling, and 0.10 and 0.10 for the North American pooling. It is worth noting that these patterns differed from those found in studies of miners, where analyses exhibited declining radon effects with age and greater radon effects for non-smokers [C36]. The reason for this difference is unknown. In both the European and the North American residential studies, the radon exposure–response relationship was greater for small cell carcinoma cases, although variations by histology were not statistically significant in either data set. Histology was not accurately assessed in all subjects in the Chinese studies and was not analysed.

265. Lubin et al. showed that a linear ERR model, with an ERR estimate of 0.0117 (WLM$^{-1}$), provides a good approximation to the BEIR VI models for exposures under 50 WLM [L60]. Using standard assumptions for occupancy, equilibrium factors for radon and its progeny, and differences between mine and dwelling conditions [C36], residing for 30 years in a dwelling with a radon concentration of 100 Bq/m$^3$ results in about 12 WLM of exposure, and an EOR of 0.14 for 100 Bq/m$^3$ based on miner models [K39]. Since lung cancer is a rare disease and often rapidly fatal, the estimate of the ERR for lung cancer mortality is comparable to the EOR for lung cancer incidence, and thus the miner-based estimate of 0.14 for 100 Bq/m$^3$ is in excellent agreement with estimates from the residential pooling analyses of 0.13 for China, 0.08 for Europe and 0.11 for North America.

266. Assessment of residential radon exposure for many years in the past is subject to substantial uncertainties. Radon measurements vary spatially within rooms of a dwelling, between rooms and between dwellings, and over time. In addition, there is variability associated with the measurement device and the measurement processing. This variation introduces random variability when assessing long-term mean radon concentrations [D24]. In addition, uncertainties in exposure assessment may also arise from lifestyle changes of residents, structural changes in homes or long-term systematic changes in radon concentrations.

**Figure XIV. Odds ratios for categories of residential exposure to radon and fitted linear odds ratio models based on summary results of pooled analyses of original data from China [L61], Europe [D24] and North America [K38]**



Uncertainties in the estimation of radon exposure are influenced by gaps in residential histories for which no measurement exists because measurement protocols may exclude short-term residences, houses that no longer exist or are no longer used as residences, or houses for which the current owners refused measurement. Finally, uncertainties may also arise from ignoring exposures that may contribute to risk, for example exposures beyond 30 or 35 years in the past. The approaches to addressing the consequences of these uncertainties differed among the pooled analyses. The European project used replicate measurement data from the Czech Republic, Italy, Sweden and the United Kingdom to estimate measurement variability for all the study populations [D30], and integrated those estimates into their exposure–response modelling using either regression calibration [C12] or integrated likelihood [R19] methods. With their adjustment for random uncertainties, the estimated radon effects increased the EOR from 0.08 to 0.16 for 100 Bq/m$^3$. Assessments of exposure uncertainties in the North American pooling and the Chinese pooling were conducted by restricting subjects on the basis of length of occupancy in the current house, under the assumption that contemporary measurements of radon more accurately reflect true concentrations throughout the ETW period for long-term residents, and also by restricting subjects to those with increased coverage of the ETW with measurement data, under the assumption that greater coverage of the ETW resulted in less supposition for values of missing data [K38, K39]. In the North American pooling, risk estimates increased consistently with increasing stringency of coverage of the ETW, and when subjects were limited to those residing in one or two homes in the ETW. For example, EORs were 0.11 per 100 Bq/m$^3$ with no residency restriction, and 0.14 for subjects with 20 years or more of coverage of the ETW. For subjects residing in one or two homes, EORs were 0.15 per 100 Bq/m$^3$ with no residency restriction, and 0.18 for subjects with 20 years or more of coverage. In the Chinese pooling, the overall EOR was 0.13 per 100 Bq/m$^3$; it increased to 0.32 for subjects with 25 years of coverage of the ETW and to 0.33 for subjects who lived in exactly one residence. In a separate evaluation, investigators for the Gansu study in China conducted a 3-year radon measurement study to evaluate temporal and spatial variation [L66]. The adjustment for uncertainties increased risk estimates by 50–100%, similar to the impact found in the European pooling and the North American pooling.

267. Alternative methods for reducing uncertainties include the use of an improved dosimeter and improved study design. A surface dosimeter measures residual radiation from $^{210}$Po, which is embedded in glass artefacts, such as glass mirrors and picture frames, following recoil from decay of $^{210}$Pb [L67, M43]. It is believed that measurements of residual radiation in glass objects that are retained and displayed over many years and in multiple homes provide a more accurate estimate of cumulative radon exposures, although concerns have been raised about the effects of increased particulate levels from the presence of smokers on plate-out rates [W26]. In the United States, a study of Missouri women reported an EOR of 0.63 (95% CI: 0.1, 1.9) per 100 Bq/m$^3$ using a glass surface monitor, but found no excess risk when dosimetry was based on standard air radon detectors accumulating exposure over a year [A9]. A Swedish study estimated an EOR of 0.33 (95% CI: –0.12, 2.0) per 100 Bq/m$^3$ with dosimetry based on radon measurements in air, and 0.75 (95% CI: –0.04, 4.30) with dosimetry based on surface monitors [L67]. Surface monitors may offer an improved measurement technology, but do not eliminate temporal uncertainties from misspecification of the age of the artefact, or address spatial uncertainties from the exact location of the artefact and within-home variation. Uncertainties can also be reduced through study design. In the United States, the Iowa radon study enrolled only long-term (20 years or more) residents of a single dwelling, thereby minimizing uncertainties from residential mobility [F12], and carried out radon measurements throughout the house, adjusting for residential occupancy and time spent in other buildings and outdoors [F12, S63]. The EOR ranged from 0.16 (95% CI: 0.0, 0.6) per 100 Bq/m$^3$ for all subjects to 0.33 (95% CI: 0.02, 1.23) per 100 Bq/m$^3$ for living subjects [F12, S63]. A study in Finland also restricted participation to persons with 20 years or more of residency in their current dwelling, and estimated an EOR of 0.11 (95% CI: 0.09, 1.3) per 100 Bq/m$^3$ [A26].

268. Recent works have largely resolved the decade-long debate over results of “ecological studies” [M44]. Starting in the early 1990s, Cohen published a series of reports showing decreasing lung cancer mortality rates in United States counties with increasing average radon concentrations in dwellings grouped by counties [C14, C21, C22, C23]. Indeed, the “ecological” model predicted a protective effect of radon concentrations above 50 Bq/m$^3$ relative to lower radon concentrations. The most recent of these correlation analyses used combined mortality data for the years 1979–1994 [C23]. Radon measurements were based on data from three sources: a University of Pittsburgh project conducted in the period 1986–1991; survey measurements made by the United States Environmental Protection Agency; and measures made by state agencies [H46]. Smoking data were not available either for individuals or for counties, but were extrapolated for each county using data from a 1985 survey and using models that included county-specific socio-economic factors and state-level cigarette smoking data. The smoking estimates were further adjusted to reflect prevalence in the 1960–1970 period. Results from the correlation analyses contrast markedly with results from all cohort studies of radon-exposed miners and nearly all case-control studies of lung cancer and residential radon concentration, where data on radon exposure and on smoking and other factors are specifically collected on individuals.

269. Arguments against the validity of the “ecological studies” were based on both theoretical and practical grounds. “Ecological analysis” involves grouped data, and can be related directly to individual-level effects only when

the relationship between exposure and outcome is linear [L68]. In the case of lung cancer and radon, where a linear relationship does not hold, results are subject to a variety of biases, many of which do not exist for studies of individuals. Radon studies are particularly vulnerable to biases associated with the use of radon levels averaged over geographical areas, because of extreme variation in radon levels within areas. Greenland and Robins illustrated that the absence of, or adjustment for, confounding at the group level does not imply the elimination of confounding at the individual level [G13]. This is particularly important in the case of indoor radon, because of the dominant role of smoking habits on lung cancer risk. Whereas smoking habits are the main potential confounder in an individual-level study, the corresponding potential confounder in an "ecological study" consists of the smoking-risk-weighted distribution of historical radon concentrations for smokers and "never-smokers" within each area [L69]. Thus adjustment for the effects of tobacco use in "ecological analyses" of radon and lung cancer is not likely to be adequate without detailed information on smoking habits and radon exposure histories within counties, for example from independent population surveys [P27, S64]. Lubin demonstrated the potential for "ecological bias" theoretically by showing that aggregate disease rates may be strongly influenced by small correlations of factors within groups [L68]. There has been a further exchange of correspondence between Cohen and Lubin in relation to this study [C49, L97]. Muirhead et al. [M45] and Piantadosi et al. [P28] demonstrated that correlations between factors could be greatly affected, even resulting in a reversal of sign, when the unit of analysis was subject to further aggregation.

270. More recent criticisms of Cohen's results have focused more directly on the "ecological" regression between radon concentration and lung cancer. Smith et al. [S65] reported that a negative correlation seen in the state of Iowa disappeared when mortality data were replaced by incidence data, although the value of these data has been disputed [C24, F17]. In a particularly revealing analysis, Puskin explored the adequacy of Cohen's adjustment for smoking by evaluating the regression of mortality rates for a variety of cancer sites grouped by the strength of their association with cigarette smoking [P29]. Puskin found strongly negative correlations with average county indoor radon concentrations for cancers (lung, oral cavity and pharynx, larynx and oesophagus) strongly linked to smoking, moderately negative correlations for cancers (bladder and pancreas) moderately linked to smoking, and essentially zero correlations for cancers (prostate, colon and breast) not linked to smoking. Since the lung is the only cancer site that has been associated with radon exposure [C36], Puskin's study indicates that Cohen's results are very likely to be the consequence of incomplete control for the smoking factor. There has been a further exchange of correspondence between Cohen and Puskin and others in relation to this study [C47, P49]. In a report coordinated by the United States National Council on Radiation Protection and Measurements, Heath et al. reanalysed Cohen's data and showed that, after adjustment for smoking, the negative trend was largely confined to counties with mean concentrations of below about 50 Bq/m$^3$, and the regression was generally flat from this level to about 175 Bq/m$^3$. Data were too sparse to evaluate above 175 Bq/m$^3$ [H46]. The analysis suggested that the trend may be influenced by confounding from smoking, which was greater for the counties with lower average radon concentrations. It suggests that "systematic errors and uncertainties in Cohen's data and analysis … preclude estimating to what degree or in what direction lung cancer mortality is altered by exposure to … radon" [H46]. Cohen has responded to these criticisms, questioning a number of the statements made by Heath et al. in relation to his analysis, and also disputing the flatness of the dose response in the range 50–175 Bq/m$^3$ [C48].

### 7. Transfer of risk estimates

271. Estimates of ERR per unit dose for lung cancer from several studies involving medical exposures in predominantly Caucasian patients are lower than those based on survivors of the atomic bombings (table 27). Although this might indicate that absolute risks are more comparable than RRs, the lower ERR estimates may also have resulted from other differences in the study populations, particularly the much higher doses in several of the medical studies. Lung cancer rates in Japan have increased in the past few decades. Because of this increase, lung cancer rates for the LSS cohort are generally lower than current Japanese rates, an important consideration in transferring risk estimates for the LSS cohort to another population.

272. Because much of the variation in underlying lung cancer rates among countries is likely to be due to differences in smoking habits, the finding that the joint effect of smoking and radiation exposure on lung cancer risks in survivors of the atomic bombings is well described by an additive model [P17] lends support to the use of absolute risk transfer. Nevertheless, studies of lung cancer risks in underground miners exposed to radon [C36] or in Hodgkin's disease patients treated with high doses of radiation [G23] rejected additive interactions and found that multiplicative interactions were compatible with the data. However, the high doses involved in these studies may make them less relevant for estimating risks of low-dose exposures.

### 8. Summary

273. Lung cancer risk has been associated with external low-LET radiation in survivors of the atomic bombings, in persons exposed at high doses for medical reasons and in Mayak workers exposed at high doses. Based on data for the survivors of the atomic bombings, the ERR per unit dose (Sv$^{-1}$) was larger for females than for males, but the EARs were similar for both sexes. Unlike the case of many other solid cancers, there is little evidence that the ERR for lung cancer declines with increasing age at exposure. The

evidence regarding the interaction of radiation and smoking is conflicting, with data on survivors of the atomic bombings supporting an additive interaction, while studies of persons exposed therapeutically support a multiplicative, and possibly even a supramultiplicative, interaction. Most studies of low-dose protracted exposure have failed to demonstrate dose–response relationships for lung cancer, but this may be because of limited statistical power. Particularly noteworthy is the lack of dose response for lung cancer among tuberculosis patients who received multiple chest fluoroscopies, where it was possible to demonstrate that the ERR per unit dose was incompatible with that based on survivors of the atomic bombings. However, findings for patients with a lung disease may not be typical for the general population.

274. With regard to high-LET radiation, there is little evidence that lung cancer risk is related to internal exposure from Thorotrast or radium, although this may be due to limitations in the available data. However, lung cancer risk has been strongly linked with internal exposure, predominantly via inhalation, to plutonium in studies of Mayak workers in the Russian Federation, and there is a wealth of data linking lung cancer risk with exposure to radon and its progeny. More is said about radon dosimetry and risks in annex E of the UNSCEAR 2006 Report, "Sources-to-effects assessment for radon in homes and workplaces".

## K. Malignant tumours of the bone and connective tissue

### 1. General background

275. Malignant tumours of the bone account for about 0.5% of malignant neoplasms in humans [M56], while soft-tissue sarcomas, which include connective tissue malignancies, account for about 1% of all malignancies [Z9]. There is not much variation in incidence rates worldwide: annual age-standardized world incidence rates vary from less than 0.3 per 100,000 among both men and women in some parts of Japan to more than 3 per 100,000 among men in parts of Italy [P19]. Among bone sarcomas, dissimilarities in cell type between osteosarcoma 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 sarcoma, as well as by the linkages of osteosarcoma with hereditary retinoblastoma and the Li–Fraumeni syndrome [M56]. Li–Fraumeni syndrome has also been investigated together with connective tissue malignancies [Z9]. As will be described below, a variety of studies on external low-LET and internal high-LET 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 nickel and the risk of bone and soft-tissue malignancies [M56].

### 2. Summary of UNSCEAR 2000

276. Among the survivors of the atomic bombings overall, although not reported in the incidence data [T1], the estimated trend in risk per unit dose is statistically significantly positive, but is based on very small numbers (34 cases). There are indications that the risk is higher for exposure in childhood than in adulthood [T1]. Statistically more powerful information comes from studies of patients treated for cancer in childhood. Three studies with reasonably large numbers of cases [H27, T10, W11] have reported a statistically significant trend of increasing risk with (external low-LET) dose, based on mean doses of between 10 and 30 Gy; another such study reported similar results, although with fewer details [D16]. However, few studies of adult external low-LET exposure are informative, owing in part to the rarity of malignant tumours of the bone or connective tissue. For example, the study of cervical cancer patients involved mean doses comparable to those in the above childhood cancer studies [B8]; in that instance, no significant trend of increasing 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 [W8]. In a group of over 120,000 women in Sweden treated for breast cancer, the incidence rate of soft-tissue sarcomas was about double that expected from national rates [K18].

277. In relation to the effects of internal high-LET exposure, there is strong evidence that large intakes of radium have induced increased numbers of bone sarcomas in a group of patients in Germany [N2, S79] and in radium dial workers in the United States [C11, F4, R18, R27]. 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 EAR 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 Sv. The $^{224}$Ra data are consistent with a linear dose response over a range up to more than 100 Sv, although there is uncertainty in extrapolating the findings down to doses of a few sieverts. 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.

### 3. New or updated studies

278. Table 30 summarizes the risk estimates for cancer and cancer mortality based on epidemiological studies of radiation exposure.

#### *(a) External low-LET exposures*

279. An excess risk of bone and soft-tissue cancers, in particular angiosarcoma, has also been found in other recent

studies of women treated with radiotherapy for primary breast cancer [E2, H3, Y8], although detailed dosimetry is lacking in these studies.

280. Virtanen et al. [V11] studied bone and soft-tissue sarcomas among 295,712 Finnish patients who had been treated for certain cancers during the period 1953–2000, and identified 147 cases against 88.5 expected from Finnish national rates, the excess becoming apparent 10–14 years after treatment. Patients who received radiotherapy alone constituted 43% of the total person-years of follow-up, those who received chemotherapy alone 5%, and those who received both radiotherapy and chemotherapy 3%. The SIR for those who were treated with radiation alone was 2.1 (95% CI: 1.6, 2.6), with those diagnosed below 55 years of age having an SIR of 3.4 (95% CI: 2.5, 4.6). When the cancer rate for those patients treated with radiation alone was compared with that for patients who had received neither radiotherapy nor chemotherapy, the crude RR was 1.6 (95% CI: 1.0, 2.6), and the RR adjusted for age, sex and type of primary cancer was 1.5 (95% CI: 0.9, 2.6). There was no statistically significant difference between the effect of radiation upon the risk of bone versus soft-tissue sarcoma [V11].

281. In an international study of second cancers after treatment for Hodgkin's lymphoma [D46], elevated SIRs for bone cancers (3.8; 95% CI: 1.7, 7.2) and soft-tissue cancers (5.1; 95% CI: 3.5, 7.2) were found for a group of 32,591 patients. The SIR of 7.0 (95% CI: 3.3, 10.5) for bone and soft-tissue sarcomas in patients who had been treated with radiation compares with an SIR of 3.4 (95% CI: 2.0, 5.3) among those who were not, an SIR of 15 being apparent among those receiving radiotherapy 10–19 years after treatment. The RR of bone and soft-tissue sarcomas decreased significantly with increasing age at treatment [D46]. In a similar study of a British cohort of 5,519 survivors of Hodgkin's lymphoma, Swerdlow et al. [S77] found a raised SIR for bone cancers (10.7; 95% CI: 3.3, 24.8) and for soft-tissue sarcomas (3.9; 95% CI: 1.0, 10.1), and all the cases occurred in patients who had been treated with radiation. The SIR for bone and soft-tissue sarcomas combined was greatest for those treated before the age of 25 years and was significantly elevated in the period 5–14 years after first treatment [S77].

282. In a cohort of 6,597 persons treated for breast cancer in France, 12 bone or soft-tissue sarcomas developed after high-dose radiotherapy (doses of more than 10 Gy) [R52]. There is a trend of increasing risk of bone/soft-tissue sarcoma with radiation dose, although the ERR is not large (ERR = 0.05 (95% CI: indeterminate, 1.18) $Gy^{-1}$; the lower confidence bound did not converge). The best fit was obtained with a quadratic dose–response model. Excluding three cases of women with Stewart–Treves syndrome, the trend was highly statistically significant ($p < 0.01$).

283. Although not considered in the UNSCEAR 2000 Report [U2], the 1997 study of Artalejo et al. [A32] reported an excess of bone tumours among workers for the Spanish Nuclear Energy Board. This excess (SMR = 2.95; 95% CI: 1.1, 6.4) was based on only 6 cases of cancer, of which 3 were among the 27% of the cohort who had been miners and may have been exposed to alpha radiation [A32].

*(b) Internal high-LET exposures*

284. Workers at the Mayak nuclear complex in the Chelyabinsk region of the former Soviet Union were exposed to high levels of external radiation and plutonium ($^{239}$Pu) during the production of weapons materials, especially during the early years of operations in the late 1940s and the 1950s. Substantial doses to the lung, liver and skeleton were received from $^{239}$Pu. Koshurnikova et al. [K46] examined mortality risks from bone cancer before 1997 among 10,797 Mayak workers employed during the period 1948–1958. Nineteen bone cancers together with four deaths from tumours sited in soft tissues close to bone surfaces were included in the analysis; 21 of these deaths occurred among 9,381 workers monitored for exposure to external sources of radiation (mean recorded cumulative dose with a two-year lag = 1.23 Sv), and five deaths were in the group of 954 workers with cumulative external doses in excess of 3 Sv.

285. Of 5,521 workers with plutonium body burdens that were considered to be known (i.e. either the workers were monitored for exposure to plutonium or worked in areas with a low potential for exposure), 2,207 had detectable levels of plutonium in urine samples (mean body burden = 4.5 kBq, mean bone surface dose from plutonium = 3.8 Gy), and six bone cancers occurred in this exposed group [K46]. Three bone cancers were in the group of 251 workers with plutonium body burdens in excess of 7.4 kBq. A further 5,276 workers were considered to have had the potential to have been exposed to plutonium, but were unmonitored, and 13 bone cancer deaths occurred in this group. Seven of these deaths were among 2,142 workers in the plutonium plant, where the highest exposures tended to be experienced [K46].

286. Uniformly raised levels of bone cancer mortality rates were found for the various groups of Mayak workers when compared with either Russian or United States reference rates, but given the potential for bias when comparing with rates based upon external populations, most reliance should be placed upon the findings using comparisons within the Mayak workforce [K46]. Indications of an increase in bone cancer risk with increasing cumulative external dose, treated as a categorical variable, were found, but because full account could not be taken of the influence of the dose from plutonium, reliable conclusions could not be drawn.

287. Further analyses treating the estimated plutonium body burden as a continuous variable indicate an increasing risk of bone cancer with increasing body burden ($p < 0.001$) [K46]. Overall, the evidence from this study strongly suggests that exposure to high levels of plutonium at Mayak has increased the risk of bone cancer, but risk coefficients cannot at present be determined, because of the lack of comprehensive estimates of doses to bone surfaces from

plutonium. Shilnikova et al. [S28] also examined cancer mortality among the Mayak workforce, but they considered bone, liver and lung cancers (i.e. those cancers most likely to be related to plutonium deposition) as a group, so that the study does not provide information on bone cancers alone.

288. An update of mortality data for Portuguese patients injected with Thorotrast [D27] found a statistically significant ($p < 0.001$) SMR for bone cancer (12.8) when using Portuguese mortality rates as a comparison, but the ratio of this SMR to that for unexposed patients was not significant: rate ratio = 7.60 (95% CI: 0.85, 359). Travis et al. [T30] studied cancer incidence and mortality rates for Thorotrast patients from Denmark, Sweden and the United States, and found a statistically significant ($p < 0.05$) SMR for bone cancer among United States patients (13.9, based upon 2 deaths), but also found no case of bone cancer among the Scandinavian patients (although the expected number of cases, while not presented, would have been small). They pointed out that $^{224}$Ra, a bone-seeking radionuclide, is present in the decay chain of $^{232}$Th, and that the total skeletal dose from all radionuclides in the decay chain could be in the range from 3 to 9 Gy, so that an excess risk of bone cancer among Thorotrast patients is plausible.

#### 4. Summary

289. As in the UNSCEAR 2000 Report [U2], studies of patients treated for childhood cancer demonstrate an increasing risk of bone and soft tissue sarcomas with dose, over a range of several tens of grays (low-LET). These studies are not informative about risks at doses below a few grays, 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 RR is lower for exposure in adulthood than in childhood. Studies of persons receiving high-LET radiation, in particular $^{226}$Ra, $^{228}$Ra and $^{224}$Ra, strongly suggest an exposure-related increased risk of bone tumours. The major new study to appear in relation to internal high-LET exposure is that of the Mayak workers exposed to $^{239}$Pu, which also suggests a radiogenic excess bone tumour risk. However, until the bone dosimetry for this cohort is established, in particular identifying the components of dose due to $^{239}$Pu and to external low-LET radiation exposure, quantitative risk estimates cannot be derived from this study.

### L. Cutaneous malignant melanoma

#### 1. General background

290. Cutaneous malignant melanoma is a comparatively rare tumour in many populations, although incidence rates are increasing around the world [A14]. The incidence of malignant melanoma is strongly related to ultraviolet radiation (UVR) exposure, with exposure at all ages likely to be important for various stages of development of the tumour (initiation, development of naevi, and invasive melanoma) [T22]. For this reason, possible depletion of atmospheric ozone may exacerbate these trends [A15]. The incidence of malignant melanoma is strongly correlated with skin pigmentation, but it is about 10 times less common than non-melanoma skin cancer. Age-standardized world annual incidence rates for melanoma vary from about 0.5 per 100,000 persons in Algeria to over 40 per 100,000 in parts of Australia [P19, T22]. Unlike many tumours of adults, melanoma arises relatively frequently among the young and the middle aged. Malignant melanoma incidence rises steeply with age until about age 50, after which the rate of increase slows [A18]. Much of the increase in incidence in the last few decades appears to be due to solar exposure [A16]. A number of recent case-control studies have provided corroborating evidence for this proposition, but have indicated that the exposure–response relationship is complex [A17, A18, A20, T22]. In contrast to non-melanoma skin cancer, both cumulative exposure and intermittent exposure of untanned skin are risk factors for the disease [A17, A18, A20, T22]. Melanoma can usually be classified into one of three histopathological types: superficial spreading melanoma, lentigo malignant melanoma (also known as Hutchison's melanotic freckle melanoma), and nodular melanoma, although this classification is controversial [A18]. As noted above, skin pigmentation is a very important risk factor [A18], and there is considerable evidence also for familial susceptibility, hormonal factors (e.g. use of oral contraceptives and reproductive status) and immune suppression as risk factors [A18, T22]. Some studies have suggested associations with diet, and in particular that intake of vitamin E is a protective factor for the disease [A18]. Further details on the epidemiology are to be found in reference [A18].

#### 2. Summary of UNSCEAR 2000

291. The UNSCEAR 2000 Report indicated that no relationship of melanoma with radiation exposure has been demonstrated in the major exposed groups [U2], including the survivors of the atomic bombings [R25]. As shown in table 31, there is a moderate ERR of melanoma within the LSS cohort of 0.21 (90% CI: <0, 3.15) $Sv^{-1}$, with wide confidence intervals, based on 13 cases (6 with unweighted colon doses of more than 0.01 Gy) [R25, T1].

292. In the past there were concerns that an excess incidence of cutaneous malignant melanoma at the Lawrence Livermore National Laboratory in the United States might be due to radiation exposure [A19]. However, a later study concluded that the supposed excess was most likely due to factors relating to host constitutional factors, such as skin reactivity and number of moles, and to exposure to sunlight [M28].

### 3. New or updated studies

#### *(a) External low-LET exposures*

293. An association between external ionizing radiation and melanoma risk was suggested by a study of United States radiologic technologists who had first worked before 1950 (RR = 1.8; 95% CI: 0.6, 5.5), particularly among those who worked 5 or more years before 1950 (RR = 2.4; 95% CI: 0.7, 8.7; 2-sided $p = 0.03$) [F11]. Beginning work before 1940 was associated with a greatly increased risk (RR = 8.6; 95% CI: 1.0, 72.7), but this observation was based on only 4 cases. Risk was also moderately elevated among technologists who did not customarily use a lead apron when they first started employment (RR = 1.4; 95% CI: 0.8, 25) [F11]. As with the various other analyses of this cohort, no individual doses had been estimated. The study relies on self-reported diagnoses, although pathological records were obtained for a sample of 160 (66%) of the 243 reported melanomas; 140 of these 160 cases had the diagnosis confirmed. Information on hair and eye colour, skin tone and family history of melanoma was only requested in the second (of two) questionnaires; no information on history of sunburn was collected. In view of this limited information with which to adjust for solar exposure and constitutional factors, the association with ionizing radiation is not convincing.

294. The analysis of cancer incidence in relation to occupational dose in the National Dose Registry of Canada has documented a statistically significant increased SIR for melanoma of 1.16 (90% CI: 1.04, 1.30) [S8]. The trend with dose of melanoma incidence in this cohort is not statistically significant: there is a high ERR of 4.3 (90% CI: <0, 19.6) $Sv^{-1}$, with wide confidence intervals [S8]. However, as with the parallel analysis of the mortality data associated with this cohort [A8], concerns have been expressed about the reliability of record linkage, a possible source of bias [G16]. Moreover, there is no information on solar exposure and constitutional factors in this study.

295. Analysis of cancer incidence in a small group of children who underwent cardiac catheterization yielded an SIR among males of 4.87 (95% CI: 1.0, 14.2). However, there were no cases (of any cancer) among the female children, and the authors did not calculate an overall SIR for the combined group, so that it is difficult to interpret this finding. No radiation dose estimates exist for this cohort [M27]. There is also no information on constitutional factors or exposure to sunlight in this study, so that it is difficult to infer any link between melanoma and ionizing radiation exposure from the results of this study.

296. Analyses of melanoma incidence in a group of 4,401 survivors of childhood cancer treated at French and British centres and 25,120 survivors of cancer treated before the age of 20 at various centres in the Nordic countries found 16 melanoma cases. An excess risk at borderline levels of statistical significance was observed at high local doses, >15 Gy, for which the OR was 13 (95% CI: 0.94, 174) [G31]. Likewise, a continuous model fitted to these data suggested a trend of risk that increased with dose at borderline levels of statistical significance (2-sided $p = 0.05$) [G31].

#### *(b) External high-LET exposures*

297. Because aircrew receive elevated radiation doses, which can range up to 6 mSv per year, with a substantial neutron component (25–50% of the absorbed dose) [B22, G15], there has been much interest in studies of this group. To date there have been various, generally small, studies of aircrew, whether of pilots or flight attendants. The largest studies to date are three large pan-European studies, the first of flight attendants [Z4], the second and third of male cockpit crew [B23, L48]. The first study, of flight attendants, found a statistically non-significant increase in mortality from melanoma (SMR = 1.93; 95% CI: 0.70, 4.44) among male crew, but no suggestion of increased risk among female staff (SMR = 0.36; 95% CI: 0.04, 1.37) [Z4]. The second study, of male cockpit crew, found a statistically significant increase in mortality from melanoma (SMR = 1.78; 95% CI: 1.15, 2.67) [B23]. No consistent association between employment period or duration and cancer mortality was observed, whether for melanoma or any other end point, in either study [B23, Z4]. In the third study, there was no indication of a trend of melanoma risk with radiation dose ($p = 0.481$), so that, for example, the RR associated with doses of greater than 25 mSv was 0.33 (95% CI: 0.06, 1.85) [L48]. Radiation doses were measured only in the third study [L48]. There is no assessment of solar exposure or constitutional factors in any of these three studies. The aircrew studies have recently been reviewed, and evidence has been found of a consistent excess risk of melanoma, non-melanoma skin cancer and breast cancer [S35]. However, as with the three large studies discussed above, there is generally no relation with duration of employment. Since the only study implying a risk of cutaneous melanoma did not estimate radiation doses [B23], and in the absence of individual information on solar exposure in all three studies [B23, L48, Z4], it would be difficult to ascribe the excess risks observed in these studies to ionizing radiation exposure [S35].

### 4. Summary

298. Solar UVR has the potential to seriously confound the ionizing radiation dose response for melanoma, because it is a known risk factor for this end point and may well be correlated with cumulative ionizing radiation dose. In general, there will be appreciable positive bias in any estimated radiation dose response if solar UVR is not taken into account.

299. As for the UNSCEAR 2000 Report [U2], there remains only weak evidence that cutaneous melanoma is inducible by ionizing radiation. Most of the studies that sug-

gest that there might be such risks do not have adequate radiation dosimetry, and do not properly control for constitutional factors and sunlight exposure.

## M. Non-melanoma skin cancer

### 1. General background

300. Non-melanoma skin cancer (NMSC) is extremely common in Caucasian populations but relatively rare in populations with highly pigmented skin [S36]. The two main types of NMSC are squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) or epithelioma (otherwise known as a rodent ulcer as it appears to erode the surrounding skin) [L42]. Both SCC and BCC of the skin are derived from keratinocytes [P20, S37]. SCC occurs as a result of the neoplastic transformation of cells in the epidermis—the suprabasal cells; this tumour may occasionally metastasize to other organs. BCCs are particularly slow growing and originate from the basal cells of the epidermis or hair follicles; this tumour does not usually metastasize. In Caucasian populations, the incidence of BCC is almost always greater than that of SCC. Scotto and colleagues [S38] reported a sex- and age-adjusted rate for SCC in eight regions of the United States as 41 per 100,000 persons per year, compared with a rate of 192 per 100,000 per year for BCC. The BCC:SCC incidence ratio was about 4:1 for males and about 6:1 for females [S38]. Very similar ratios have been reported in a number of other surveys ([A21], but see also the reviews in references [L42, S36]). However, because of the higher fatality rate for SCC than for BCC (principally because of the greater metastatic potential of SCC), the numbers of deaths due to SCC are generally rather higher than for BCC [W18]. Annual age-standardized world incidence rates for NMSC vary from about 0.8 per 100,000 persons in parts of China to over 100 per 100,000 in parts of Switzerland [P19]. Since most NMSC cases are routinely treated in doctors' surgeries, whereas cancer registries routinely rely on inpatient records from hospitals, reporting of NMSC is often very incomplete, and some cancer registries do not report it at all. Therefore population-based estimates of NMSC incidence require special surveys involving the collection of data from office records and outpatient files [S36].

301. NMSC is believed to be induced predominantly by exposure to UVR [A20]. NMSC incidence rates rise rapidly with age, with such cancers being common among the elderly [S36]. Over the past decades, there has been a substantial increase in the incidence rate of NMSC, by about 15–20% over a decade [A21, M29]. Much of the increase in incidence appears to be due to sun exposure. Total accumulated exposure appears to be the main risk factor for SCC, although for BCC a combination of cumulative exposure and intermittent exposure is more relevant [A20]. NMSC is a generally treatable malignancy with a very high cure rate: fewer than 1 in 500 patients with SCC dies from this cancer [P20]. In the United Kingdom there were 46,741 diagnosed cases of NMSC in 1999, and in the same year 368 deaths [O5, O6]. Several chemical carcinogens have been linked to an increased risk of NMSC, in particular arsenic, polycyclic aromatic hydrocarbons (PAHs) and psoralens [S36]. Cigarette smoking and diet have also been suggested as risk factors in some studies [S36]. As noted above, constitutional factors, in particular skin pigmentation, are very important risk factors [S36], and risks are also increased in persons with certain rare genetic disorders, in particular naevoid basal cell carcinoma syndrome and xeroderma pigmentosum [E4, S36]. Immune status is also clearly important, with increased risks seen in various groups with immune suppression [S36]. Further details on the epidemiology are to be found in references [L42, S36].

### 2. Summary of UNSCEAR 2000

302. An association between external ionizing radiation and NMSC risk has been demonstrated in the LSS of the survivors of the atomic bombings [L30, L42, R25], the New York (United States) and Israeli tinea capitis studies [R16, S15], the Rochester thymus study in the United States [H26, S22] and in various other groups (reviewed in references [L42, U2]).

303. In the latest data from the LSS, a strong dose–response relationship was demonstrated for BCC (ERR = 1.9 (90% CI: 0.83, 3.3) $Sv^{-1}$) (table 32), but not for SCC (ERR $\leq$–0.1 (90% CI: <–0.1, 0.1) $Sv^{-1}$) [R25]. There was non-linearity in the BCC dose response [R25]. 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 as well [R25]. In earlier evaluations of all NMSC in the LSS, non-linearity was highly statistically significant; the indicated models had non-zero thresholds in dose, or were functions involving powers of dose that were greater than 1, combined with exponential terms representing cell sterilization [L30]. The ERR decreased strongly and highly statistically significantly ($p < 0.001$) with increasing age at exposure [L30, R25].

304. There is evidence that the risk of BCC in the LSS cohort is lower for parts of the body exposed to the sun [R25], in contrast to the evidence presented by an ICRP Task Group [I13]. As discussed by Little et al. [L42], there is evidence that the ICRP analysis may have been confounded by the effects of age at exposure. Most (all but one) of the sites exposed to UVR considered by the ICRP [I13] were for exposures in childhood, whereas most (all but one) of the sites shielded from UVR were for exposures in adulthood. As noted above, there is an appreciable reduction of ERR with increasing age at exposure. A complication in comparing UVR exposure status for the LSS with that for other groups is that the patterns of solar radiation exposure in the Japanese population may be different from

those in most Caucasian populations [L42]. Present-day Japanese women are rarely exposed to UVR, because they use parasols when outside even for short walks; Japanese men often use wide-brimmed hats when working in the sun. However, it seems that the patterns of solar radiation exposure in the Japanese population four or five decades ago may have been appreciably different from the present pattern. For example, 50 or so years ago it was common for Japanese manual labourers to be clad only in a *fundoshi*, a simple loincloth, particularly in summer when much of Japan can be quite humid [L42].

305. To date, there has been little indication of an association between ionizing radiation and SCC, but the data are sparse [L42]. As with many other cancers [U2], the ERR of BCC decreases with increasing age at exposure [R25]. Data on the dose–response relationship for BCC 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 SCC, and to clarify the role of UVR relative to ionizing radiation.

### 3. New or updated studies

#### *(a) External low-LET exposures*

306. The New York tinea capitis study has recently been updated [S7]. There were 128 cases of NMSC in the group of 2,224 irradiated persons, and 21 in the control group of 1,380 persons. Of the 128 irradiated people with NMSC, 125 were Caucasian and 3 African-American; of the people with NMSC in the control group, all 21 were Caucasian, i.e. none were African-American [S7]. Almost all the cases among the Caucasians were of BCC: 124 out of 125 cases among Caucasians in the exposed group were of BCC. The ratio of EAR associated with ionizing radiation exposure for the Caucasians relative to the African-Americans was 10.0 (95% CI: 3.2, 31), which the authors take as implying a large enhancement of radiation risk for persons 'effectively' exposed to UVR (i.e. for those whose skin was not shielded by melanin). This does not necessarily contradict the findings from the LSS data. Shore et al. [S7] calculate EARs, whereas in the LSS [R25] the measure used is ERR. The number of BCCs occurring on skin unexposed to solar UVR will be very much less than the number occurring on skin exposed. Thus the ERRs could well be much greater than on UVR-exposed skin, yet the EARs on UVR-shielded skin be rather less on UVR-exposed skin. The ERR for BCC on the scalp of 1.7 $Gy^{-1}$ is slightly but not statistically significantly ($p = 0.24$) greater than the ERR of 0.6 $Gy^{-1}$ for the margins of the scalp, which are presumed to receive more solar UVR, in support of the findings from the LSS data [R25]. Shore et al. [S7] argue for considering normalized risk, i.e. excess BCCs per unit area of skin per unit dose, similar to the measure proposed by the ICRP [I13]. If this is done, then EARs for UVR-exposed skin are greater than for skin unexposed to UVR. Case ascertainment was via four surveys. About 88.1% of the people in the original exposed group and 84.4% of those in the control group were contacted and answers to questionnaires obtained. In the exposed group, 94.4% of reported cases were medically verified. This is undoubtedly a high-quality study. However, the very small number of cases of NMSC (3) among African-Americans and possible lifestyle differences between this group and the Caucasian group mean that caution should be exercised in ascribing the differences in radiation risk between these groups to their UVR exposure status.

307. An association between exposure to external ionizing radiation and risk of BCC was suggested by a study of white United States radiologic technologists. The risk of BCC adjusted for the total numbers of years worked decreased in a statistically significant manner with earlier calendar years of first employment [Y4]. There were no suggestions of increased risks for SCC [Y4]. Among those working before 1950, there was no suggestion of a dose response for BCC based on the number of years worked. The RR for those working for up to 5 years was 1.45 (95% CI: 1.06, 1.97), compared with an RR of 1.14 (95% CI: 0.74, 1.75) for those working for more than 5 years [Y4]. Among those working in the period 1950–1959, there were more indications of a dose response for BCC. The RR for those working for up to 5 years was 1.29 (95% CI: 1.03, 1.62), compared with an RR of 1.59 (95% CI: 1.23, 2.06) for those working for more than 5 years [Y4]. The risk of BCC associated with exposure to ionizing radiation (based on years first worked) was not modified by UVR exposure as an adult or in childhood, although there were significant modifying effects due to skin pigmentation. As with other analyses of this cohort [F11], the study is reliant on self-reported diagnoses, although confirmatory pathological records were obtained for a sample of 668 (49%) of the 1,355 reported BCC cases and 79 (29%) of the 270 reported SCC cases [Y4]. Information on hair and eye colour was only requested in the second (of two) questionnaires. Solar ultraviolet B (UVB) exposure in adulthood was estimated on the basis of information about the state within the United States in which residence was held and the length of that residence. Solar UVB exposure in childhood was estimated from the state of birth. No information on sunburn or family history was collected [Y4]. In view of the limited information with which to adjust for solar exposure and constitutional factors, and the lack of ionizing radiation dosimetry, the association with ionizing radiation exposure is not convincing.

308. There is a small, and statistically non-significant, excess risk of NMSC mortality for United Kingdom radiologists in the early years of practice, 1897–1920, specifically 2 deaths compared with 0.46 expected (SMR = 4.35) [B2]. These deaths are very likely to be cases of SCC. Yoshinaga et al. [Y5] reviewed all the radiologist and radiologic technologist studies and concluded that several studies provide evidence for a radiation effect on the risk of NMSC, in particular the studies of United States radiologists [M30] and of Chinese medical X-ray workers [W3].

However, the only one of the cohorts considered by Yoshinaga et al. [Y5] that had individual dose measurements was the small cancer incidence study by Andersson et al. [A6] of 4,151 persons employed at two radiotherapy departments in Denmark, in which the trend of NMSC risk with dose is not statistically significant.

309. In the United States, a case-control study in New Hampshire has evaluated risks of BCC and SCC in relation to previous therapeutic exposure [L43]. Persons with BCC or SCC diagnosed from a population-based ascertainment programme [K29] and age- and sex-matched controls were recruited. Information was collected by interview on medical history (including previous radiotherapy treatment), sun exposure history and sun sensitivity. Medical records of those reporting treatment with radiotherapy were obtained. Although limited radiation dosimetry appears to exist (probably only treatment planning or skin entrance doses), no dose–response analysis has been attempted. Excess risks of both BCC and SCC in relation to previous radiotherapeutic exposure are suggested. For BCC, excess risk was noted both among those who tend to burn in sunlight and among those who tend to tan [L43]. In contrast, for SCC, excess risk was noted only among those who tend to burn in sunlight, and not among those who tend to tan [L43]. The main problem with this study is the lack of proper radiation dosimetry, which makes it difficult to evaluate NMSC risks quantitatively.

#### *(b) External high-LET exposures*

310. Because aircrew receive elevated doses, which can range up to 6 mSv per year, with a substantial neutron component (25–50% of the absorbed dose) [B22, G15], there has been much interest in studies of this group. To date there have been various, generally small, studies of aircrew, whether pilots or flight attendants. The largest studies to date are three large pan-European studies, the first of flight attendants [Z4], the second and third of male cockpit crew [B23, L48], but these consider mortality risks only, and so are not very useful for study of the risk of NMSC. The only large study to assess cancer incidence is that of Nordic aircrew by Pukkala et al. [P21]. (This meta-analytical study includes a number of previously studied national cohorts.) There was a statistically significant increase in SIR of 2.08 (95% CI: 1.74, 2.79) based on 27 cases. However, in Poisson regression analyses, there was no significant trend of NMSC risk with dose (2-sided $p = 0.14$), nor was there for BCC (2-sided $p = 0.17$) [P21]. In the absence of data on solar exposure or constitutional factors for individuals, the findings of this study are difficult to interpret.

### 4. Summary

311. As for melanoma, solar UVR has the potential to seriously confound the ionizing radiation dose response, because it is a known risk factor for this end point and may well be correlated with cumulative ionizing radiation dose. In general, one would expect appreciable positive bias in any estimated radiation dose response if solar UVR were not taken into account.

312. As for the UNSCEAR 2000 Report [U2], there is strong evidence that NMSC, and specifically BCC, is inducible by ionizing radiation, with the RR strongly decreasing with increasing age at exposure. There are suggestions of upward curvature in the BCC dose response. An unresolved issue is that of interaction between exposure to solar UVR and to ionizing radiation. The available data [R25, S7] suggest that ERRs may be lower for sites exposed to sunlight, whereas EARs may be higher for such sites.

## N. Breast cancer

### 1. General background

313. Breast cancer is the most commonly diagnosed cancer among women in most countries. Rates vary considerably between regions, with standardized rates for North America and Western Europe being at least two to three times higher than those in East Asian countries and higher still in comparison with those seen in African countries [A30, P19]. For example, annual age-standardized world incidence rates for breast cancer vary from fewer than 25 per 100,000 women in many parts of Africa to over 100 per 100,000 in parts of the United States [P19]. Despite the wide variation across populations, breast cancer incidence rates exhibit a fairly consistent pattern of increase with age that differs from that seen for most other cancers. In particular, rates increase markedly up to about age 50, after which the rates increase much less rapidly. For most other solid cancers, incidence rises steeply until age 70 or 80, after which there is some slackening of the rate of increase. The well-documented dependence of breast cancer rates on age and on reproductive factors (including the association of increased risk with decreasing parity and increased age at first full-term pregnancy [P39, S76], and the transient increase in risk seen during the five years following childbirth [L76]) highlights the importance of hormonal factors for breast cancer risks. This has been demonstrated more directly in a number of recent studies [C29, K45, N15]. Other non-hereditary factors for which there is evidence of an association with breast cancer risk include factors related to energy balance (e.g. height, weight and obesity, diet and activity levels) [D39, S76] and history of benign breast disease [P40].

314. There are well-established effects on breast cancer incidence from and clear associations with a family history of breast cancer [C30]. In a recent study of breast cancer risks in twins, it was suggested that about one quarter of all breast cancer cases are associated with genetic effects or gene–environment interactions [L77]. A number of cell cycle and DNA repair genes have been found to be

associated with breast cancer susceptibility, including BRCA1, BRCA2 and ATM. However, it is currently believed that only about 20% of breast cancer cases are attributable to mutations in known susceptibility genes [T37].

315. Breast cancer rates among women have been increasing for many decades and were recently estimated to have increased by 30–40% between the early 1970s and the late 1990s [A30]. The increasing trends have been especially sharp in Asian countries [A30]. This increase, particularly in developed countries, has been generally attributed to increased detection using mammographic screening, while the increase in countries where the incidence was previously low, e.g. Japan, may have been due to changes in lifestyle factors. These factors, together with genetic differences, are the most plausible explanation for the large variation in rates across populations. Ionizing radiation is well documented as a cause of radiation-induced breast cancer in women, which is one of the most closely studied cancers, as described in reference [U4] and in reference [R32]. These references provide an extensive review of the current understanding of risks due to radiation exposure and factors that modify these risks.

## 2. Summary of UNSCEAR 2000

316. The UNSCEAR 2000 Report [U2] concluded that there was strong evidence of an effect of ionizing radiation on breast cancer risks that was consistent with a linear dose response. It was also concluded that the ERR per unit dose exhibited a strong dependence on age at exposure, with the largest risks for those exposed as children or young adults, and smaller RRs for women who were over 40 at the time of exposure. On the basis of the comparison of results from studies of populations from Japan and from studies of other populations it was noted that, while RRs varied considerably, excess rates appeared to be less variable, and that dose fractionation had little apparent effect on the risk per unit dose. The UNSCEAR 2000 Report contained no explicit discussion of interactions between radiation and other risk factors, although it was noted that interpretation of radiation effects in some reports "is complicated by the potential for confounding as a consequence of reproductive factors or other exposures".

317. Results from the LSS for breast cancer were based on case follow-up for the period 1958–1987 [T1] and mortality follow-up for the period 1950–1990 [P1]. The LSS incidence and mortality results were broadly similar. The summary risk estimates clearly indicate that the RR depends on age at exposure and may increase with time since exposure. However, interpretation of the results in relation to the time since exposure is complicated by the correlation between age at exposure and time since exposure.

318. With the exception of a study that involved thymic irradiation of infants [H10], the estimates of ERR per unit dose from the other studies considered in the UNSCEAR 2000 Report were generally statistically significant but much smaller than those from the LSS. These other studies involved North American and European populations whose members received therapeutic [B10, B11, B16, D17, L7, M8, M17, S5, S20, W8], diagnostic [B3, H9] or occupational [C3] exposures to ionizing radiation. It was noted that studies of internal low- and high-LET exposures [H6, H10, H24, N2, R3] have failed to provide any indication of increased breast cancer risks.

## 3. New or updated studies

319. Table 33 summarizes the risk estimates for breast cancer and breast cancer mortality from epidemiological studies of radiation exposure.

### *(a) External low-LET exposures*

320. An update of the LSS data on breast cancer incidence was published in 2003 [L78]. That paper was based on follow-up between 1950 and 1990. However, the primary analyses focused on risks after 1958, since the tumour registries did not begin operating until 1958, and the authors considered that there were indications that the minimal latent period might be of the order of the widely accepted value of 10–12 years [R32]. The paper gives an estimate for ERR of 1.7 (90% CI: 1.3, 2.1) $Gy^{-1}$, without allowing for variation in the ERR with either age at exposure or attained age. A major emphasis in this paper concerns the relative importance of attained age and age at exposure as modifiers of the ERR. It noted that there are statistically significant decreases in the ERR per unit dose with increasing attained age or age at exposure, and that, even after allowing for such effects, there is still evidence for very large RRs for cases diagnosed under the age of 35. It concluded that, after allowing for this early onset effect, there is no statistically significant variation in the ERR per unit dose with attained age, but that the ERR still exhibits a statistically significant decrease with increasing age at exposure. After allowing for an 8.5-fold (90% CI: 2.3, 48) increased risk for the early onset, the authors suggested that the ERR per unit dose decreases by about 30% (90% CI: –50%, –10%) per decade increase in age at exposure. While there was a marked decrease in risk with age at exposure, the data suggested that risks for women exposed at ages of 50 or more remain elevated, with increases of 40–50%. A non-parametric estimate of the joint dependence of the ERR per unit dose on age at exposure and on attained age given in this paper suggested that the ERR per unit dose for women exposed after age 40 is 0.5 (90% CI: 0, 1.4) $Gy^{-1}$. An ERR of this magnitude is comparable to that seen for many other solid cancers in the cohort of survivors of the atomic bombings and in other populations.

321. The other publication presenting LSS results is a pooled analysis of incidence data from eight major breast cancer cohorts [P3]. This analysis used the LSS breast cancer incidence data for the period 1958–1993 together with data on tuberculosis patients who received multiple

chest fluoroscopies as part of their treatment [B3], women with benign breast disease [M8, S5], and infants who received radiation therapy for an enlarged thymus [H10] or skin haemangioma [L4, L7]. The analysis considered variation in both the ERR and the EAR with both attained age and age at exposure, and developed pooled ERR and EAR models for the risk based on the underlying studies. Their final ERR model allowed for: a decrease in the ERR inversely proportional to the square of the attained age, and no variation with age at exposure for the LSS, tuberculosis and thymic irradiation cohorts; a large effect of age at exposure for the Swedish benign breast disease cohort; and no variation with either age or age at exposure for the mastitis or haemangioma cohorts. As for other pooled analyses of some of these data sets [L5, L79], the RRs for the survivors of the atomic bombings were significantly higher than those for United States and European populations. The authors recommended the use of a pooled EAR model in which the EAR increases with attained age, with a reduction in the rate of increase after age 50 for all cohorts and a 40% decrease in the EAR per unit dose for every 10-year increase in age at exposure for the LSS, fluoroscopy and thymic irradiation cohorts. There was a much more rapid decrease with age at exposure in the Swedish benign breast disease cohort and a non-significant increase in the mastitis cohort. Risks per unit dose were low in the haemangioma cohort even after allowing for infancy at the time of exposure. In general, the results suggested that no relatively simple pooled model can adequately describe the risks of all the cohorts, and that factors such as a history of breast disease may have a marked effect on risk. The ERR results suggested that more attention needs to be given to descriptions of breast cancer risks that allow for the effects of both attained age and age at exposure.

322. Studies of second primary cancers diagnosed among Hodgkin's disease (HD) survivors have been an important source of information on the risks of breast cancer following high-dose exposures. Updated results have been published for several of the major HD survivor cohorts. These include analyses of cancer incidence in a United States cohort of 1,380 childhood HD survivors (including 480 women with an average follow-up of 17 years per person) treated before age 16 [B46], and a United Kingdom HD cohort that includes 5,519 survivors (including 2,085 women) of all ages with an average follow-up of about 8.5 years per person [S77]. Both incidence [V8, V9] and mortality [A31] risks have recently been examined in a Dutch cohort that takes in 1,261 people (including 539 women) treated prior to age 41 with an average follow-up of about 20 years per person. The nested case-control study with 48 breast cancer cases and 175 controls based on the Dutch cohort of van Leeuwen et al. [V8] is one of the most important since, unlike other studies of HD survivors, it makes use of individual dose estimates, and the authors make a concerted effort to investigate effect modification by chemotherapy and other factors. The study of those women treated under the age of 30 forms part of a meta-analysis of HD survivors [T25]. In 2000, Metayer et al. [M52] presented results of a pooled analysis of cancer incidence among 5,925 European and North American paediatric HD survivors who were under 21 years of age at the time of treatment. The pooled analysis cohort includes 2,737 women with an average follow-up of about 9.5 years per person.

323. Despite the problems in separating the effects of chemotherapy and radiotherapy, all of these studies provide clear indications of large, statistically significant increases in breast cancer risk from high-dose radiotherapy. There are also indications that the risks decrease with increasing age at exposure. The pooled analysis of paediatric HD survivors [M52] reports an O/E of 14 ($p < 0.05$). In the United Kingdom study [S77], the SIR estimate for breast cancer associated with radiotherapy among women treated prior to age 25 is 14 (95% CI: 6, 29), while for women aged between 25 and 55 the estimated SIR is about 2 and not significantly greater than 1. The Dutch study of breast cancer incidence [V9] reports an SIR of 17 (95% CI: 8, 32) for paediatric HD cases and of about 4 for women treated after age 20. The United States study of paediatric HD survivors [B46] finds an SIR of 52 (95% CI: 40, 76).

324. In a cohort of 1,814 female 3-year survivors of childhood cancer in France and the United Kingdom, 16 persons developed breast cancer [G29]. Radiation doses to the breast averaged 5.06 Gy. There was a trend of increasing breast cancer risk with dose at borderline levels of statistical significance; ERR = 0.13 (95% CI: <0, 0.75) $Gy^{-1}$ (2-sided $p = 0.06$).

325. As noted above, the Dutch nested case-control study [V8] is the only HD follow-up study to make use of individual dose estimates. The authors provided an estimate for the ERR of 0.06 (95% CI: 0.01, 0.13) $Gy^{-1}$ among women treated using only radiotherapy. They also noted that risk estimates were about 50% lower for women who received both chemotherapy and radiotherapy. They carried out analyses which suggested that this difference is largely attributable to early onset of menopause induced by the chemotherapy. These estimates of ERR per unit dose and of the SIR and O/E discussed above are considerably lower than the risks that would be predicted on the basis of linear risk estimates from the LSS or from other populations with lower doses (i.e. less than about 5 Gy), supporting the concept of effects due to cell-killing at high doses.

326. Initial results from a cohort study of more than 90,000 United States radiologic technologists employed between 1926 and 1982 have been published in recent years [M10, S29]. Analyses indicated that the breast cancer incidence rate for this population was higher than that for women recorded in the SEER cancer registries in the United States, with an overall SIR of 1.16 (95% CI: 1.09, 1.23) based on 177 cases. The breast cancer risks were particularly high for women employed in earlier years and declined with later years of initial employment. This pattern lends support to the idea that the increased risks are associated with occupational exposures to radiation. Since there are

currently no individual dose estimates for cohort members, this study does not yet estimate dose response.

327. As noted in Section II.H, because aircrew receive elevated doses, which can range up to 6 mSv per year, with a substantial neutron component (25–50% of the absorbed dose) [B22, G15], there has been much interest in studies of this group. To date there have been various, generally small, studies of aircrew, whether pilots or flight attendants. Breast cancer mortality in a large pan-European study of flight attendants was slightly elevated, but this was not statistically significant: the SMR was 1.11 (95% CI: 0.82, 1.48), based on 59 deaths [Z4]. There was no trend of breast cancer mortality with years of service [Z4]. Likewise, breast cancer incidence in a cohort of Norwegian airline cabin attendants demonstrated a slight, but statistically non-significant, increase in breast cancer incidence: there were 38 cases compared with 34.0 expected (SIR = 1.1; 95% CI: 0.8, 1.5). Again there was no trend of incidence with duration of employment; for example, the RR for 15 or more years of service compared with less than 5 years of service was 1.0 (95% CI: 0.3, 3.0) [H58]. In a study of Icelandic cabin attendants, there is a more pronounced (but still statistically non-significant) elevation in risk associated with increased years of service, so that the relative breast cancer risk among those with 5 or more years of service compared with those with less than 5 years of service was 2.10 (95% CI: 0.93, 4.73) [R53]. For those with 5 or more years of service before 1971 compared with those with less than 5 years of service before 1971, the RR was 5.24 (95% CI: 1.58, 17.38). This study is unusual among studies of these cohorts in that reproductive history (nulliparity and age at first birth) was adjusted for in the analysis. A study of Finnish airline cabin attendants adjusted for reproductive history, and for familial and lifestyle risk factors, and, unusually, also had individual radiation dose estimates. However, there was no suggestion of increased risk associated with radiation dose. The adjusted OR was 0.93 (95% CI: 0.68, 1.27) for 10 mSv [K55]. In the absence of individual information on radiation dose and lifestyle factors for most of these groups, it would be difficult to ascribe the generally modest excess risks observed in these studies to ionizing radiation exposure [S35].

328. As discussed above, age at exposure is widely acknowledged as an important modifier of the radiation dose response for breast cancer. The LSS provides some indication of especially high RRs for early onset (diagnosis prior to age 35) of breast cancer among women exposed early in life [L78]. An early onset effect is also suggested by the Dutch cohort study [V8, V9]. Such an effect may be suggestive of a genetically susceptible subgroup, but may also reflect a modification of the ERR by attained age. More analyses are needed to address this issue.

329. The most comprehensive analysis of interactions between known radiation risk factors and radiation effects remains the study of 196 breast cancer cases and 566 matched controls conducted using the LSS data [L80, L81]. The results of this study suggested that the presence of known protective factors, such as early first childbirth and multiple births, reduces the excess risk of breast cancers due to radiation exposure at least as much as it reduces the underlying risks of breast cancer. The recent Dutch HD analyses [V8] mentioned above suggested that this reduction might be even greater than that suggested from the LSS data. The results of the recent pooled analysis [P3] suggest that a history of benign breast disease may increase the risk of radiation-associated breast cancer. This observation is given some support by the findings of a recent case-control study of the effects of medical exposures to radiation on breast cancer risks [H51]. This study reported that a significant association between medical radiation exposures and breast cancer risks was seen only among women with a history of benign breast disease. However, the study was based on self-reported radiation exposure histories, so there is some possibility of recall bias.

330. Breast cancer is quite rare among men, accounting for less than 0.5% of all cancers in men and less than 1% of all breast cancers [P19]. Because it is so rare, it has seldom been considered in analyses of radiation-associated cancer risks. However, a recent report on male breast cancer in the LSS of survivors of the atomic bombings [R33] noted a statistically significant increase in the risk with increasing radiation dose. Because of the small number of cases, the risk estimate is extremely imprecise.

#### *(b) Internal low-LET exposures*

331. A study of 6,841 Swedish, French and Italian patients treated with a mixture of conventional (external beam) radiotherapy and $^{131}$I for thyroid cancer recorded a statistically significant increase in breast cancer incidence (SIR = 1.3; 95% CI: 1.0, 1.5; 128 cases) [R38]. However, there was no trend of increasing breast cancer risk with administered quantity of $^{131}$I: adjusted for external radiotherapy. The ERR was –0.01 (95% CI: indeterminate, 0.04) GBq$^{-1}$ of $^{131}$I (the 2.5 percentile estimate did not converge). There was a (statistically non-significant) positive trend with administered $^{131}$I among those people who did not receive external radiotherapy. The ERR was 0.002 (95% CI: indeterminate, 0.07) GBq$^{-1}$ of $^{131}$I (the 2.5 percentile estimate did not converge) [R38]. A highly statistically significant ($p$ = 0.004) trend of increasing breast cancer mortality with dose was observed in the study of persons exposed to weapons test fallout in the Semipalatinsk area of Kazakhstan [B58]. Based on an internal analysis, the aggregate ERR was 1.28 (95% CI: 0.27, 3.28) Sv$^{-1}$. However, when the analysis was restricted to the exposed group and based on individual dose estimates, the trend estimate was slightly reduced and no longer statistically significant: 1.09 (95% CI: –0.05, 15.8) Sv$^{-1}$. As noted in section II.D, "ecological bias" may operate in this study, so these findings should be treated with caution.

#### *(c) Internal high-LET exposures*

332. As noted in the UNSCEAR 2000 Report, there are few published data on the effects of internal high-LET

exposures to ionizing radiation on breast cancer risks. The primary published data concern the effects of doses arising from $^{224}$Ra administered for therapeutic purposes [N3]. This study found no indication of elevated risks associated with the radiation exposure.

333. The potential for studies of the Mayak worker [K2] and Techa River [D40, K6] cohorts to provide information on breast cancer risks from internal radiation exposures was noted in the UNSCEAR 2000 Report [U2]. However, while some information on risks for these cohorts is now available [G2, G12, K46, S28], the reports do not provide information on breast cancer risks.

#### 4. Summary

334. Radiation effects on female breast cancer risks have been widely studied because breast tissue appears to be relatively radiosensitive and because breast cancer is the most common cancer among women. As outlined above and recently reviewed in reference [R32], there is compelling evidence for effects of radiation exposure on breast cancer rates. The dose response appears to be linear for doses of up to several grays, while epidemiological studies of populations who received radiotherapy suggest that cell-killing may reduce the relative effectiveness at very high doses. There is accumulating information to delineate the complex modifying effects of age at exposure and attained age. There seems to be fairly strong evidence supporting the notion that age at exposure is an important risk factor, with younger women having higher risks than women exposed later in life. However, more attention should be paid to characterization of the ERR as a function of attained age, and of the relative effect of attained age and age at exposure on the risk of radiation-associated breast cancer. Comparison of the LSS results with those from studies on European and United States populations suggests that radiation may act additively with respect to many of the factors responsible for differences between the underlying breast cancer rates of Japanese and of Western populations. On the other hand, the limited data on the joint effects of radiation and known risk factors for breast cancer suggest that radiation may act multiplicatively with respect to reproductive factors. Furthermore, some factors, such as a history of benign breast disease, may markedly increase the risk of radiation-associated breast cancer.

### O. Uterine cancer

#### 1. General background

335. Uterine cancer includes cancer of the body (corpus) of the uterus and cancer of the uterine cervix. Most cancers of the uterine corpus are adenocarcinomas of the lining of the uterus (endometrium); sarcomas arise in the muscular tissue of the corpus (myometrium) but are rare [G25]. Most cancers of the uterine cervix are SCCs [S51]. Annual age-standardized world incidence rates for corpus uterine cancer vary from less than 5 per 100,000 women in most of Asia to more than 20 per 100,000 in parts of the United States [P19]. Annual age-standardized world incidence rates for cervical cancer vary from less than 15 per 100,000 women in most of Western Europe to over 30 per 100,000 in parts of South Asia [P19].

336. Cancers of the uterine cervix and corpus have very different aetiologies. Human papillomavirus (HPV) appears to be involved in nearly all cervical cancers, although other factors must also be involved, since HPV infection is much more common than cervical cancer [S51]. Different strains of HPV have different degrees of oncogenicity [S51]. The usual mode of transmission is sexual intercourse. Cigarette smoking is also associated with risk [D5, L2]. With the introduction of cervical cytological screening ("Pap smear") programmes, the incidence and mortality rates for cervical cancer have declined precipitously in developed countries; nonetheless, cervical cancer is the second most common cancer in women worldwide [P38, S51]. Unlike cervical cancer, corpus cancer appears to be more common in women of higher socio-economic status [G25]. Risk factors for endometrial cancer include menstrual and reproductive characteristics, obesity, use of hormones and certain medical conditions [A2, G25]. Risk factors for uterine sarcomas have not been studied extensively and are poorly understood. Data on uterine cancer logically should be subdivided into those for the uterine cervix and for the uterine corpus; however, a number of the available radiation studies have combined data on cervical and corpus cancers. Table 34 notes when the data for the two types were combined in the various studies.

#### 2. Summary of UNSCEAR 2000

337. Uterine cancer was not considered in the UNSCEAR 2000 Report [U2].

#### 3. New or updated studies

##### *(a) External low-LET exposures*

338. Neither cancer of the uterine corpus nor cancer of the uterine cervix appeared to be related to radiation exposure in studies of the survivors of the atomic bombings [T1]. Corpus cancer showed a non-significant inverse association with radiation dose (ERR at 1 Sv = –0.25; EAR = –0.26 $(10^4 \text{ PY Sv})^{-1}$. A non-significant negative association also was seen for cervical cancer: ERR at 1 Sv = –0.07 (95% CI: –0.29, 0.27) and EAR = –0.37 (95% CI: –1.57, 1.38) $(10^4 \text{ PY Sv})^{-1}$. For all cancers of the uterus combined, there was no significant modifying effect of age at exposure, time since exposure or attained age. In the most recent mortality analysis for the LSS cohort [P9], the ERR for all uterine cancers combined was 0.17 (95% CI: –0.10, 0.52) $\text{Sv}^{-1}$,

and the EAR was 0.44 (95% CI: –0.27, 1.3) ($10^4$ PY Sv)$^{-1}$. Cancer of the uterine corpus is uncommon in Japan [P19].

339. Within the AHS subset of the LSS cohort, the incidence of benign uterine myoma was associated with radiation dose, and the association did not appear to be readily explicable in terms of better detection among the more highly exposed women [Y3]. If a high proportion of women with myomas went on to have hysterectomies, this could introduce a downward bias in the dose response for uterine cancer, particularly for corpus cancer.

340. Cancer of the uterine corpus was increased significantly 15 or more years after radiotherapy for cervical cancer (RR = 6.0), and the RR increased with dose ($p = 0.14$) [B5]. Most women in the study received radiotherapy for their cervical cancer, and doses were extremely high; indeed, women with doses to the uterus of up to 100 Gy constituted the reference group for dose–response analyses. Controls for the uterine corpus cases had to have an intact uterus at the time of diagnosis of the matched case. There was some indication that the risk was greater for adenocarcinoma of the uterus than for sarcoma of the uterus, but this comparison was limited by the small number of sarcoma cases.

341. Several studies have reported increased incidence [W30] and mortality rates [D7, I4] of uterine cancer among women irradiated for benign gynaecological disorders associated with excessive or irregular uterine bleeding. However, interpretation is complicated by the possible relation between uterine cancer and the underlying gynaecological conditions for which the radiotherapy was given. These include hyperplasia of the endometrium, uterine fibroids and endometrial polyps, all of which are thought to be related to hormonal factors [K44]. Furthermore, the frequency of hysterectomy for women with such disorders might differ from that for women in the general population. Wagoner [W30] reported a significantly elevated incidence of uterine cancer among Connecticut (United States) women irradiated for benign gynaecological disorders (observed = 83, expected = 29.3, SIR = 2.8 ($p < 0.01$)). The risk of uterine sarcoma or carcinosarcoma was especially high relative to that for women in the general population (observed = 12, expected = 1.5, SIR = 8.0 ($p < 0.01$)). Approximately half of the women were irradiated by external beam X-rays and half by intracavitary $^{226}$Ra. Among women from Massachusetts or Rhode Island (United States) irradiated by intrauterine radium, Inskip et al. [I4] reported a significantly elevated overall SMR of 1.8, with some indication of an increasing risk with increasing follow-up time. However, there was little evidence of a dose response (ERR = 0.006 (90% CI: –0.01, 0.05) Gy$^{-1}$). The median dose to the uterus was 32 Gy. Death due to cervical cancer occurred less often than expected (SMR = 0.5). In extended follow-up of a cohort of Scottish patients irradiated with X-rays for metropathia (with a mean dose to the uterus of 5.2 Gy), Darby et al. [D7] observed a non-significantly elevated SMR for cervical cancer (SMR =1 .31; 95% CI: 0.67, 2.28) and for all uterine cancer combined (SMR = 1.41; 95% CI: 0.91, 2.08). The estimated ERR for uterine cancer was 0.09 (95% CI: –0.02, 0.19) Gy$^{-1}$, and there was no clear trend of increasing RR with increasing follow-up time.

342. A statistically non-significant, negative trend of uterine cancer incidence with radiation dose was observed in a Swedish group treated for haemangioma in infancy: 22 such tumours were observed [L10].

343. In general, no significant trends of uterine cancer risk with external radiation dose have been observed in various groups of radiation workers. For example, in the United Kingdom there were 15 deaths due to uterine cancer in the NRRW, compared with 14.9 expected. There was a large but statistically non-significant trend with external film badge dose: the ERR was 16.8 (90% CI: <–1.95, 130.3) Sv$^{-1}$ [M12]. Likewise, in the IARC three-country nuclear worker study, there were positive trends with dose for both uterine cervix and other uterine cancer deaths, which for the latter end point approached statistical significance (1-sided $p = 0.092$) [C3].

344. Rates of cancer of the uterine corpus were slightly, but not significantly, increased among women treated with radiation to the ovaries and pituitary gland for infertility (SIR = 1.44; 95% CI: 0.52, 3.13) [R30]. The mean dose to the uterus was 0.97 Gy, and there was no indication of increasing risk with increasing dose. Excess cancers of the uterine corpus also have been observed following ovarian ablation therapy for breast cancer [E9], but not among ankylosing spondylitis patients [W8].

345. Cancer of the uterus (including corpus and cervix cancer) did not occur more often than expected in a cohort of 69,524 radiologic technologists compared with the incidence rate in the general female population (SIR = 0.80; 95% CI: 0.69, 0.90) [S29]. The risk of cancer of the uterus (including cervix) was not associated with low-dose radiation exposure (mean dose = 1.75 mSv) in a cohort of occupationally exposed women from Canada (SIR = 0.71; 95% CI: 0.63, 0.80) [S8]. Only 77 women in this cohort had doses of 100 mSv or greater.

#### *(b) Internal low-LET exposures*

346. A study of cancer incidence following radioiodine treatment for hyperthyroidism [F1] reported that there was no overall excess of uterine cancer in the treated group compared with the general population but did find a dose–response association: for ≤220 MBq, SIR = 0.52 (95% CI: 0.28, 0.96); for 221–480 MBq, SIR = 0.73 (95% CI: 0.41, 1.32); for >480 MBq, SIR = 2.11 (95% CI: 1.2, 3.7); $p = 0.002$ for trend. The uterus does not concentrate radioiodine, and it is questionable whether it would receive meaningful exposure from this treatment. Death due to cancer of the uterus occurred significantly less often than expected in another large cohort of hyperthyroid patients treated with radioiodine compared with mortality rates in the general female population [R3].

*(c) Internal high-LET exposures*

347. The International Thorotrast Study [T30] did not find any elevation in uterine cancer incidence rates associated with Thorotrast administration. There were 6 cases of uterine cervical cancer in the Thorotrast-exposed group and 9 in the comparison group in the Denmark–Sweden part of this study, resulting in an RR of 0.6 (95% CI: 0.2, 1.8). There were 5 cases of uterine corpus cancer in the Thorotrast-exposed group and 10 in the comparison group in the Denmark–Sweden part of the study, resulting in an RR of 0.6 (95% CI: 0.2, 1.8) [T30]. No uterine (or other organ) dose estimates have been made for the study, and no trend with administered Thorotrast volume was reported.

### 4. Summary

348. Available evidence indicates that there is no strong ionizing radiation dose response for uterine cancer [B44, T1]. An absence of association between cervical cancer risks and radiation exposures is a consistent finding, including exposures at very high doses. The evidence is not quite so universally negative for cancer of the uterine corpus but suggests that, if there is an effect, it is largely confined to the region of very high doses, i.e. in the tens of grays or more. These inferences must be tempered by the possibility that radiation dose is also related to treatment of conditions that lead to hysterectomy, which would preclude the possible future occurrence of uterine corpus cancer. Dose-dependent removal of the organ at risk could exert a downward bias in the dose response for uterine cancer.

## P. Ovarian cancer

### 1. General background

349. Ovarian cancer will affect 1–2% of women in developed countries during their lifetime [W25]. Annual age-standardized world incidence rates for ovarian cancer vary from fewer than 6 per 100,000 women in most of China to more than 10 per 100,000 in most of the United States [P19]. The ovarian cancer mortality rate is high, and it is the fourth most common cause of cancer mortality in women, accounting for 1% of their total mortality. There has been a steady increase in mortality from ovarian cancer in industrialized countries [Y2]. There are several histological types, with epithelial tumours clearly dominating. Risk factors, other than reproductive patterns and hormone levels, are not well understood. It has been shown that occupational exposures to asbestos and talc may be associated with this cancer. Further details on the epidemiology of ovarian cancer can be found in Weiss et al. [W25].

### 2. Summary of UNSCEAR 2000

350. Ovarian cancer was not considered in the UNSCEAR 2000 Report [U2].

### 3. New or updated studies

*(a) External low-LET exposures*

351. The number of epidemiological studies providing results for ovarian cancer risk is quite limited. The largest number of cases comes from the case-control and cohort studies of women treated with radiation for cervical cancer [B8, K1]. Excess risk of ovarian cancer due to radiation exposure was not observed; however, the doses were exceptionally large (e.g. 32 Sv), which probably resulted in cell killing. A non-significant excess risk was observed in a group of women treated with $^{226}$Ra for uterine bleeding. The ERR was 0.4 (95% CI: –0.7, 1.5) based on 37 cases [I4].

352. The best evidence for an effect due to radiation exposure comes from the studies of the incidence and mortality data for the survivors of the atomic bombings (LSS). Up to the end of 1987, 66 cases of ovarian cancer were observed in women with exposures of greater than 0.01 Sv. The estimated RR was 0.99 (95% CI: 0.12, 2.34) at 1 Sv [T1]. For mortality, there is longer follow-up of the data (up to the end of 1997), and 85 deaths due to ovarian cancer were observed among women receiving more than 0.005 Sv [P9]. A significant ERR of 0.94 (95% CI: 0.07, 2.0) at 1 Sv was estimated (see table 35). In a previous mortality analysis [P1], this dose–response relationship was clearly linear, although the numbers of cases were limited. There was also a suggestion, although statistically non-significant, that exposures at either young (less than 10 years old) or older (more than 40 years old) ages were a greater risk.

*(b) Internal low-LET exposures*

353. Very few data are available to relate ovarian cancer and internal low-LET radiation exposures. Patients treated for hyperthyroidism [R3] showed no increase in ovarian cancer incidence rates (based on 86 cases), but the dose was low (less than 0.1 Sv). A (statistically non-significant) positive trend of ovarian cancer incidence rates with radiation dose was observed in a Swedish group treated for haemangioma in infancy: 15 such tumours were observed, yielding an ERR of 0.62 $Gy^{-1}$ [L10].

354. In general, no significant trends of ovarian cancer with external radiation dose have been observed in various groups of radiation workers. For example, in the United Kingdom there were 13 deaths due to ovarian cancer in the NRRW, compared with 16.2 expected; there was a large but statistically non-significant trend with external film badge dose: the ERR was 82.8 (90% CI: <–1.95, 2583) $Sv^{-1}$ [M12]. Likewise, in the IARC three-country nuclear worker study, there were positive (but statistically non-significant)

trends of ovarian cancer mortality with dose (1-sided $p = 0.312$) [C3].

*(c) Internal high-LET exposures*

355. The International Thorotrast Study [T30] found elevated risks of ovarian cancer associated with Thorotrast administration. There were 9 cases of ovarian cancer in the Thorotrast-exposed group and 3 in the comparison group in the Denmark–Sweden part of this study, resulting in an RR of 4.3 (95% CI: 1.1, 24.3) [T30]. No ovarian (or other organ) dose estimates have been made for this study, and no trend with administered Thorotrast volume was reported.

### 4. Summary

356. Although the body of evidence is not strong, the LSS provides evidence that ovarian cancer is inducible by ionizing radiation.

## Q. Prostate cancer

### 1. General background

357. Prostate cancer is one of the most commonly occurring cancers among men in Europe, Africa and the Americas, with particularly high incidence rates in the United States, especially among black people. Rates are considerably lower throughout Asia, particularly in Japan and China [P19], where, despite increases in recent years, they remain an order of magnitude or more lower than those in the United States and other high-risk countries [H28, S78]. For example, annual age-standardized world incidence rates for prostate cancer are less than 10 per 100,000 men in most of China, whereas in some parts of the United States, rates exceed 180 per 100,000 [P19]. Because of relatively effective treatments, mortality rates are lower than those of lung, stomach and other relatively common cancers. There are some indications that in recent years prostate cancer mortality rates are declining in many developed countries [B47]. Both the increase in incidence rates and the possible decline in mortality rates reflect, at least in part, the effects of increased screening.

358. Prostate cancer is extremely rare before age 40, after which rates increase more rapidly than for other cancers. The rate of increase with age is largely independent of regional variations in rates [P19]. Little is known about risk factors for prostate cancer; however, migration and family studies [M53, R34] have suggested that, while genetic predisposition has some role in explaining the large regional differences in the risk of prostate cancer, other factors are also important. Dietary factors, particularly levels of body fat [R34, V10, W33], and levels of sex hormones [H38] are suspected risk factors.

### 2. Summary of UNSCEAR 2000

359. Studies of the risk of prostate cancer following radiation exposure are limited by the fact that prostate cancer largely occurs at older ages, and that few studies have sufficient follow-up or sample size to have appreciable power to detect excess risk at levels comparable to that seen for most other cancers linked with radiation exposure. It was noted that several studies have provided some evidence for a radiation effect on prostate cancer incidence, most notably the long-term follow-up of the United Kingdom cohort of ankylosing spondylitis patients who received X-ray treatments [W8], and United Kingdom Atomic Energy Authority workers with internal low-LET radiation exposures [R14]. However, it was concluded that there is no compelling evidence for a radiation effect on prostate cancer risks. This conclusion was based on the lack of a significant dose response in the studies on survivors of the atomic bombings [T1], in a United States study of men who had received radiotherapy for peptic ulcers [G6] and in the study of the large pooled cohort of nuclear workers [C3].

### 3. New or updated studies

*(a) External low-LET exposures*

360. Table 36 summarizes the risk estimates for prostate cancer and prostate cancer mortality from epidemiological studies of radiation exposure.

361. While mortality among survivors of the atomic bombings has been presented in recent publications [P9, P10], these reports do not explicitly consider prostate cancer risks. However, the Radiation Effects Research Foundation has released the data set used in the analyses for reference [P9], and this data set does contain information that permits analyses of possible radiation effects on prostate cancer mortality risks for the period 1950–1997. An update of the peptic ulcer study on cancer mortality has been published recently [C4]. Unfortunately, since the publication of the UNSCEAR 2000 Report [U2], there have been no new reports on prostate cancer incidence for the survivors of the atomic bombings, nor have any of the other studies considered in the UNSCEAR 2000 Report been updated. Prostate cancer is routinely considered in many follow-up studies of cancer survivors (e.g. [A31, V9]), but because of the relatively short follow-up period and the ages of most members of these cohorts, they do not provide useful information on the relation between radiation exposure and prostate cancer risks.

362. The latest follow-up data on mortality among the survivors of the atomic bombings [P9] include 53 deaths due to prostate cancer among 19,992 male members of the cohort with dose estimates of greater than 5 mGy. The estimate for ERR per unit dose of prostate cancer reported by Preston et al. [P9] is 0.21 (90% CI: <–0.3, 0.96) $Gy^{-1}$.

As with the incidence data [T1], there is no indication of a statistically significant increase in prostate cancer risk with radiation exposure. The point estimate for the ERR per unit dose is about half of that seen for all solid cancer deaths among men in the LSS, but the uncertainty on both estimates is such that there is no evidence that the ERR for prostate cancer is significantly lower than that for all solid cancers.

363. The study of cancer mortality in the peptic ulcer study has been updated to include follow-up to the end of 1998 [C4]. The cohort includes 2,914 men, half of whom received radiotherapy, with an average of 25 years of follow-up per person. There have been 72 prostate cancer deaths. As in the earlier analyses of this cohort, the observed number of deaths due to prostate cancer was higher than expected number based on the general male population for both the radiotherapy and the non-radiotherapy group, with the ratio of observed to expected smaller (1.24) in the radiotherapy group than in the non-radiotherapy group (1.47). These results do not suggest that radiation exposure is increasing prostate cancer rates in this cohort.

364. Prostate cancer and prostate cancer mortality risks have been considered for the 21,000 men in the cohort of United States radiologic technologists. Individual dose estimates are not yet available for this cohort. However, comparisons with expected numbers of cases based on national incidence [S29] and mortality rates [M10] do not suggest that prostate cancer rates are associated with occupational exposures for this cohort. Based on 222 cases of prostate cancer, the estimated SIR was 1.02 (95% CI: 0.89, 1.16), while the SMR for the 87 deaths due to prostate cancer was 0.89 (95% CI: 0.7, 1.1). Recent studies of mortality among 47,000 male workers in the United States nuclear power industry led to a large negative estimated ERR of prostate cancer of –2.50 (95% CI: <–2.51, 26.4) $Sv^{-1}$, which was not significant, however [H44]. No significant effects due to radiation exposure were found for prostate cancer in the latest analysis of mortality data among Japanese nuclear workers [I14].

365. Atkinson et al. [A22] have studied mortality follow-up in a cohort of 51,367 United Kingdom Atomic Energy Authority workers, extending a previous study of Beral et al. [B59]. The trend of prostate cancer risk with dose failed to be statistically significant (2-sided $p = 0.13$), although the trend remained statistically significant for those workers followed up until 1979 (2-sided $p < 0.01$) [A22], somewhat corroborating the previous findings in this cohort [B59]. A study of 12,540 workers at the Capenhurst uranium enrichment facility in the United Kingdom did not suggest any elevated risk of prostate cancer: the trend of prostate cancer risk with cumulative external dose was negative [M4]. Likewise, a study of 13,960 radiation workers at the Springfields uranium production facility in the United Kingdom did not suggest any increased incidence or mortality rates for prostate cancer [M5]. A study of 2,628 workers at the United Kingdom Chapelcross site found a statistically significant positive trend of mortality due to prostate cancer with cumulative external dose (1-sided $p = 0.036$ for a 10-year lag, adjusted for age, sex, calendar year, industrial status, worker status and time since first exposure), based on 8 deaths [M6]. However, with increasing lag time the significance of the trend progressively decreased, so that with a 20-year lag time, the trend was no longer conventionally statistically significant (1-sided $p > 0.05$) [M6]. None of the 8 deaths had been monitored for tritium, $^{51}Cr$, $^{59}Fe$, $^{60}Co$ or $^{65}Zn$, the radionuclides suggested by the study of Rooney et al. [R14] as being associated with elevated risk. Some of these cohorts include substantial groups who were heavily exposed to tritium [A22, B59, M4, M6], although in general, doses from tritium do not appear to have been estimated.

366. Although not considered in the UNSCEAR 2000 Report [U2], the study of Artalejo et al. [A32] reported a slight deficit of prostate cancer mortality among workers for the Spanish Nuclear Energy Board; the SMR was 0.73 (95% CI: 0.29, 1.51), based on only 7 cancer deaths, of which 1 was among the 27% of the cohort who had been miners and who may have been exposed to alpha radiation [A32].

#### *(b) Internal high-LET exposures*

367. The International Thorotrast Study [T30] found elevated risks of prostate cancer associated with Thorotrast administration. There were 14 cases of prostate cancer in the Thorotrast-exposed group and 4 in the comparison group in the Denmark–Sweden part of this study, resulting in an RR of 4.5 (95% CI: 1.6, 16.3) [T30]. There was a single death from prostate cancer in the Thorotrast-exposed group and there were 2 in the comparison group in the United States part of this study, resulting in an RR of 0.2 (95% CI: 0.0, 5.1) [T30]. Prostate (or other organ) doses were not estimated for this study, and no trend with administered Thorotrast volume was reported.

### 4. Summary

368. There is little indication of effects due to radiation exposure on prostate cancer risks. Despite the relatively long follow-up and large cohort size, the power of the studies of the survivors of the atomic bombings is somewhat limited by the low underlying rates of prostate cancer in Japan and the relatively low mean dose for the survivors. It is of some interest that the United Kingdom ankylosing spondylitis study led to a statistically significant result, with an estimate for the ERR per unit dose that is similar to that seen from the LSS. Occupational cohorts and studies of people who received radiotherapy provide little indication that external or internal radiation exposure increases prostate cancer risks.

## R. Cancer of the urinary bladder

### 1. General background

369. Bladder cancer accounts for less than 5% of total cancer incidence and less than 2% of total 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 rates increase steeply with age, and this cancer is substantially more common among men than women: in some countries the ratio can reach 5:1 [H37, P19]. The incidence rate increased from the 1960s to the 1980s, but recently has begun to stabilize. Mortality rates have been decreasing for both men and women and for all ages. The temporal trends are influenced by changes in detection and improvements in survival.

370. Cigarette smoking is a leading cause of bladder cancer. In Western countries, approximately 50% of the cancers in men and 30% in women would be attributable to smoking. Occupational exposures to carcinogens, particularly to aromatic amines, and urinary tract infections, especially among women, also are associated with an increased risk of bladder cancer. Use of phenacetin-containing analgesics and cyclophosphamide, as well as exposure to arsenic in drinking water and *Schistosoma haematobium* infection, are also suspected risk factors for bladder cancer [H37, M33, S44].

### 2. Summary of UNSCEAR 2000

371. The UNSCEAR 2000 Report concluded that there was convincing evidence of a relation between low-LET radiation exposure and bladder cancer risk based on the LSS incidence and mortality data [P1, R10, T1], as well as on studies of several populations medically exposed to radiation for benign diseases [D7, I4, W8] and populations receiving radiotherapy for malignant diseases [B8, B50, N9, T27, T28]. The risk estimates from the studies of the survivors of the atomic bombings were generally greater than those from most other studies. However, this difference may be related to the phenomenon of cell killing arising from the very high doses involved in many of the medical studies.

372. In the LSS, the effects of age and sex on bladder cancer risk were unclear. A statistically significant difference between the risks for the two sexes, with the ERR for females exceeding that for males by a factor of about 5, was seen in the incidence data; however, no significant difference was observed when an EAR model was used [T1]. Based on the mortality data, the point estimates of the ERRs and EARs for males were higher than those for females, although the differences were not statistically significant [P1]. Neither the mortality data [P1, S3] nor the incidence data [T1] exhibited statistically significant variation with age at exposure for either the ERR or the EAR. The UNSCEAR 2000 Report indicated that potential interactions between smoking and radiation exposure needed to be studied.

373. Information on bladder cancer risks from internal low-LET radiation exposure was limited, and there was little evidence of a link between bladder cancer and exposure to $^{131}$I [D18, H2, H6, H24, R3], with the exception of two relatively small studies of thyroid cancer [E8] and of hyperthyroid patients [F1] treated with $^{131}$I.

374. The risk of bladder cancer associated with exposure to high-LET radiation was unclear. No risk was seen among patients exposed to Thorotrast as a contrast medium [A5, D15, M14, V4]. In one study of patients treated with $^{224}$Ra [N2], there was a suggestion of an elevated risk, but this was not found in another study of similarly treated patients [W15].

### 3. New or updated studies

#### *(a) External low-LET exposures*

375. The results from studies reported in the UNSCEAR 2000 Report and the new and updated studies are presented in table 37. The most recent LSS report stated that 150 bladder cancers occurred between 1950 and 1997. Of these, 99 occurred among survivors exposed to 5 mSv or more, of which about 16% would be attributable to radiation exposure [P9]. While there was little difference in the ERR between the sexes for exposure at age 30, the estimated EAR for males was about twice that for females (0.7 and 0.33, respectively). No information on time patterns was provided in this report.

376. The Chicago study of mortality due to peptic ulcer was updated in 2002 [C4]. Based on a small number of deaths due to bladder cancer among irradiated and non-irradiated patients (13 and 8, respectively), the RR for radiotherapy was estimated as 1.49 (95% CI: 0.50, 4.4) in the period 11–62 years after treatment. With a mean bladder dose of 0.2 Gy, an ERR of 2.5 (90% CI: <0, 17.2) could be estimated.

377. 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. As described in the UNSCEAR 2000 Report, elevated risks of bladder cancer were associated with radiotherapy in studies of patients with non-Hodgkin's lymphoma [T29], or with cancers of the ovary [K31, T27], cervix [B8], testis [T28] or prostate [B50, N9, P23]. Results from two new studies of bladder cancer following radiotherapy for prostate cancer are inconsistent. Pickles and Phillips [P24] observed an elevated risk of bladder cancer 10 or more years after radiotherapy for prostate cancer. However, no excess risk was reported in a much

smaller series of patients from the Mayo Clinic in the United States [C16].

378. No clear excess of bladder cancer incidence or mortality has been shown in a number of studies of nuclear radiation workers, including those of the Canadian National Dose Registry [S8], the United Kingdom NRRW [M12], the combined analysis of workers in Canada, the United Kingdom and the United States [C3], and several smaller studies [A22, F2, I14, M4, M5, M6, M34, W6]. An elevated risk of bladder cancer has been reported among Chinese radiology workers, particularly those who worked before 1970 [W3]. In contrast, neither bladder cancer incidence nor mortality was increased in a cohort of United States radiologic technologists [M31, S29].

*(b) Internal low-LET exposures*

379. High doses of $^{131}$I are often used to treat thyroid cancer. Because the bladder is one of the few organs that concentrate iodine [U2], the $^{131}$I dose to the bladder from this treatment is about 2 Gy. An excess risk of bladder cancer was reported in one small study of thyroid cancer patients [E8], but not in two others [D18, H2]. In the only new study of low-LET radiation exposure, bladder cancer incidence rates were elevated, but the lower confidence interval did not include unity (SIR for $^{131}$I therapy compared with no $^{131}$I therapy = 1.6; 95% CI: 0.6, 4.5) following $^{131}$I exposure during treatment for thyroid cancer [R38]. This study was the largest conducted to date and included cohorts of patients from France, Italy and Sweden.

*(c) Internal high-LET exposures*

380. In an analysis of Danish, Swedish and United States patients injected with Thorotrast as a contrast medium, bladder cancer incidence and mortality rates did not differ significantly from those observed in a comparison group [T30]. These results are consistent with earlier studies of internal high-LET exposure from Thorotrast [A5, D15, M14, V4].

381. In a Finnish study of persons exposed to dissolved radioactive material (predominantly $^{222}$Rn, but also $^{234}$U, $^{238}$U, $^{226}$Ra, $^{210}$Po and $^{210}$Pb), an elevated incidence rate of urinary bladder cancer was not statistically significantly associated with ingested aggregate quantities of radon, radium or uranium, or with the aggregate bladder dose [K56].

#### 4. Summary

382. Updated mortality information from studies of the survivors of the atomic bombings continues to demonstrate a positive radiation dose response for bladder cancer. In the aggregate, studies of cancer patients treated with high-dose radiotherapy also demonstrate an association between radiation exposure and risk of bladder cancer. Studies of nuclear workers do not provide evidence of a radiation-related bladder cancer risk, but because the radiation exposure of these workers was low, the statistical power of the studies is quite limited. One relevant study of occupational exposure in medicine with presumably high exposures has reported an excess incidence of bladder cancer. In the recent BEIR report [C37], the estimate of lifetime mortality due to bladder cancer, 0.90% (95% CI: 0.3, 2.90) $Sv^{-1}$, is similar to that proposed by the ICRP [I11], and is between the two estimates proposed in the UNSCEAR 2000 Report, although it is much closer to the estimate based on an absolute risk transfer model.

### S. Kidney cancer

#### 1. General background

383. The estimated annual number of cases of kidney cancer worldwide is approximately 189,000, and the associated annual number of deaths is about 91,000 [F14]. The incidence rate of renal cell carcinoma is about eightfold higher in developed countries than in developing ones, with a worldwide range of annual age-standardized world incidence rate from 0.5 per 100,000 persons in parts of India to 20.0 and 10.2 per 100,000 men and women, respectively, in parts of the Czech Republic [P19]. Part of this difference is due to the relative availability of ultrasound, computerized tomography (CT) and magnetic resonance imaging (MRI) scans [G26]. Well-documented risk factors for the disease include cigarette smoking, obesity, hypertension and acquired polycystic kidney disease. Risk factors for which there is some evidence, but for which links are as yet unproven, are renal transplantation, infection with human immunodeficiency virus (HIV), exposure to heavy metals (especially to cadmium and lead), chlorinated solvents, asbestos and phenacitin analgesics, and urinary tract infections. Other factors, such as higher levels of physical activity, of vegetable consumption, and of calcium and vitamin E supplements, may be protective [G26, M50]. There is a clear familial component to the disease: the RR for a sibling, but not for the parents, of an affected person is about 2.5, thereby suggesting recessive genetic risk [H50]. A study in Iceland reported that nearly 60% of kidney cancer patients also had a first or second degree family member with kidney cancer [G27]. At the molecular level, common findings in familial and sporadic renal cell carcinoma are a loss of the terminal portion of the small arm of chromosome 3, sometimes with a translocation near the breakpoint 3p13 in familial cases, and/or a somatic mutation or hypermethylation in the 3p segment on or near the von Hippel–Lindau (VHL) gene locus [G26].

#### 2. Summary of UNSCEAR 2000

384. Kidney cancer was not assessed in the UNSCEAR 2000 Report [U2].

### 3. New or updated studies

#### *(a) External low-LET exposures*

385. The data are quite sparse for radiation exposure and kidney cancer risk. In the LSS cohort, the association between radiation dose and kidney cancer incidence was not statistically significant, although the point estimate of the effect was similar to that seen for many other sites (ERR = 0.71 $Sv^{-1}$) [T1] (see table 38). Similarly, in the LSS mortality data, the dose–response association was not statistically significant for either males or females, although the risk was nominally larger for females (ERR = 0.97 (90% CI: <–0.3, 3.8) $Sv^{-1}$) than for males (ERR = –0.02 (90% CI: <–0.3, 1.1) $Sv^{-1}$) [P9]. Studies of several cohorts of cervical cancer patients receiving radiotherapy did not indicate significant elevations in risk (compared with general population rates or non-irradiated comparison groups) [B11, K1, S20]. However, a case-control study nested within the largest cervical cancer cohort study showed a positive but not statistically significant ($p$ = 0.17) dose–response relationship (ERR = 0.71 (95% CI: 0.03, 2.2) $Sv^{-1}$) [B8]. The United Kingdom ankylosing spondylitis study also showed an elevation in kidney cancer risk in association with generally high (radiotherapeutic) doses (ERR = 0.10 (95% CI: 0.02, 0.20) $Sv^{-1}$) [W8]. Two smaller studies of radiotherapy for uterine bleeding or peptic ulcer did not exhibit raised risks [I4, C4], but they had low statistical power.

386. A number of studies of radiation workers have shown no positive dose–response association or clear excess of kidney cancers. For example, the United Kingdom nuclear worker study [M12] observed 83 deaths due to kidney cancer compared with 89.7 expected, and a statistically significant negative trend with external film badge dose: the ERR was <–1.95 (90% CI: <–1.95, –0.96) $Sv^{-1}$. Likewise, there is a negative trend, albeit not a statistically significant one ($p$ = 0.848), with increasing film badge dose in the IARC three-country study, based on 88 deaths from kidney cancer [C3]. The Canadian National Dose Registry [S8] reported 69 kidney cancer deaths versus 91.1 expected (SMR = 0.76; 90% CI: 0.61, 0.93) among male workers, and 21 kidney cancer deaths versus 26.5 expected (SMR = 0.79; 90% CI: 0.53, 1.14) among female workers. Generally (non-significant) negative trends of kidney cancer mortality with external dose were observed in a United Kingdom cohort of workers at a uranium production facility. Only with a 20-year lag is the trend with dose (non-significantly) positive [M5]. Likewise, generally negative trends of kidney cancer mortality rates with external film badge dose are observed among workers at the Chapelcross plant in the United Kingdom [M6]. The study of Artalejo et al. [A32] reported a slight excess of kidney cancer mortality among workers for the Spanish Nuclear Energy Board; the SMR was 1.26 (95% CI: 0.34, 3.21), based on only 4 cancer deaths, of which 2 were among the 27% of the cohort who had been miners and may have been exposed to alpha radiation [A32]. The statistical power of all of the occupational studies is limited by the low levels of dose.

#### *(b) Internal low-LET exposures*

387. Three studies have examined kidney cancer risk in relation to internal exposure to low-LET radiation. A Swedish study of cancer incidence following $^{131}I$ treatment for hyperthyroidism reported significantly more kidney cancers in the $^{131}I$-treated group than expected on the basis of general population rates. However, a dose–response analysis was not reported, so it is unknown whether the excess was associated primarily with hyperthyroidism or with radiation exposure [H6]. A United States study of mortality following hyperthyroidism treatment showed no excess risk for kidney cancer [R3]. A study of 6,841 Swedish, French and Italian patients treated with a mixture of conventional (external beam) radiotherapy and $^{131}I$ for thyroid cancer recorded a modest, and statistically significant, increase in kidney cancer incidence rate (SIR = 2.6; 95% CI: 1.7, 3.8; 31 cases) [R38]. However, there was no relation with $^{131}I$ exposure; risks were comparable in the group treated with and that treated without $^{131}I$ (SIR = 2.6 in both cases) [R38].

#### *(c) Internal high-LET exposures*

388. The only recent study of kidney cancer risk in relation to internal high-LET radiation exposure was of a group of Danish, Swedish and United States patients who received the diagnostic contrast medium Thorotrast, and a companion group who received a non-radioactive contrast medium [T30]. There were 12 cases of kidney cancer in the exposed group and 4 in the control group, representing an RR of 5.7 (95% CI: 1.9, 21.0, $p < 0.05$) [T30]. The RR also increased with increasing interval of follow-up ($p < 0.001$), suggesting a causal association between Thorotrast exposure and the risk of kidney cancer; however, there was no statistically significant trend with increasing volume of injected Thorotrast ($p$ = 0.23). No statistically significant excess of kidney cancer has been observed in German or Japanese Thorotrast-exposed groups [M19, V4]. Ishikawa et al. [I15] have estimated that the kidney in Thorotrast patients would typically receive a relatively modest radiation dose, of about 1.5 mGy per year. Given that the kidney appears to be relatively radio-resistant, it is unlikely that the excess risk observed in the three-country study is causally associated with the Thorotrast exposure.

389. In a Finnish study of persons exposed to dissolved radioactive material (predominantly $^{222}Rn$, but also $^{234}U$, $^{238}U$, $^{226}Ra$, $^{210}Po$ and $^{210}Pb$), the incidence of kidney cancer was not statistically significantly associated with ingested aggregate quantities of radon, radium or uranium, or with the aggregate kidney dose [K56].

### 4. Summary

390. There is weak evidence linking the risk of kidney cancer with radiation exposure. The strongest evidence is from those studies (on patients with cervical cancer and ankylosing spondylitis) where the kidney doses were likely

to have been high (in the radiotherapy range), suggesting that there is no strong dose response for kidney cancer.

## T. Brain and central nervous system tumours

### 1. General background

391. The most common types of tumour of the brain and central nervous system (CNS) are gliomas, meningiomas and schwannomas. Schwannomas (also known as neurolemmomas) and most meningiomas are benign, whereas gliomas are malignant. Depending on tumour location, benign and malignant tumours of the CNS can have similar symptoms and outcomes. As a result, the two types of tumour are not always easily distinguished, and many tumour registries routinely include benign and malignant histological types in their evaluations of CNS tumour incidence [I20, P32].

392. Annual age-standardized world 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 the reporting of benign tumours is inconsistent among registries, international comparisons of reported CNS tumour incidence rates can be misleading [P19]. The fact that lower incidence rate values are reported primarily by cancer registries with uncertain completeness of ascertainment suggests that country-to-country variation is probably considerably smaller than current reporting indicates. Over the last few decades, brain tumour incidence and mortality rates have increased, especially for the elderly, but whether this is a real increase or a result of better diagnosis and reporting is controversial [I20, P32]. Meningiomas are more common in females than in males, but malignant CNS tumours occur more frequently among men [P19]. This section will consider both benign and malignant CNS tumours occurring within the cranium (brain, cranial nerves and cranial meninges), spinal cord, spinal meninges and peripheral nervous system, because of the potential problem of misclassification or inconsistent classification according to tumour behaviour. In addition, since the rates used for comparison in some studies are derived from tumour registries that combine all CNS tumours into one category, results are reported for all CNS tumours together and not only for malignant tumours.

393. Primary malignancies of the CNS are among the most lethal of cancers. In the United States, 5-year survival for malignant CNS tumours is approximately 30% [R28]. Survival for benign meningiomas has improved considerably over the past few decades but, depending on tumour size and location, the quality of life can be severely impaired [L74].

394. While the aetiology of CNS tumours remains elusive, therapeutic irradiation of the head and neck during childhood is an established risk factor [I20, P32]. Findings of inverse associations between risk of glioma and self-reported history of asthma or allergies has prompted interest in the possible importance of immune system factors [B45, S52, W31, W32]. A small proportion of brain and nervous system tumours occur in association with family cancer syndromes, such as Li–Fraumeni syndrome, neurofibromatosis types 1 and 2, and hereditary retinoblastoma [L73].

### 2. Summary of UNSCEAR 2000

#### *(a) External low-LET exposures*

395. A significant relationship between radiation dose and CNS tumour risk was demonstrated in the Israeli tinea capitis study [R17] and in various other studies of radiotherapy used to treat non-malignant conditions [A7, H10, H26, K14, K15, L4, S45, S53, S54, S68]; however, CNS tumour incidence rates were not elevated in a Swedish study of persons treated for haemangioma in childhood [L10].

396. A higher than expected number of second primary CNS tumours among survivors of childhood cancers has been noted in several studies [B43, D16, D19, E7, L16, L24, N14, W11]. There is evidence of risk being higher for benign CNS tumours than for malignant CNS tumours [L24, R17]. 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 [B13], but lower doses, of 0.6 Gy, are not associated with an increase in CNS tumour incidence or mortality rates in two small cohorts of infertile women whose pituitary glands and ovaries were irradiated [R29, R30]. Ankylosing spondylitis patients did not have an excess of mortality from spinal cord tumours after their spinal cords were exposed to high radiation doses [W8].

397. Radiation workers in general receive low, fractionated doses with relatively little exposure of the brain. To date, most occupational studies have been negative with respect to brain cancer [C3, M12, W29].

398. Dental diagnostic X-ray exposures have been assessed in several studies conducted by Preston-Martin et al. in relation to various types of CNS tumour [P33, P34, P35, P36]. They found associations between meningioma and both frequent full-mouth X-ray examinations and X-ray examinations performed many years ago, when radiation doses were relatively high. In other studies, however, brain tumour cases did not have a history of dental X-ray exposure significantly more often than controls [R31].

399. The issue of whether CNS tumours are related to foetal exposure to radiation remains controversial. Doll and Wakeford [D37] 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 (OSCC). In the OSCC, mortality from childhood CNS tumours was associated with foetal irradiation (RR = 1.4; 95% CI: 1.2, 1.7) [B2]. Miller and Boice [B42, M48] expressed concern about the OSCC results, noting that all childhood cancers were increased by about 40%, whereas such commonality is not seen in either animal or human studies. Among survivors of the atomic bombings exposed in utero, an association between dose and cancer mortality risk has not been found, but the in utero survivor cohort is small, with consequently limited statistical power, and the negative result is therefore compatible with a wide range of possible risk values [D14].

*(b) Internal low-LET exposures*

400. 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, although since the dose to the brain was less than 10 mGy, the observed excess is not likely to be due to the radiation exposure [H8]. Significant excess risks were not demonstrated for patients receiving $^{131}$I therapy for hyperthyroidism [H6, H24, R3] or thyroid cancer [D38, E8, G24, H2]; however, among 10-year survivors, the brain tumour incidence rate was significantly elevated in the Swedish hyperthyroid patients [H6].

*(c) Internal high-LET exposures*

401. Danish patients exposed to Thorotrast, a radiographic contrast agent associated with internal exposure to alpha-particle-emitting radionuclides, 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 to 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 [S50] or radon among miners [D10].

### 3. New or updated studies

*(a) External low-LET exposures*

402. As summarized in table 39, the epidemiological literature provides evidence for an association between ionizing radiation and tumours of the CNS.

403. A detailed investigation of CNS tumours in the LSS updated data on tumour incidence up to 1995, and included thorough tumour ascertainment and a pathology review [P33]. The intracranial tumours included 43 gliomas, 88 meningiomas and 33 schwannomas. There were nearly statistically significant elevations in risk for glioma (ERR = 0.56 (95% CI: –0.2, 2.0) $Sv^{-1}$) and meningioma (ERR = 0.64 (95% CI: –0.01, 1.8) $Sv^{-1}$, and a stronger association for schwannoma (including both intracranial and others, ERR = 4.5 (95% CI: 1.9, 9.2) $Sv^{-1}$ (table 39). For nervous system tumours other than schwannomas, the linear dose–response model fits very well, while, for schwannomas, the dose–response relationship tended to curve downwards at high doses (>2 Sv), albeit not significantly ($p$ = 0.09) [P33]. For nervous system tumours other than schwannomas, there was a suggestion of greater risk following radiation exposure at earlier ages ($p$ = 0.06 for trend), such that those exposed before age 20 had ERR = 1.2 (95% CI: 0.3, 2.9) $Sv^{-1}$, and those after age 20 had ERR = 0.2 (95% CI: <–0.2, 1.0) $Sv^{-1}$. There was no indication of modification of risk due to time since exposure, suggesting that elevated risks may persist throughout the lifetime. For nervous system tumours other than schwannomas, there was a greater radiation risk for males than females (ratio of ERRs per unit dose = 14, $p$ = 0.05). The dose response for tumours of the nervous system remained significant when analysis was limited to persons with brain doses of less than 1 Sv.

404. It was estimated that 14% of the first primary tumours of the CNS and pituitary gland occurring in the LSS cohort would have been attributable to radiation [P33], and clinical characteristics of the tumours occurring in this study population were similar to those of spontaneous tumours in population-based studies [Y6]. While in North America and Europe, tumours of neuroepithelial origin predominate, meningioma is the most common neural tumour in Japan.

405. As in earlier reports, the most recent analysis of mortality data from the survivors of the atomic bombings does not show a statistically significant association between mortality due to tumours of the brain or CNS and radiation dose [P9]. An earlier analysis showed virtually no association with brain tumour risk but a non-significant positive association with the risk of CNS tumours other than those of the brain [P1].

406. A significant relationship between radiation dose and CNS tumour risk was demonstrated in the latest follow-up of the Israeli tinea capitis study [S48]. The mean age at the time of irradiation was 7.1 years. Risks of both benign meningioma and malignant brain tumours were associated with dose in this tinea capitis cohort [S48]. The dose–response relationship was stronger for meningioma than for malignant brain tumours. The ERR was 4.63 (95% CI: 2.43, 9.12) $Gy^{-1}$ for meningioma and 1.98 (95% CI: 0.73, 4.69) $Gy^{-1}$ for malignant tumours. The EAR was 0.48 (95% CI: 0.28, 0.73) $(10^4 \text{ PY Gy})^{-1}$ for meningioma and 0.31 (95% CI: 0.12, 0.53) $(10^4 \text{ PY Gy})^{-1}$ for malignant brain tumours. The ERR for malignant tumours was inversely associated with age at irradiation, varying from 3.56 $Gy^{-1}$ for those under age 5 at the time of exposure to 0.47 $Gy^{-1}$ for those over age 10. The ERR per unit dose for meningioma

showed little relation to age at exposure. The risk of both types of tumour remained elevated after 30 years. The EAR increased with increasing follow-up time, reaching 0.31 ($10^4$ PY Gy)$^{-1}$ and 2.03 ($10^4$ PY Gy)$^{-1}$ after 30 years for malignant brain tumours and meningioma, respectively. The ERR per unit dose did not appear to differ between the sexes. The malignant brain tumours were predominantly (75%) of neuroepithelial origin. The results of this study are therefore consistent with earlier reports of larger risks for benign brain tumours than for malignant brain tumours [L24].

407. Recent follow-up of a cohort of 4339 Dutch patients given nasopharyngeal radium irradiation did not reveal evidence of increased brain cancer incidence or mortality rate [R4, R41]. The average dose to the brain was 1.8 cGy. A smaller study from Maryland (United States) noted an elevated number of brain tumours, three of which were malignant and four benign, but the RR estimate was highly unstable (RR = 14.6; 95% CI: 0.76, 286.3) [Y7].

408. For patients irradiated for hereditary retinoblastoma, the risk of developing a brain cancer was 16 times that for the general population [K43]. Young children who received cranial irradiation as a conditioning regimen before bone marrow transplantation were found to have a significantly elevated RR of developing brain or other CNS cancers. However, it was likely that earlier cranial radiotherapy to treat acute lymphoblastic leukaemia prior to bone marrow transplantation (and associated whole-body irradiation) played an important role in the development of these neural malignancies [C26].

409. Data on adult exposures are considerably more limited. Longstreth et al. [L75] reported an association between meningioma risk and having had six or more full-mouth X-rays 15–40 years before diagnosis, but little evidence of a dose–response relationship. These data somewhat support the earlier studies of Preston-Martin et al. discussed above [P33, P34, P35, P36].

410. As was true of the earlier studies of radiation workers, most occupational studies to date have been negative with respect to this site of cancer, in particular two studies of radiologists and radiologic technologists [S29, Y5]. A recent study of 191,333 workers in Canada exposed occupationally to very low doses of radiation (mean dose of 6.64 mSv) did not show an increased incidence rate of brain cancer relative to the general population (SIR = 0.79; 95% CI: 0.67, 0.93) [S8].

411. Although not considered in the UNSCEAR 2000 Report [U2], the study of Artalejo et al. [A32] reported a slight excess of brain and CNS cancer mortality among workers for the Spanish Nuclear Energy Board; the SMR was 1.33 (95% CI: 0.61, 2.52), based on 9 cancer deaths, of which 2 were among the 27% of the cohort who had been miners and may have been exposed to alpha radiation [A32]. Rogel et al. [R54] reported excess mortality due to brain and CNS cancer at borderline levels of statistical significance compared with French national mortality rates among radiation workers of Électricité de France (16 observed versus 10.3 expected deaths; SMR = 1.56; 90% CI: 0.98, 2.37); there was no statistically significant trend of mortality with dose (ERR = –4.1 (90% CI: –9.9, 28.9) Sv$^{-1}$).

#### *(b) Internal low-LET exposures*

412. There have been no new studies since the UNSCEAR 2000 Report [U2].

#### *(c) Internal high-LET exposures*

413. There has been a recent analysis of cancer mortality in a group of Danish and Swedish patients who underwent cerebral angiography with Thorotrast and in a comparison group of patients who underwent cerebral angiography with a non-radioactive contrast agent [T30]. The RR was not significantly different from 1.0, suggesting that apparent increases seen in previous analyses [A5] may have been due to pre-existing brain tumours rather than to radiation exposure. Radiation doses to the brain were very low relative to those to the liver, spleen or bone marrow.

### 4. Summary

414. Ionizing radiation can induce tumours of the CNS, although the relationship is not as strong as for several other tumours, for example breast and thyroid cancer or leukaemia, and most of the observed radiation-associated tumour risk occurs for tumours that are benign. Overall, exposure during childhood appears to be more effective in tumour induction than adult exposure, but the data on adult exposures are fairly sparse, and the most recent study of survivors of the atomic bombings demonstrated ERRs for neurilemmoma following exposure at all ages. Little is known about other factors that modify risk. The association between the risk of benign tumours, particularly meningioma and neurilemmoma, and radiation exposure appears to be substantially stronger than the risk of malignant tumours. Additional data are needed to better characterize the dose response for CNS tumours of various histological types, especially for glioblastoma.

## U. Thyroid cancer

### 1. General background

415. Thyroid cancer is one of the less common forms of cancer, and cases constitute somewhat less than 2% of all cancers [P19]. Unlike most cancers, the thyroid cancer incidence rate is relatively high before age 40 years, increases comparatively slowly with age, and is about three times higher in women than men. This predominance among

females is also observed for benign thyroid tumours. Incidence (world adjusted) rates for much of the world range between 1 and 2 cases per 100,000 males and between 2 and 8 per 100,000 females [P19]. Data from many countries suggest that incidence rates are increasing while mortality rates are falling [F16].

416. Papillary, follicular and anaplastic thyroid carcinomas originate from cells derived from the follicular epithelium, and they constitute about 95% of thyroid cancers. Medullary cancers also arise from epithelial cells, but from the calcitonin-producing parafollicular or C-cells. The degree of malignancy varies widely with histological type, ranging from the rapidly fatal anaplastic type to the relatively benign papillary type [R42, S87]. Overall 5-year survival is close to 90%, because papillary carcinoma is the predominant type (usually over 65% of cases) of thyroid cancer, whereas anaplastic carcinoma is relatively rare (generally less than 15% of cases).

417. Ionizing radiation is a well-documented cause of thyroid cancer. For the most part, radiation-related thyroid cancers are papillary carcinomas, and their clinical course is similar to that of other thyroid cancers [S87]. The RR of thyroid cancer is substantially increased among persons with a history of self-reported benign nodules and goitre, but the causal role of these benign diseases is unclear. 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 [R42, S87].

### 2. Summary of UNSCEAR 2000

418. The UNSCEAR 2000 Report [U2] concluded that the thyroid gland is highly sensitive to the oncogenic effects of external radiation exposure during childhood and that a linear dose–response relationship was consistent with the published data. Age at exposure is an important modifier of risk, with a strong tendency for the risk to decrease with increasing age at exposure.

419. A pooled analysis of studies of external irradiation of the thyroid [R6] allowed a more detailed evaluation of the dose–response relationship and of modifying factors than had previously been possible. 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 was 7.7 (95% CI: 2.1, 28.7) $Gy^{-1}$, and 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 [R6]. No single study was found to have an undue influence on the overall estimates of risk.

420. The ERR per unit dose for females was nearly twice that for males, but the results were not consistent across studies [R6]. Since thyroid cancer naturally occurs two to three times more frequently among females than males, the absolute radiation-induced risk was correspondingly higher for 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 [W14]. The ERR per unit dose was highest between 15 and 29 years following childhood exposure, but it remained high for more than 40 years after exposure [R6]. The latter finding was also reported from an extended follow-up study of the Stockholm skin haemangioma cohort in Sweden [L13]. In contrast to the well-described carcinogenic effects of external exposure in childhood, data are sparse regarding exposure after age 20 years. To date, there is little evidence of an excess thyroid cancer risk associated with adult exposure [R6, S14]. Among survivors of the atomic bombings exposed after age 40 years, the ERR was negative [T1].

421. Elevated risks of thyroid cancer were reported for patients treated with high-dose radiotherapy for Hodgkin's disease [H19, T5], for childhood cancers [B63, D50, H5] and for bone marrow transplant patients undergoing high-dose whole-body radiation [C26]. Few studies, however, described the shape of the dose response or reported quantitative risk estimates.

422. Information about occupational exposure to radiation and risk of thyroid cancer is limited. Radiation workers generally receive low, fractionated doses to the thyroid gland. The low doses and the relative rarity of the disease make increased risks difficult to observe in most epidemiological studies. A few studies have reported elevated risks [A34, B64, C46, W29], but they had several methodological limitations. Results were based on a small number of cases, individual dose estimates were not available and multiple comparisons were tested.

423. The carcinogenic effects of internal exposure to $^{131}I$ are less well understood. Most epidemiological studies have evaluated the risk of thyroid cancer for patients receiving diagnostic $^{131}I$ or high-dose $^{131}I$ treatment for hyperthyroidism or thyroid cancer. Results from these investigations have provided little evidence of increased risk following a wide range of exposure levels, but almost all of the study patients were adults at the time of exposure, and the studies therefore do not allow strong inferences about the risks of childhood exposure. In addition, although individual thyroid doses have not been calculated, the intention of treatment with $^{131}I$ for hyperthyroidism is to deliver 60–100 Gy of radiation to destroy thyroid gland function [B53]. Thus there is a substantially reduced chance of subsequently developing thyroid cancer. In two [F1, R3] out of the three [F1, H6, R3] cohort studies of hyperthyroid patients treated with $^{131}I$, small elevated risks of thyroid cancer were observed soon after therapy, but no dose response was demonstrated. These findings suggest that some of the observed excess may be due to close medical surveillance and to the underlying thyroid disease.

424. Early studies of populations exposed to radiation following the Chernobyl accident indicated that exposure to radioactive iodine, primarily $^{131}I$, during childhood was linked to thyroid cancer development, but the level of risk was at that time not well quantified [A35, B65, D47, K53, L94, S86, T40, T44]. The risk appeared to increase with decreasing age at exposure [A10, K52, P44, W13], and some data suggested that risks were beginning to stabilize for individuals who were in their teens at the time of the accident [K52, T40]. "Ecological studies" of thyroid cancer risks due to exposure arising from the Chernobyl accident reported strong associations between childhood exposure to $^{131}I$ and early development of thyroid cancer [J7, J8, L94, L95], with EARs and ERRs generally being lower and higher, respectively, than those observed in studies of external radiation exposure.

### 3. New or updated studies

#### *(a) External low-LET exposures*

425. Studies conducted since the 2000 UNSCEAR Report was issued (table 40) continue to demonstrate clearly a strong association between external low-LET radiation exposure and increased risk of thyroid cancer. New data on radiation-related thyroid cancer in AHS members, a subgroup of the LSS of survivors of the atomic bombings, were published recently [I28]. In a population of 3,185 members of the AHS with DS02 dose estimates and who participated in a special thyroid screening examination conducted between 2000 and 2003, the prevalence of malignant thyroid tumours was 2.2%. Almost 60 years after the bombings, a significant linear dose–response relationship was found ($p < 0.001$), and the EOR was 1.95 (95% CI: 0.67, 4.92) $Sv^{-1}$ for a person aged 10 years at the time of exposure. This risk is about one third of those found in the 1958–1987 tumour-registry-based follow-up including the members of the full LSS cohort who were about the same age at exposure [T1]. This is partly due to the difference in statistical models used and to the fact that only a small subgroup of the LSS cohort was evaluated in the current report. The ERR is decreasing somewhat with time since the bombings, and the study shows a small reduction (about 10%) in risk related to the use of the new dosimetry system [P10].

426. Risk decreased with increasing age at exposure, although the effect of age at exposure was not statistically significant ($p = 0.10$). The EORs for persons exposed at ages 0–9, 10–19 and 20+ years were 3.45 (95% CI: 0.92, 10.51) $Sv^{-1}$, 1.49 (95% CI: 0.37, 3.74) $Sv^{-1}$ and 0.25 (95% CI: –0.29, 1.96) $Sv^{-1}$, respectively. The major limitation of this study is the low participation rate. Of the 11,028 AHS members alive in 1990, 8,995 were invited to the biennial AHS examination. Of these only 4,552 actually presented themselves for the examination, and 4,091 participated in the special thyroid examination. This resulted in an overall participation rate of 37% of living AHS members or 46% of the invited members.

427. Two studies of X-ray treatment for benign medical conditions have been published. One study, conducted in northern Sweden, was of thyroid cancer following X-ray treatment for benign conditions of the cervical spine (50% females) [D1], and the other was a new follow-up (the median follow-up time was 39 years) of the New York tinea capitis study [S68]. The Swedish study is notable because the patients were adults at the time of radiation treatment. Out of three series totalling 27,415 patients who were treated with X-rays, 8,144 had received such treatment to the cervical spine. For these, the thyroid gland was in the primary beam. The remaining 19,271 persons who received X-ray treatment other than to the cervical spine served as a comparison group.

428. The X-ray series consisted of three treatments given at 2–3 day intervals, with a skin dose of 100–200 R at each treatment: 84% received one treatment series, 13% two series, and 3% three or more series. The average thyroid dose was about 1.0 Gy. For the other 19,000+ members of the cohort, the thyroid doses were very low. In the whole cohort, 51 thyroid cancers were diagnosed: 22 in the high-dose group and 29 in the low-dose group. The ERR was 0.58 $Gy^{-1}$.

429. In the tinea capitis study in the United States, 2 thyroid cancers occurred among 2,224 irradiated subjects, whereas none occurred among the 1,380 controls [S68]. The expected number of thyroid cancers in the irradiated group was 2.04, and the mean thyroid dose was 0.06 Gy, resulting in an ERR of –0.67 (95% CI: –29.96, 86.41) $Gy^{-1}$ [S68], which is lower than, but not inconsistent with, the Israeli tinea capitis study [R9], and is exactly the risk obtained in the pooled analysis of external radiation [R6]. The EAR based on an earlier follow-up [S14] was 1.5 (90% CI: 0, 9.4) $(10^4 \text{ PY Gy})^{-1}$, which is consistent with several other studies of external radiation exposure in childhood.

430. Because survival for childhood cancer patients has increased substantially, the risk of developing a second primary cancer has become a more prominent concern. As noted earlier, the thyroid gland is particularly sensitive to radiation exposure at early ages, and therefore quantifying the risk of developing thyroid cancer following radiotherapy for childhood cancer is important. Elevated radiation-related risks of thyroid cancer have been noted among young patients receiving radiotherapy for Hodgkin's disease, non-Hodgkin's lymphoma, neuroblastoma, Wilm's tumour, leukaemia, Ewing's sarcoma and malignancies of the central nervous system [I27, K7]. Since the UNSCEAR 2000 Report, a number of new studies on secondary thyroid cancer have been published demonstrating that the primary thyroid cancer incidence rate following radiotherapy for a first childhood malignancy is significantly greater than expected. The magnitude of the risk estimates, however, is generally substantially lower for patients receiving radiotherapy for cancer than those found for people receiving treatment for benign disease, or for survivors of the atomic bombings. This appears to be due to flattening out of the

dose response at doses above several grays, because of the competing effect of cell killing, in which the cells available to transform into malignant cells are, for the most part, depleted. Little and Wright [L26] have shown that, as the average or maximum dose in the medical studies increases, the ERRs derived in medical studies become smaller relative to those of subgroups of survivors of the atomic bombings of similar age and sex distribution.

431. In Italy, 113 children who underwent bone marrow transplants between 1981 and 1991 and survived at least 3 years were followed to determine the incidence of subsequent thyroid cancer [C44]. Eight patients developed secondary thyroid cancer between 3 and 16 years after the transplant. When a multiple regression analysis was performed, there was a suggestion of an association between increased thyroid cancer risk and radiotherapy doses of more than 10 Gy compared with doses of less than 10 Gy (RR = 4.3; 95% CI: 0.67, 7.3). However, the number of cases was small, and the result did not reach statistical significance.

432. Secondary thyroid cancers occurred in excess following radiotherapy for childhood neuroblastoma in a cohort of 544 patients who had survived 5 years and who were treated in eight centres in France and the United Kingdom [R47]. Slightly more than 294 (50%) of the patients were treated between 1948 and 1986 with radiation (214 received both radiotherapy and chemotherapy). The mean thyroid dose was 3.4 Gy. Among the 5 patients who developed a secondary thyroid cancer, the mean thyroid dose was 6.7 Gy. However, the dose distribution was extremely variable, with 3 patients receiving doses of less than 1 Gy and 2 patients receiving doses of more than 10 Gy (specifically, 14 and 19 Gy). None of the 5 patients was treated with chemotherapy. The ERR was 0.50 (95% CI: <0, 16) $Gy^{-1}$. The authors noted, however, that the treatment protocols used during the study period have since been changed, and the more recent protocols involve less radiotherapy and more intensive chemotherapy, so this finding may not reflect current practice.

433. In a study of 446 children with childhood malignancies who survived 5 years and who were treated with radiation between 1954 and 1980, 3 subsequent thyroid cancers were diagnosed when only 0.2 were expected, resulting in an RR of 13.7 (95% CI: 2.8, 38) [G20]. No other information about the thyroid cancers was provided in the report.

434. The largest and most comprehensive study of radiotherapy-related secondary thyroid cancer was published recently [R48, S88]. This nested case-control study included 69 cases of secondary thyroid cancer and 265 controls. Controls were matched paediatric cancer survivors who did not have a subsequent thyroid cancer. Both the cases and the controls were identified from the cohort of over 14,000 5-year survivors enrolled in the Childhood Cancer Survivor Study, and all had individual thyroid dose estimates. The first cancers were diagnosed between 1970 and 1986, so the data on these represent the effects of early treatment protocols. Radiotherapy was associated with an increase in the risk of developing a secondary thyroid cancer, and the risk rose with increasing radiation dose up to 29 Gy. Above 30 Gy, a downturn in the RR was seen. No association with chemotherapy was noted.

435. In a paper describing more detailed analyses [R48], the authors reported an ERR of 0.51 $Gy^{-1}$ over the whole range of doses. The linear model, however, was not the best fitting model. The best fitting model described an ERR of 1.3 (95% CI: 0.4, 4.1) $Gy^{-1}$ at doses of below 6 Gy, with a significant downturn in the risk above 6 Gy. At 40 Gy, the ERR per unit dose had decreased by about 95%. At doses of less than 6 Gy, the risk appeared to decrease with increasing age at treatment.

436. When taken together, the current research provides clear evidence of an increase in thyroid cancer risk among patients treated with high-dose radiotherapy for childhood cancer; however, the risks per unit dose are smaller than those observed for persons receiving lower doses. The exact shape of the dose–response curve at doses of above 10 Gy, as well as the role of age at treatment for the first cancer, type of first cancer and sex, are not yet well characterized.

437. Few studies of thyroid cancer occurring subsequent to radiotherapy given to adult cancer patients have had adequate information on doses. Using the United States SEER cancer registry data, Huang et al. [H11] investigated the risk of thyroid cancer for 48,495 women who received radiotherapy between 1973 and 1993 for breast cancer during the first four months after diagnosis compared with 146,303 breast cancer cases from the same years who did not receive radiotherapy during the first four months after diagnosis. A total of 28 women in the radiotherapy cohort and 112 women in the unexposed cohort subsequently developed thyroid cancer. Up to 20 years after diagnosis of breast cancer, there were no differences in thyroid cancer risk between the two groups (RR = 1.0; 95% CI: 0.7, 1.5). However, a subgroup of women who were more likely to have received higher doses of radiation to the thyroid gland had an RR of 1.7 (95% CI: 0.9, 3.2).

438. The main limitations of this study were that follow-up times tended to be short, radiation doses to the thyroid gland were not known, radiotherapy data were available only at the time of initial treatment and information on other treatments was not available.

439. Information on fractionated and low-dose-rate exposures can come from studies of occupational exposure to radiation. However, occupational studies of thyroid cancer generally are not very informative, because thyroid doses are rarely available; many occupational groups, e.g. nuclear workers, are predominately male; and cancer mortality often has been the study end point, thereby missing most cases of thyroid cancer, which are usually survivable. Finally, it

is the thyroid of the young that has been shown to be very sensitive to radiation, whereas workers are obviously exposed as adults. Studies that considered thyroid cancer since the UNSCEAR 2000 Report was published have been negative on the whole [A22, M4, M34], but have had too few cases of thyroid cancer to draw any clear conclusions.

440. Thyroid cancer incidence rates were elevated among Canadian radiation workers, mainly medical workers, compared with national Canadian cancer rates [S8]. Dose response was not evaluated, because of the few cases with significant doses. Similarly, thyroid cancer incidence rates were higher than expected among United States radiologic technologists compared with rates for the United States population [S29]. It should be noted, however, that when comparing medical workers with the general population, presumed better medical diagnosis and reporting among the workers warrant attention.

441. As a consequence of the Chernobyl accident, large numbers of men from all over the former Soviet Union were brought in to participate in decontamination and other clean-up activities at the reactor and in the surrounding 30 km zone. Approximately 600,000 workers (often called "liquidators" or "clean-up workers") were involved; about 240,000 of them worked during 1986 and 1987. Recovery operation workers were exposed to varying levels of external gamma and beta radiation, depending on their specific jobs and the time period and duration of their work. Internal exposure due to radioiodines was minor after the first few weeks, but a small number of workers who were on-site soon after the accident may have been irradiated internally, resulting in sizeable thyroid doses [U2]. Doses to the thyroid are very uncertain, but the estimated mean thyroid dose is about 0.2 Gy. The majority (about 65%) of workers are likely to have received doses to the thyroid of less than 0.15 Gy [K10].

442. To date, there is no evidence of a dose response for thyroid cancer incidence among the recovery operation workers [I10, R11, R49]. A combined cohort of 10,332 Latvian and Estonian recovery operation workers, with a mean external whole-body dose of 109 mGy, was followed until 1998 using national population, mortality and cancer registries [R49]. Compared with age-, sex- and calendar-year-specific national cancer rates, the recovery operation workers had a significantly elevated risk of thyroid cancer based on 3 cases. There was, however, no correlation with dose, and the workers were under close medical surveillance, suggesting that the enhanced incidence rate of thyroid cancer seen was related to medical care practices rather than radiation exposures. Given the low doses and older ages at exposure, these negative findings are consistent with data from the LSS of survivors of the atomic bombings [T1].

443. Within the framework of large studies of Russian Chernobyl recovery operation workers [I30], thyroid cancer incidence between 1986 and 1998 was evaluated among 99,024 workers [I29]. Fifty-eight thyroid cancers occurred during the study period. Similar to the results described above for Estonian and Latvian recovery operation workers, the incidence rate of thyroid cancer was significantly higher (SIR = 4.33; 95% CI: 3.29, 5.60) among Russian recovery operation workers compared with rates for the Russian male population, but the risk of thyroid cancer was not significantly elevated when an internal comparison based on external dose was performed. The workers' elevated thyroid cancer incidence rate compared with that for the general Russian population was likely to be due to more frequent and comprehensive medical examinations.

### *(b) External high-LET exposures*

444. No new studies of external high-LET radiation exposures and thyroid cancer risks have been published since the UNSCEAR 2000 Report.

### *(c) Internal low-LET exposures*

445. Since the UNSCEAR 2000 Report, a large body of data on internal low-LET radiation exposure, especially to $^{131}$I, has accumulated from studies of situations involving medical and environmental exposures. New information has come from studies of radioactive deposits from the Hanford nuclear weapons plant emissions and from the Chernobyl accident.

446. Hahn et al. [H1] studied thyroid cancer subsequent to diagnostic administration of $^{131}$I to German patients under 18 years of age. Among the 2,262 patients who received diagnostic $^{131}$I, 74% were females, the median age at first examination was 14.9 years, the mean follow-up time was 20.9 years and the average thyroid dose was about 1.0 Gy.

447. In a small subgroup of examined study participants, 2 thyroid cancers were found among the 789 irradiated patients, and 3 were found in the unexposed group of 1,118 children who underwent other thyroid diagnostic procedures. The ERR was –0.14 (95% CI: –0.9, 4.1). Thus there was no evidence of risk associated with administration of $^{131}$I.

448. It should be noted that only 20% of the study population were younger than 11 years of age at the time of $^{131}$I exposure, and 9% were less than 6 years of age; hence most of the exposures were received when the subjects were older than the most radiosensitive ages for thyroid cancer induction. Only 35% of the exposed subjects and 41% of the unexposed subjects participated in the examination programme, and such low participation rates increase the likelihood of selection biases. Additional opportunity for selection biases may have occurred in that several of the 10 participating hospitals had either only exposed patients or mostly/only unexposed patients, so that institutional imbalances could have biased the results. Because of the small sample size, the study had 80% statistical power to detect RRs on the order of fourfold. Since 80% of the subjects were older than age 10 at exposure, an RR of 4 or more for a 1 Gy exposure would probably not be expected.

449. The follow-up to the Swedish study of the long-term effects of diagnostic $^{131}$I administration has been extended 8 years to 26 years on average, and tabulations of thyroid cancers included those observed more than 2 years after $^{131}$I administration (rather than the 5-year minimum period of previous reports) [D42]. For the 1,767 patients who had received previous external radiation to the head and neck, and the 11,015 patients who had been referred because of suspicion of a thyroid tumour, there were elevated risks, SIR = 9.8 (95% CI: 6.3, 14.6) and SIR = 3.5 (95% CI: 2.7, 4.4), respectively. For the group of 24,010 patients without external radiation exposure or referral for suspicion of thyroid tumour, the most common reasons for diagnostic administration of $^{131}$I were suspected hyperthyroidism (62%), hypothyroidism (25%) or hypercalcaemia (12%). For this group, there was no excess risk (SIR = 0.91; 95% CI: 0.64, 1.26), nor was a dose–response association seen. However, only 2,367 patients in this group were under age 20, and about 300 under age 10, at the time of exposure to $^{131}$I. Among those under age 20 and without prior external radiation exposure or referral for suspicion of thyroid tumour, 2 thyroid cancers were observed compared with 2.08 expected (SIR = 0.96; 95% CI: 0.12, 3.46). In interpreting this null result, consideration should be given to the small numbers of cases and to the fact that so few were exposed before age 10, the group for whom the associated risk is expected to be the highest.

450. While the data from these studies are informative, the uncertainties associated with estimating thyroid doses due to $^{131}$I, especially for persons with thyroid abnormalities, reduce the precision of the risk estimates. The non-uniformity of the dose distribution in the thyroid gland following $^{131}$I administration results in some areas of tissue receiving high doses and other areas receiving much lower doses [N19]. Thus the tumorigenic effects of the exposure might be lower than would be expected on the basis of the average dose. Overall, there is little evidence that radiation exposure to adult patients treated for hyperthyroidism or examined with diagnostic levels of $^{131}$I or examined to evaluate potential thyroid disease results in a measurably increased risk of thyroid cancer. Data regarding risks of exposure in childhood remain sparse. The three studies of the diagnostic use of $^{131}$I in Germany, Sweden and the United States found that, among 6,659 children examined, with a mean thyroid dose of 0.89 Gy, 9 thyroid cancers were detected against 8.99 expected [B61].

451. Determining the role of continuous low-dose exposure to radionuclides from living near nuclear plants and waste sites has been a concern to members of the public in many countries having nuclear weapons plants or power plants. These environmental exposures of the thyroid are primarily due to $^{131}$I, but can also be due to short-lived radioiodines and to some external radiation.

452. The largest evaluation of environmental exposures of the thyroid is of people living near the Hanford nuclear weapons site in the United States [D48]. Between 1944 and 1957, the Hanford site in Washington state released 20–25 PBq of $^{131}$I into the atmosphere during fuel processing. In total, 5,199 people born between 1940 and 1946 in seven counties in eastern Washington state were identified for study. Ninety-four per cent were located, 4,350 (84%) were alive and 3,441 agreed to participate in the study. Thyroid doses were estimated for the 3,193 study participants who had lived near Hanford during the time of the radioiodine releases. The remaining 248 participants had moved from the Hanford area and received little or no exposure. The $^{131}$I doses to the thyroid glands of the people who continued to live near Hanford ranged from 0 to 2.84 Gy (median 0.10 Gy), with only a small percentage receiving doses at the higher end of the range.

453. Nineteen 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, even though the population was exposed at young ages. Although there are large uncertainties in the dose estimates [N18], taking these into account does not appear to change the results materially.

454. A recent study compared cancer mortality in four counties in Washington state (presumably heavily exposed to $^{131}$I from the Hanford plant) with that in five other counties (much less heavily exposed) [B61]. There was no elevation in thyroid cancer mortality in the heavily exposed counties: the RR was 0.84 (95% CI: 0.56, 1.26), based on 33 deaths in the highly exposed counties and 76 in the control counties [B61].

455. On 1 March 1954, an unanticipated change in wind direction caused people living on the Marshall Islands to be exposed to high levels of radioactive fallout from a United States nuclear weapons test in the Pacific Ocean [C45, R13]. About 80–90% of the dose to the thyroid was from short-lived radioisotopes and gamma radiation, and very little was from $^{131}$I [R13]. Following the accidental exposure, an elevated risk of thyroid cancer and other thyroid diseases was linked to the radiation exposure [C45, H25].

456. In a recent evaluation, an international team of researchers examined 3,709 Marshall Islanders who were born before 1954, using ultrasound and neck palpation. Thirty thyroid cancers were diagnosed. An additional 27 examinees had had surgery for thyroid cancer in the past. There was evidence of a weak association between thyroid cancer prevalence and an increasing surrogate measure of thyroid dose [T41, T42].

457. From 1949 to 1962, the former Soviet Union conducted over 100 atmospheric nuclear tests at the Semipalatinsk test site in Kazakhstan [B62, G21, R51]. Local fallout was particularly high from three tests conducted in 1949, 1951 and 1953. Approximately 10,000 persons living near the test site and 40,000 living in the Altai region in the Russian Federation received more than

250 mSv effective dose. The first analytical study of the health effects on the populations living near Semipalatinsk was published by Bauer et al. [B58]. They studied solid cancer mortality in a cohort of 19,544 exposed and comparison subjects living near the Semipalatinsk test site, and found a significant dose response for all solid cancers and several specific cancer sites. However, they did not report on thyroid cancer.

458. Following the 1986 accident at Chernobyl, about 5 million people living in Belarus and in extensive areas in Ukraine and the Russian Federation were exposed to radioactive materials. Persons living in the contaminated areas of the three countries received external exposure from radionuclides deposited on the ground and internal exposure from ingesting milk and leafy green vegetables. The principal component of dose to the thyroid gland was from the atmospheric releases of $^{131}$I, although there was also very limited exposure to shorter-lived radioisotopes, e.g. $^{132}$I, $^{133}$I and $^{135}$I [U2].

459. Four years after the Chernobyl accident, a substantial increase in childhood thyroid cancer in the contaminated regions of Belarus, Ukraine and the Russian Federation was observed [H13, M11]. Although the exact number of thyroid cancers diagnosed among persons who were living in these areas and who were younger than 18 years old at the time of the accident is not known, at least 4,000 were reported between 1992 and 2000. Because thyroid cancer is frequently indolent, efficiency and uniformity of ascertainment are crucial to establishing unbiased estimates of risks. Variations in the efficiency of screening may have a role to play in explaining some of the excess incidence, although the magnitude of the excess leaves little doubt that much of it is associated with radiation exposures resulting from the accident [U2]. However, variations in screening efficiency over time could bias inference of trends in excess risk with age and time. A recent study showed that, whereas official screening programmes contributed little to the observed increase in the thyroid cancer incidence rate in the affected countries, other factors, such as the introduction of ultrasound examinations, increased attention to thyroid diseases during normal medical examinations and improved reporting, increased the apparent underlying incidence in Belarus and in the more highly contaminated regions of Ukraine from 1988 to 1999 by a factor of 3 [J11]; in the other parts of Ukraine, the corresponding factor was assessed to be 2.

460. Since the UNSCEAR 2000 Report, a number of new studies have been conducted [C2, D49, H52, J9, K11, T43], and a few have reported quantitative risk estimates for thyroid cancer related to $^{131}$I exposure. A small population-based case-control study conducted in Bryansk, Russian Federation, included 26 cases diagnosed between 1991 and 1997 and twice the number of controls [D49]. Cases and controls were younger than 19 years of age at the time of the accident, and individual thyroid doses due to $^{131}$I were reconstructed for all study subjects. A strong dose response was demonstrated ($p < 0.01$), but because of the small study size, little other information was available.

461. Cardis et al. [C2] recently reported on a larger population-based case-control study that included 276 cases and 1,300 matched controls from Gomel and Mogilev in Belarus and from Bryansk, Kaluga, Orel and Tula in the Russian Federation. Cases were diagnosed between 1992 and 1998. Individual thyroid doses due to $^{131}$I, external radiation, and intake of other short-lived and long-lived radioiodines were reconstructed. A strong association between thyroid cancer risks and childhood exposure to $^{131}$I and to all radioiodines was observed. Based on a linear dose–response model, the ERR ranged from 5.5 (95% CI: 2.2, 8.8) Gy$^{-1}$ to 8.4 (95% CI: 4.1, 17.3) Gy$^{-1}$, depending on the statistical model used. Of particular interest is the finding that, depending on whether dose due to all exposures, due to all iodine isotopes or due to $^{131}$I alone was evaluated, the risk estimates remained virtually unchanged. The ERR per unit dose was three times greater in areas where dietary iodine was deficient than in regions with sufficient dietary iodine. The modifying effect of dietary iodine levels was noted also by Shakhtarin and colleagues [S4], who reported a twofold risk of childhood thyroid cancer in iodine-deficient areas of Bryansk, Russian Federation, compared with that in iodine-sufficient areas. While the Cardis et al. [C2] study has significantly added to what is known about $^{131}$I, more information is still needed about the role of iodine deficiency, the effects of age at exposure and for each sex, and the pattern of risk over time. The results of the study could be biased by large uncertainties in the dose estimates, which are based on retrospective determination of consumption rates and assumptions about the contamination of the ingested food. In particular, as discussed by the authors, such uncertainties in the dose estimates could account for at least part of the marked saturation of the dose response above 2 Gy [C2].

462. Risk estimates for radiation-related thyroid cancer have been published from "ecological studies" [H52, J7, J8, J9, L95, S86]. While these studies have provided important information about risks from radiation exposure due to the Chernobyl accident, they have inherent methodological problems [G13, P15] that need to be considered when interpreting their results. In the most recent "ecological study" of thyroid cancer risk following childhood exposure to radiation due to the Chernobyl accident, thyroid cancer cases and thyroid dose data for 426 settlements in Belarus and 608 settlements in Ukraine were analysed [J9]. Thyroid doses were based on 166 012 individual dose estimates for people who had direct measurements of $^{131}$I activity. There were 1,089 thyroid cancers observed between 1990 and 2001 in the cohort of people born between 1968 and April 1986. The estimated linear coefficient of the EAR was 2.66 (95% CI: 2.19, 3.13) $(10^4 \text{ PY Gy})^{-1}$ and the quadratic coefficient was –0.145 (95% CI: –0.171, –0.119) $(10^4 \text{ PY})^{-1}$ Gy$^{-2}$. The linear coefficient of the ERR was 18.9 (95% CI: 11.1, 26.7) Gy$^{-1}$ and the quadratic coefficient was –1.03 (95% CI: –1.46, –0.60) Gy$^{-2}$. The EAR was higher for females than

males, decreased with age at exposure and increased with attained age. The ERR was higher for males than females and decreased with age at exposure and attained age.

463. The results from this and earlier "ecological studies" differ from the Cardis et al. [C2] case-control study and studies on the effects of external radiation exposure [R6]. The estimates of the EAR in the "ecological studies" are about half that reported from the pooled analysis of external low-LET radiation [R6] (table 40). Estimates of the ERR, on the other hand, are considerably larger than the estimate from the pooled analysis or from the most recent Chernobyl case-control study [C2].

464. The link between thyroid cancer risks and exposure of adults to radioiodine from the Chernobyl accident has not been studied extensively, but when adult patients received similar doses of $^{131}$I from diagnostic examinations, little evidence of an association was seen [D42], suggesting that the effects of radiation exposure due to the accident would be small. The thyroid cancer incidence rate among Russians born in the contaminated region of Bryansk between 1917 and 1971, i.e. who were between the ages of 15 and 69 years at the time of the accident, was elevated compared with rates in the general population for the same sex and for similar ages and calendar year periods [I31]. As in several other studies of persons exposed to radioactive contamination resulting from the Chernobyl accident, the increased thyroid cancer rates compared with rates in the general population appear to be due to heightened medical surveillance rather than to the radiation exposure. Indeed, when internal comparisons were made, the ERR was –0.9 (95% CI: –2.4, 0.8).

465. To date, there have been few reports of increased risk of thyroid cancer after in utero exposure [H13]. This is an area for which data are clearly lacking and for which efforts should be made to carefully collect more data.

#### *(d) Internal high-LET exposures*

466. No new studies of internal high-LET radiation exposures and thyroid cancer risks have been published since the UNSCEAR 2000 Report.

### 4. Summary

467. The thyroid gland is highly susceptible to the carcinogenic effects of external radiation exposure during childhood. Age at exposure is an important modifier of risk, and a very strong trend of decreasing risk with increasing age at exposure is observed in most studies. Although thyroid cancer naturally occurs more frequently among women, the role of sex in determining radiation risk is unclear. The BEIR VII Committee [C37] estimates the lifetime risks of thyroid cancer at 0.32% Gy$^{-1}$ for men and at 1.6% Gy$^{-1}$ for women. Among people exposed during childhood, elevated risks persist throughout life, but some data suggest that the ERR begins to decline at about 20 years after exposure. The carcinogenic effects from $^{131}$I doses are less well understood. Most epidemiological studies of medical exposures have shown little risk following a wide range of dose levels; however, most of these studies were of adult exposures. A follow-up study of persons who lived near the Hanford nuclear facility in the United States when they were children provides no evidence of an association between $^{131}$I doses and thyroid cancer risk. In contrast, results from studies of people exposed as a result of the Chernobyl accident demonstrate that exposure to radioactive iodine during early childhood is significantly linked with the risk of thyroid cancer development. The risk appears to be modified by the amount of stable iodine in the diet. Similar to the data on external low-LET radiation exposure, the data from the Chernobyl accident studies suggest that risk decreases with increasing age at exposure. The effect of sex is not consistent in all studies. In the last few years, information about $^{131}$I exposures has improved; however, the thyroid cancer risk from $^{131}$I exposure is still not adequately quantified.

## V. Non-Hodgkin's lymphoma

### 1. General background

468. 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 classification that is widely used is the Revised European–American Lymphomas classification [H42].

469. Annual age-standardized world incidence rates for NHL range from about 3 to about 25 per 100,000 persons, with rates tending to be highest in North America and somewhat lower in African and Asian countries. However, since the diagnosis of this tumour is inconsistent among registries, international comparisons of NHL rates can be misleading [P19]. Rates of NHL have increased in many countries over the past few decades, particularly for older ages [B28, H39], with no indication that rates have peaked. In part this increase 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 apparent increases [H39]. Chronic lymphocytic leukaemia, which had been regarded as a distinct entity, is now thought to be a variety of NHL [J12]. Epidemiological studies have shown associations with chronic immunosuppression, for example, among transplant recipients and other patients who received immunosuppressive therapy [H43, K33]. However, such factors may explain only a small percentage of the temporal increase in NHL rates [Z7]. Associations with certain viruses, such as Epstein–Barr virus (EBV) [M37] and HIV [S55], have also been identified. Some studies suggest elevated risks for people employed in agriculture, particularly

those working with pesticides (e.g. [C17]), although other studies have not shown such a link (e.g. [W21]). No workplace exposures have been conclusively identified as causes of NHL [B4, C1]. The role of the immune system in relation to NHL is discussed further in annex D to the 2006 UNSCEAR Report, "Effects of ionizing radiation on the immune system".

## 2. Summary of UNSCEAR 2000

470. The results from the studies considered were mixed, with many of the studies having failed to show a statistically significant association with radiation exposure. The LSS 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 was negative. The latter findings might appear to contradict those for the cervical cancer patients, where there was borderline evidence of a positive dose response; however, among exposed patients, there was little indication of an increasing risk with increasing dose [B8]. Furthermore, studies of women treated for benign gynaecological disorders [D7, I1] have not suggested associations with radiation. Comparison of the LSS 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. [W8] reported that NHL mortality among spondylitis patients was raised significantly compared with national rates (RR = 1.73; 95% CI: 1.23, 2.36), and that this elevated risk appeared to disappear beyond 25 years after exposure; however, no dose–response analysis was performed. In another study of a mostly male population, Cardis et al. [C3] did not find an association between NHL risks and external radiation exposure among nuclear industry workers, although the precision of the study was limited by the generally low doses. The same limitation affected a study of patients undergoing diagnostic X-ray procedures [B17], which also did not show an association when based on a two-year lag time; however, this study used numbers of X-ray procedures as a surrogate of exposure rather than actual doses.

471. In summary, results from studies of NHL risk among groups exposed to external low-LET radiation were mixed. Studies of the survivors of the atomic bombings as a whole did not show an association, although there was some evidence of a trend of increased incidence with dose among males (but not females). Findings from other studies were variable, with no clear consistency. Overall, there was little evidence of an association between the risk of NHL and external low-LET radiation exposure.

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

## 3. New or updated studies

### *(a) External low-LET exposures*

473. At present, there are no new data on NHL for the survivors of the atomic bombings. However, there are some new findings from studies of other groups exposed to external radiation. Among patients in the United States treated with radiation for peptic ulcer [C4], the mortality rate for NHL was raised relative to national rates (see table 41). However, there was a suggestion that the NHL mortality rate was also raised among patients who did not receive radiotherapy. Overall, the evidence for an increased risk to patients receiving radiotherapy compared with that to other peptic ulcer patients was weak. A few other studies of medically exposed groups (e.g. [M35, R4]) have suggested elevated risks of NHL relative to unexposed comparison groups. However, the small numbers of cases observed imply that the statistical precision of these results is low. Furthermore, in instances where this has been examined, there have been at most very weak indications of any trend of increasing risk with increasing dose [R4].

474. A few recent studies of radiation workers have provided extra information on NHL risk in relation to occupational radiation exposure (see table 41). One of these studies was a population-based case-control study conducted for parts of the United States that involved 1,056 NHL cases, of whom 114 reported occupational exposure to radiation [E10]. The study showed no elevated risk associated with reporting having ever been occupationally exposed to radiation (RR = 0.90; 95% CI: 0.74, 1.10), nor any trend in risk with either estimated cumulative dose or duration of exposure. Although a reasonably large number of cases, ascertained from population-based cancer registries, and pathological reviews are notable strengths of this study, it is limited by the lack of objective measures of radiation exposure and by the low doses likely to have been received by exposed workers (mean dose $\approx$ 0.015 Gy, low-LET radiation). Another study examined cancer incidence in a group of about 191,000 workers included in the Canadian National Dose Registry [S8]. Again this was based on a reasonably large number of NHL cases, identified from cancer registry data, although in this instance information on radiation exposure was obtained in an objective manner. While NHL incidence in this group of workers was substantially less than expected from national rates, the central estimate of the trend in risk with dose within the cohort was positive, although with a very wide confidence interval (90% CI for ERR = (<0, 31.8) $Sv^{-1}$). Rogel et al. [R54] reported no excess mortality due to NHL compared with French national mortality rates among radiation workers of Électricité de France (5 observed versus 5.6 expected deaths; SMR = 0.89; 90% CI: 0.35, 1.88).

475. Other studies have provided generally little additional information on the risk of NHL in relation to occupational radiation exposure. An updated follow-up of male radiologists in the United Kingdom indicated an excess rate

of mortality due to NHL relative to social-class-specific national rates, but based on only small numbers (9 observed, 3.74 expected) [B2]. In contrast, a study of United States radiologic technologists, based on a much larger number of deaths, showed that the rate of mortality due to NHL was close to that expected from national rates, for both males and females [M31]. An analysis of NHL incidence in the same cohort did not show any association either with the number of years worked as a radiologic technologist or with the year of starting this work [L11]. The lack of dosimetric data is a limitation of these last two studies.

*(b) External high-LET exposures*

476. While various studies have been conducted of cancer risks among aircrew who have been exposed externally to both high- and low-LET radiation, results have not always been reported specifically for NHL. Some studies have reported elevated risks for male cabin attendants; for example, the rate of mortality due to NHL in a cohort study conducted in eight European countries was twice that expected from national rates [Z4]. However, large excesses of AIDS-related mortality seen among the same workers indicate that HIV/AIDS is the explanation for the findings in relation to NHL. A similar analysis conducted of male cockpit crew from nine European countries indicated that the rate of mortality due to NHL was less than expected from national rates (SMR = 0.71; 95% CI: 0.42, 1.15) [B23].

*(c) Internal low-LET exposures*

477. There is no new information that would materially affect the previous assessment. Findings from earlier studies are summarized in table 41.

*(d) Internal high-LET exposures*

478. A difficulty in interpreting the literature has been the small number of occasions on which findings have been presented specifically for NHL, as opposed to those for all lymphomas or all lymphopoietic and/or haematopoietic neoplasms together. It would appear that larger disease groupings have often been chosen for presentation because of the very small numbers of cases involved. For example, Travis et al. [T30] presented findings for NHL among Thorotrast-exposed patients in Denmark and Sweden, but not for a smaller cohort of patients in the United States. In the former instance, while the SIR for NHL was greater than 1, only four cases of NHL were observed among the Danish and Swedish Thorotrast patients, and rates in this group were consistent both with national rates and with those in a comparison group [T30].

479. A large population-based case-control study of childhood cancer in the United Kingdom found that, if anything, radon concentrations in the homes of NHL cases may have been lower than those in the homes of control children [U16]. However, the similarity in findings seen across a range of childhood cancer types in this study suggests that differences in participation rates both between cases and controls and by level of deprivation might have led to some bias.

### 4. Summary

480. Findings from recent studies do not change the assessment made by the Committee in its 2000 Report. The results from studies of NHL risk among groups exposed to external low-LET radiation are mixed, with little evidence of an association overall. There is still limited information on NHL risk in relation to either high-LET radiation (external or internal) exposure or internal low-LET radiation exposure, and interpretation of the available data is difficult.

## W. Hodgkin's disease

### 1. General background

481. About 62,000 cases of Hodgkin's disease (HD) are diagnosed annually worldwide, and the disease causes about 25,000 deaths per year [F14]. HD is distinguished from other lymphomas mainly by the presence of giant Reed–Sternberg cells. Overall rates of the disease have not changed greatly in recent decades; rates have increased in adolescents and young adults in a number of populations but have decreased at older ages [C27]. Mortality rates have decreased sharply in most countries, reflecting mainly improved treatment [C27]. At younger ages, disease rates in Asian populations tend to be much lower than those in European and North American populations; at older ages, they are about half the rates in Europe and North America [C27]. For example, annual age-standardized world incidence rates for HD are generally less than 0.5 per 100,000 persons for most Chinese registries, whereas rates exceed 3.5 per 100,000 for certain North American registries [P19]. There is substantial evidence for a viral aetiology or cofactors for HD. Particularly suspect is EBV. About 50% of cases of HD are EBV-seropositive in Western developed countries and 90% in developing countries [T36]. Elevated EBV titres have been demonstrated in pre-disease sera, compatible with a causal role for EBV [M51]. An elevated risk of HD has been shown among those with HIV, especially around the time of AIDS onset, suggesting an association with immunosuppression [S49]. Other studies of immunosuppression or immunodeficiency have shown mixed results. Elevated HD risk has been found among allogeneic bone marrow transplant patients but not generally among renal transplant patients, while there is a suggestion of an elevated risk among primary immunodeficiency patients [S49]. Several studies have documented a familial risk for HD, and a study of identical versus fraternal twins demonstrated a strong genetic component to HD risk. However, probably only around 5% of HD cases are

attributable to a genetic risk [C27, S49]. Lifestyle factors (e.g. smoking, alcohol consumption and diet) appear to play little role in the aetiology of HD, while early childbirth may be protective for women [C27].

### 2. Summary of UNSCEAR 2000

482. The UNSCEAR 2000 Report indicated that there were few studies that had evaluated dose–response associations for HD. The LSS data on HD incidence did not show a statistically significant dose–response relationship, but the number of cases was relatively small, so the statistical power was low [P4] (see table 42). Studies of people treated with external X- or gamma radiation for benign gynaecological disorders and studies of people occupationally exposed to radiation were also null for HD risk, but again there were limitations in the data because of the small number of cases and/or low radiation doses. Two studies of people undergoing internal low-LET irradiation, namely a Swedish [H6] and a United States [R3] study of $^{131}$I treatment for hyperthyroidism, had small numbers of HD cases and failed to show an association of risk with radiation exposure. Finally, two studies of Thorotrast patients [A5, V4] and one of miners exposed to radon [D10] also had small numbers of HD cases and failed to show a radiation effect. It was concluded that the available data did not indicate an association between the risk of HD and radiation exposure, either for external or for internal exposure, but that the data were very limited.

### 3. New or updated studies

#### *(a) External low-LET exposures*

483. The additional information considered by the Committee here includes that from an earlier report of a cohort study of patients receiving radiotherapy for cervical cancer [K1], for whom the mean dose to the bone marrow (used as a surrogate for lymphopoietic tissue) was about 7 Gy. Fifteen cases of HD were observed in this cohort, but there was no indication of excess risk (table 42). The parallel case-control study also exhibited no excess risk: there were 14 HD cases and 27 controls, with an RR of 0.63 (90% CI: 0.2, 2.6) [B8]. A cohort of patients treated with X-rays for benign diseases of the locomotor system [D2] had a mean dose to lymphopoietic tissue of 390 mGy, and there were 17 cases of HD and 21 deaths from HD (mortality was observed for a longer time than tumour cases); analyses did not show statistically significant associations of either HD risk or HD mortality risk with dose.

484. Various studies of radiation workers have reported on HD incidence or mortality rates since the UNSCEAR 2000 Report (table 42). The largest of these, the Canadian National Dose Registry [S8], reported a statistically non-significant positive dose–response relationship for HD incidence, based on 79 HD cases and a mean dose of 66 mSv. Other studies with good dosimetry included the Springfields uranium workers in the United Kingdom (10 HD cases; mean dose 21 mSv) [M5], the United Kingdom NRRW (17 deaths from HD; mean dose 31 mSv) [M12] and the Los Alamos National Laboratory workers in the United States (10 deaths from HD; mean dose approximately 16 mSv) [W6]. Two more occupational studies with limited dose characterization include that of United States radiologic technologists [M31], which had 34 deaths from HD, and the study of the early (1943–1947) workers at the Oak Ridge National Laboratory in the United States, which had 18 deaths from HD [F2]. None of the occupational studies cited here showed statistically significant associations between radiation exposure and risk of HD, but a limitation is that the dose levels were low.

#### *(b) Internal low-LET exposures*

485. There is no new information that would materially affect the previous assessment.

#### *(c) Internal high-LET exposures*

486. The only substantive new study is that of a group of Danish, Swedish and United States patients who received the diagnostic contrast medium Thorotrast, and a companion group who received a non-radioactive contrast medium [T30]. There were single cases of HD in both the exposed and the control groups among the Danish and Swedish patients, who were followed for cancer incidence, representing an RR of 1.5 (95% CI: 0.1, 81.8) [T30]. Among the United States patients, who were followed for mortality, there were 1 and 0 deaths from HD in the Thorotrast-exposed and the control group, respectively, representing a nominal RR of ∞ (95% CI: 0.1, ∞) [T30].

### 4. Summary

487. There continues to be no clear indication of an excess risk of HD associated with radiation exposure, but the data are very sparse, and most of the data sets lack dose–response analyses.

## X. Multiple myeloma

### 1. General background

488. Multiple myeloma is one of a group of plasma cell malignancies that are characterized by the presence of elevated numbers of plasma cells in the bone marrow and, very often, elevated levels of monoclonal protein in serum and urine [H33]. Plasma cell malignancies include: Waldenstrom's macroglobulinaemia, in which there is production of IgM; multiple myeloma, in which there is production of IgA, IgD, IgE, IgG or light chains; and the heavy

chain diseases, characterized by production of heavy chains (gamma, mu, delta) [H33, O7]. There is evidence that the malignant transformation causing multiple myeloma occurs at the early B-cell or lymphoid stem cell lineage [H33]. Multiple myeloma is a difficult disease to diagnose [K30]; in particular, detection of light chains requires electrophoresis or immunofixation, relatively expensive methods [H33]. Perhaps because of the limited availability of serum protein electrophoresis, the reported diagnosis of multiple myeloma varies widely by country [H33, P19], and the annual age-standardized world incidence rate varies from about 1 per 100,000 persons in China to more than 8 per 100,000 in parts of the United States [H33, P19]. It is more common among men than women and is particularly rare at young ages [C38]. Black people in the United States or the United Kingdom seem to be at particularly high risk, and Asians have relatively low risk [H33, P19]. Incidence rates have been increasing during the past few decades in various countries [H33]. While part of this increase may be due to earlier incompleteness in ascertainment, there have been increases in regions with well-established and high-quality registries [H33]. In particular, in Malmö, Sweden, the incidence rate for men increased by 60% between 1950 and 1979, although little change was seen for women over this period [T23]. Even larger increases have been reported in parts of the United States over the period 1947–1975, although not after 1975 [D25]. Multiple myeloma has been associated with autoimmune diseases, in particular rheumatoid arthritis, in a number of studies [H33]. There is weak evidence linking incidence of multiple myeloma to exposure to a number of physical agents, including asbestos, benzene and pesticides [H33]. There is little evidence of familial risk factors [H33]. Further details on the epidemiology are to be found in reference [H33].

### 2. Summary of UNSCEAR 2000

489. Of particular note is the discrepancy between the findings for incidence and mortality rates among the LSS cohort of survivors of the atomic bombings. The most recent mortality follow-up study [P1] showed a statistically significant association between multiple myeloma risk and radiation dose. However, LSS data on myeloma incidence yield a much lower estimate for the trend in risk with dose, and are consistent with there being no effect of dose [P4]. The authors of the cancer incidence report noted that the mortality findings appeared to be heavily dependent on the inclusion of questionable diagnoses and on both second primary cancers and cases in people who had received more than 4 Gy that were excluded from the disease 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.

490. There were similar discrepancies between analyses of the mortality and incidence data for other cohorts. For example, in a Swedish study of persons irradiated for benign lesions of the locomotor system, an elevated risk of mortality from multiple myeloma was observed in relation to national mortality rates, but there was no analogous increase in rates of the disease itself [D2]. In general, the studies tending to show significantly elevated risks, such as the metropathia haemorrhagica study of Darby et al. [D7] and the ankylosing spondylitis study of Weiss et al. [W8], tend to be of cancer mortality, whereas studies of cancer incidence, such as the diagnostic X-ray study of Boice et al. [B17] and the IRSCC [B8, B11], find no elevation in risk. This suggests that the classification of multiple myeloma on death certificates may have been conducted differentially according to whether there was a known past radiation exposure, although it is difficult to be certain. Given the generally better quality of diagnoses recorded in disease incidence data, the findings from the survivors of the atomic bombings, in particular, would suggest that there is little evidence of an association of risk with low-LET radiation exposure.

491. There are a few studies of persons exposed to internal high-LET radiation that suggest an association of the risk of multiple myeloma with radiation dose, but these studies are generally based on very small numbers of cases.

### 3. New or updated studies

492. Table 43 summarizes the radiation risk estimates derived from epidemiological studies of incidence and mortality rates of multiple myeloma.

#### *(a) External low-LET exposures*

493. The analysis of cancer incidence in relation to occupational dose in the Canadian National Dose Registry has documented a decreased SIR, of statistical significance, for multiple myeloma of 0.68 (90% CI: 0.49, 0.93) [S8]. The trend with dose of multiple myeloma incidence within this cohort is not reported, and is presumably not statistically significant. However, as with the parallel analysis of the mortality data associated with this cohort [A8], concerns have been expressed about the reliability of record linkage, a possible source of bias [G16].

494. Analysis of cancer mortality in relation to occupational dose for a group of Japanese nuclear workers has documented an increased but not statistically significant SMR, for multiple myeloma of 1.12 (95% CI: 0.69, 1.74) [I11]. The trend with dose of multiple myeloma within this cohort is not statistically significant, but the numerical value of the ERR (and confidence intervals) is not reported [I11].

495. Wing et al. [W7] have analysed multiple myeloma mortality for four United States nuclear sites: Hanford, Los Alamos National Laboratory, Oak Ridge National Laboratory and Savannah River. Trends of increasing

multiple myeloma mortality with whole-body dose were recorded, but were not statistically significant, with values of ERR of 0.66 (90% CI: –2.35, 3.67) $Sv^{-1}$, assuming doses were lagged by 10 years [W7]. Wing et al. went on to analyse trends of multiple myeloma mortality above certain critical ages, and found that above the age of 40 (also above 45 and 50) years of age the trends of risk with dose became much larger and generally statistically significant. For example, considering mortality above the age of 40, Wing et al. obtained values of ERR of 5.64 (90% CI: 0.61, 10.67) $Sv^{-1}$, assuming doses were lagged by 10 years [W7]. However, the values of attained age limit used (40, 45 and 50 years) are not chosen a priori. Therefore Wing et al. are effectively fitting another parameter, and if this is taken into account, it substantially reduces the nominal statistical significance of the results. The largest $\chi^2$ value calculated by Wing et al. is 5.43, and $P[\chi^2_2 > 5.43] = 0.07$, so that there is no statistically significant effect in this study.

*(b) Internal low-LET exposures*

496. There is no new information that would materially affect the previous assessment.

*(c) Internal high-LET exposures*

497. The only substantive new study is of a group of Danish, Swedish and United States patients who received the diagnostic contrast medium Thorotrast, and a companion group who received a non-radioactive contrast medium [T30]. There were 5 cases of multiple myeloma in the exposed group and 2 cases in the control group, representing an RR of 3.7 (95% CI: 0.5, 30.9) [T30].

### 4. Summary

498. As for the UNSCEAR 2000 Report [U2], there remains only weak evidence that multiple myeloma is inducible by ionizing radiation. Several studies indicate a trend of increasing risk of mortality due to multiple myeloma with external low-LET radiation exposure. However, such trends are not generally apparent in studies of myeloma incidence, even in groups such as the survivors of the atomic bombings where the parallel study of disease mortality points to increased risk. This apparent inconsistency suggests differential classification of myeloma on death certificates depending on whether there was known previous radiation exposure. At least in the LSS this is thought possible [P1]. The generally better quality of diagnostic information for the disease incidence data, and in particular the negative findings of the LSS incidence study, would suggest that there is little evidence of an association of risk with low-LET radiation exposure.

499. There continues to be limited information for internal low- and high-LET radiation exposures. Although some studies indicate elevated risk, they are based on only small numbers of cases.

## Y. Leukaemia

### 1. General background

500. Although one of the rarer cancers, leukaemia is of particular interest because there is substantial information, both epidemiological and experimental, on increased risk of this disease due to ionizing radiation exposure. In terms of the general epidemiology relating to leukaemia, the variation in rates between different populations is not as large as that for most solid tumours [U2]. For example, the annual age-standardized world incidence rate of lymphoid leukaemia varies between about 1 per 100,000 persons and 6 per 100,000 persons for most parts of Asia, Europe and North America, and a similar range is exhibited for myeloid leukaemia [P19]. 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. [B33]) 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 lymphoblastic 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 French–American–British (FAB) system [B33]; 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 [L58]. Reference will also be made to chronic lymphatic leukaemia (CLL), which has a B-cell or a T-cell lineage [L58]. CLL is now thought to be a variety of non-Hodgkin's lymphoma [J12].

501. Most cases of childhood leukaemia 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 among different countries since 1950 has been the decline in mortality rates [K32], reflecting the introduction of effective chemotherapy and cranial radiotherapy. Childhood ALL incidence rates, in contrast, have been fairly constant or have perhaps shown a small increase over the same period [D28]. While over 200 genes have been associated with chromosomal translocations, to date only MLL, TEL and AML1 have been linked with childhood leukaemia. There is increasing evidence to support the theory that gene rearrangements such as these may originate in utero [L57]. Apart from ionizing radiation exposure, risk factors for childhood ALL include exposure to alkylating chemotherapeutic agents and genetic factors such as Down's syndrome. Exposure to pesticides has been hypothesized as being a risk factor for childhood leukaemia [D51, M1, Z10], but this has not been confirmed. Greaves [G18] suggested that the increase in rates during the past century would be consistent with many acute lymphoblastic 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 [K32]. In a recent review, McNally and Eden [M36] suggested that some supportive evidence for an infectious aetiology is provided by analyses of space–time clustering and seasonal variation in the appearance of childhood leukaemia.

502. For adult leukaemia, rates at ages 75–84 years have increased in several countries since 1950 [K32]. These trends are consistent with improvements in cancer registration and in the details 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 [K32]. Rates of leukaemia also appear to be raised among patients with ataxia-telangiectasia (e.g. [O9]).

## 2. Summary of UNSCEAR 2000

503. There is a substantial amount of information on the risks of leukaemia due to 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 LSS of survivors of the atomic bombings 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 radiation exposure. These findings may reflect differences between studies in the uniformity of exposure of the bone marrow and in the degree of fractionation and protraction of exposure, as well as differences in the pattern of risk for different leukaemia subtypes. There is clear evidence of non-linearity in the dose response for leukaemia, which has a slope that decreases at lower doses.

504. A study of radiation workers in three countries suggested an elevated leukaemia risk, although the results were compatible with a range of values. Case-control studies of prenatal X-ray exposures indicated 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 survivors of the atomic bombings added uncertainty to the magnitude of the risk. Epidemiological evidence does not suggest that irradiation prior to conception gives rise to a materially increased risk of childhood leukaemia.

505. The data available on internal exposures to low-LET radiation did not indicate elevated risks of leukaemia; this may well reflect the low statistical precision associated with studies involving generally small radiation doses. There was no convincing evidence of an increased risk of leukaemia due to environmental exposures associated with the Chernobyl accident, although investigations were continuing. Excesses of childhood leukaemia were 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 the diagnostic X-ray contrast medium Thorotrast. There was less evidence for elevated risks among patients injected with $^{224}$Ra, and little or no evidence for increased risks in studies of radium dial workers or studies with individual assessments of radon exposure, either in mines or in homes.

## 3. New or updated studies

### *(a) External low-LET exposures*

506. There have been no new findings on leukaemia incidence for the survivors of the atomic bombings since the UNSCEAR 2000 Report. However, Preston et al. [P10] have reported findings from a follow-up of mortality to the end of 2000, based on the new DS02 dosimetry. The trends in the EAR of leukaemia with age at exposure and time since exposure are similar to those from the previous analysis of leukaemia mortality [P1]. In particular, the EAR decreased sharply with increasing time since exposure for those exposed in childhood, but varied little with time since exposure for those exposed in adulthood. The excess number of deaths due to leukaemia up to the end of 2000 among the cohort of 86,955 survivors was estimated to be 93 [P10]. This compares with an estimate of 87 excess leukaemia deaths based on follow-up to the end of 1990 [P1], indicating that the elevated risk has been low in recent years. The shape of the dose–response relationship is virtually unchanged using the new dosimetry system. In particular, using a linear–quadratic dose–response model, the estimated ratio of the quadratic coefficient to the linear coefficient is 0.89 (90% CI: 0.2, 6.0) $Sv^{-1}$, which is very similar to the corresponding estimate based on the DS86 dosimetry. In addition, relative to values based on DS86, the values of the risks at low doses estimated using a linear–quadratic model are reduced by about 8% as a consequence of the change in dosimetry [P10].

507. Owing to the low prevalence of CLL in Japan, the study of survivors of the atomic bombings provides little information on whether the risk of CLL might be related to radiation exposure. In a recent review, Richardson et al. [R37] suggested that the epidemiological evidence linking CLL risks and external radiation exposure is weak, but that epidemiological findings are consistent with an elevated CLL risk "after a latency and morbidity period that spans several decades". However, various studies considered in the UNSCEAR 2000 Report [U2] that show raised risks of leukaemia other than CLL in relation to external low-LET radiation exposures—for example studies of patients treated for cervical cancer [B5, K1], breast cancer [C9], cancer of

the uterine corpus [C8] and benign gynaecological disorders [D7, I1]—do not show such associations for CLL, even for latency periods of greater than 30 years [K1]. In addition, while there was a weak suggestion of raised rates of mortality due to CLL among irradiated ankylosing spondylitis patients when compared with national rates, there was also a weak suggestion of a similar increase among non-irradiated patients [W2]. More recently, Shore et al. [S68] found some evidence of a raised risk of leukaemia among irradiated tinea capitis patients in the United States, which, although based on small numbers, was confined solely to leukaemia other than CLL. In addition, analyses of occupationally exposed workers that have shown raised risks for leukaemia other than CLL (e.g. workers at the Mayak plant in the Russian Federation [S28] and radiologic technologists in the United States [L11]; see below) have, in contrast, not shown associations for CLL risks.

508. A few recent analyses of medically exposed groups have provided extra information on leukaemia risks. For example, Travis et al. [T24] found a trend of increasing risk of leukaemia with dose to the active bone marrow among patients treated for testicular cancer. Some other studies, such as those of patients treated for peptic ulcer [C4] or for cancer, e.g. [J1, R36], provide some indication of raised leukaemia risks, but the small numbers involved and the lack of dosimetric data do not allow detailed inferences on the relationship between risk and dose. A case-control study in Canada reported a raised risk of childhood ALL among those who had two or more post-natal diagnostic X-ray exposures (RR = 1.61; 95% CI: 1.13, 2.28), and it was suggested that this risk might be modified by variants in repair genes [I16]. However, a case-control study in the United States found that, after excluding exposures within the previous two years, there was generally no association between post-natal diagnostic X-ray exposures and the risk of childhood ALL [S67]. A limitation of both of these studies was their reliance on maternal reporting of diagnostic X-ray examinations.

509. Further analyses have been conducted on the risk of childhood leukaemia in relation to in utero exposure. A large case-control study in the United States reported an RR of 1.2 (95% CI: 0.8, 1.7) for childhood ALL in relation to in utero pelvimetric diagnostic X-ray exposure [S67]. However, as mentioned earlier, this study relied solely on mothers' reports of diagnostic X-ray exposures. In contrast, a population-based national study conducted in Sweden successfully ascertained the history of prenatal X-ray examinations using medical records [N4]. In this study, the RR for childhood leukaemia in relation to obstetric prenatal X-ray exposures was 1.11 (95% CI: 0.83, 1.47), and there was no indication of an increasing risk with increasing numbers of X-rays. In comparing these findings with those from earlier studies, it should be borne in mind that most of the children in these two recent studies were born in the 1970s or 1980s. It is likely that the dose to the foetus per obstetric examination was lower in this period than in previous decades, although there is no direct information on this topic from these studies. Furthermore, the frequency of obstetric X-ray examinations appears to be lower than in earlier decades; indeed, it was found in the United States study that the proportion of mothers undergoing pelvimetry was less than 3% after 1980 [S67]. When additionally statistical uncertainties are taken into account, the above findings are consistent not only with the absence of a raised risk but also with the RRs of the order of 1.4 reported from earlier studies of obstetric X-rays, such as the Oxford Survey of Childhood Cancers (OSCC), conducted during a period when both the frequency of such examinations and the associated doses per examination were higher. In a recent review, Wakeford and Little noted that, once account is taken of various sources of uncertainties, findings from the OSCC and from the cohort of survivors of the atomic bombings who were exposed in utero are consistent; the findings support a causal link between in utero irradiation and increased risk of childhood cancer, although quantification of this risk at low doses is difficult [W23]. Paragraph 79 includes additional discussion concerning the scientific debate on the nature of the association between prenatal X-ray exposures and childhood cancer.

510. Further findings have been reported in recent years from studies of workers exposed to radiation occupationally. Of these, the largest has been a study of mortality among over 400,000 nuclear industry workers from 15 countries [C41]. Many of the workers in this study had been included in earlier, smaller studies. However, this newer study focused on those workers whose radiation doses were predominantly from higher-energy photons. Since many workers with potential doses from neutrons or from internal radiation exposure also had relatively high external doses, their exclusion from the analysis meant that its statistical power was not as great as might have been expected from the studies of individual components (e.g. [M12]), or even as great as for the previous three-country study [C3]. The estimated ERR per unit dose from the 15-country study was similar to that estimated for the survivors of the atomic bombings and from some other studies of radiation workers; however, the estimate of risk was not statistically significant, and the values of the 95% confidence interval ranged from less than zero up to about five times the estimate for low doses derived from the study of the survivors of the atomic bombings (ERR = 1.93 (95% CI: <0, 8.47) $Sv^{-1}$. There was little change in this value when the lag period was increased from 2 to 10 years. There was also no indication of a decrease in the ERR per unit dose with time since exposure, although the power of this analysis was limited. Analyses that excluded workers included in earlier studies gave results similar to those from the full analysis [C41].

511. Leukaemia incidence has been studied for about 191,000 persons included in the Canadian National Dose Registry [S8]. While the incidence rate of leukaemia other than CLL was significantly lower than expected from national rates (SIR = 0.71; 90% CI: 0.58, 0.86), there was

some indication of a trend of increasing risk with increasing cumulative dose, although the 90% confidence interval for the ERR per unit dose was very wide and included zero (see table 44). The estimate of the ERR per unit dose was consistent with that obtained from earlier large studies, such as that of the United Kingdom NRRW [M12] and that of the combined analysis of nuclear workers from Canada, the United Kingdom and the United States [C3], as well as the subsequent 15-country worker study [C41], which included data on about 39,000 nuclear workers from the Canadian National Dose Registry. However, interpretation of findings from the Canadian dose registry is complicated by the fact that the estimated ERR per unit dose for leukaemia was similar to that observed for all other cancers combined, in contrast to the pattern seen in other large occupational studies (see table 13) and in other studies of radiation-exposed groups [G16]. An analysis based on a subgroup of the workers recorded in the Canadian National Dose Registry, namely those employed in the nuclear power industry, gave a higher estimate of the ERR per unit dose for leukaemia other than CLL (i.e. 52.5), but with a very wide confidence interval (90% CI: 0.205, 291) and based on only 18 deaths in total [Z6].

512. In an updated analysis of mortality among nuclear industry workers in Japan [I14], the number of leukaemias observed in a prospective follow-up of around 120,000 workers followed for an average of 4.5 years was limited; the estimated ERR per unit dose was consistent with a wide range of values, including estimates from other studies and values less than zero (see table 44). A study of an expanded cohort of workers at the Portsmouth naval shipyard in the United States followed to the end of 1996 showed that the leukaemia mortality rate among workers monitored for radiation exposure may have been slightly less than that expected from national rates, but there was some suggestion of a trend of increasing risk with increasing cumulative dose [S56, Y10]. However, confidence limits for the estimated trend were wide, reflecting the fairly small total number of deaths in this study (see table 44). The analysis described in reference [Y10] took account of the potential impact of exposure to solvents, although this did not appear to be a confounding factor. However, this analysis did not differentiate between CLL and other types of leukaemia. A small update to an earlier case-control analysis of leukaemia among Chernobyl recovery operation workers [I6] found no statistically significant association with dose, although the numbers of cases were small and the findings were very imprecise [K3].

513. Reference was made earlier in this annex to an analysis of mortality in relation to external gamma dose among about 21,500 workers at the Mayak nuclear complex in the Russian Federation [S28]. In contrast to studies of recent radiation workers, the range of doses received by these workers was very wide (with an average external dose of 0.8 Gy, low-LET). This analysis provided strong evidence of a trend of increasing risk of leukaemia other than CLL with increasing dose. After being adjusted for a surrogate measure of the exposure to plutonium, the data were consistent with a linear trend of increasing risk with external dose, although there were weak indications of a concave upward dose response. There was strong evidence that the RR was highest within 3–5 years of exposure (ERR of 6.9 (90% CI: 2.9, 15) $Gy^{-1}$) and was lower subsequently (ERR of 0.45 (90% CI: 0.1, 1.1) $Gy^{-1}$, in line with the temporal pattern seen in some other studies of radiation-exposed groups. Of the 66 observed deaths due to leukaemia other than CLL during the follow-up period, it was estimated that 40% might be associated with occupational exposure to external gamma radiation [S28].

514. Aside from those included in the Canadian National Dose Registry discussed earlier [S8], several analyses have appeared recently involving medical X-ray workers and radiologic technologists. In the study involving medical radiologic technologists in the United States, data on mortality due to ALL, AML and CML (hereafter collectively called non-CLL leukaemia) were examined in more detail for those who had completed an initial questionnaire survey, which permitted the investigators to control for other disease risk factors [M31]. The results showed that neither the length of work as a radiation technologist nor the year of first radiologic certification was associated with the risk of non-CLL leukaemia. However, the risk of non-CLL leukaemia rose with increasing length of work prior to 1950 ($p$ = 0.05 for trend). The latter finding is of note since the levels of radiation exposure were higher prior to 1950 than in more recent years. Similar findings arose from an analysis of non-CLL leukaemia incidence in the same cohort [L11]. Raised rates of leukaemia incidence have been observed among Chinese medical X-ray workers employed before 1970, but there was less evidence for an excess risk relative to other medical specialists for workers employed between 1970 and 1980 (RRs of 2.4 and 1.7, respectively) [W3]. For these X-ray workers, the RR of leukaemia was highest for those who started their work at under 20–25 years of age and peaked within 5–14 years of the start of radiation work. In addition, there was some indication of a raised risk of leukaemia mortality among United Kingdom radiologists who first registered before 1955, although the numbers of cases were small [B2]. These findings are indicative of an effect associated with radiation exposures that were larger in earlier than in later calendar periods. However, the general lack of dosimetric data makes it difficult to quantify these risks.

515. Although not included in the UNSCEAR 2000 Report [U2], the 1997 study of Artalejo et al. [A32] reported a slight deficit of leukaemia mortality among workers for the Spanish Nuclear Energy Board; the SMR was 0.70 (95% CI: 0.19, 1.80), based on only 4 leukaemia deaths, of which 1 was among the 27% of the cohort who had been miners and may have been exposed to alpha radiation [A32]. Rogel et al. [R54] reported mortality due to non-CLL leukaemia close to the values expected from French national mortality rates among radiation workers of Électricité de France (5 observed deaths versus

7.2 expected; SMR = 0.70; 90% CI: 0.27, 1.46); there was a positive but not statistically significant trend of risk of mortality due to non-CLL leukaemia with dose (ERR = 6.8 (90% CI: –8.4, 62.2) $Sv^{-1}$).

516. Further information has become available on the risk of leukaemia for young people in relation to their exposure to gamma radiation from natural sources. A large case-control study in the United Kingdom did not show any association between childhood leukaemia risks and gamma dose rate, as measured in the dwelling occupied for at least six months in the period immediately before diagnosis [U17]. Further details of this study are given in table 15. Notwithstanding the large number of subjects in this study and the collection of individual dosimetric data, the study's statistical precision is limited both by the low mean gamma dose rate (i.e. 0.843 mGy per year) and by the relatively narrow range of dose rates (from less than 0.1 to about 2 mGy per year). A national study in Sweden provided a weak suggestion of a trend of increasing risk of ALL at ages of less than 20 years with gamma radiation exposure arising from living in dwellings built from uranium-containing alum shale concrete [A24]. However, the statistical precision of these findings is low, reflecting in part the low doses received and the lack of detailed dosimetry for dwellings not known to have been built from alum shale concrete, which may have led to some misclassification of the exposures.

### *(b) External high-LET exposures*

517. Various studies have been conducted of leukaemia risks among aircrew exposed externally to both high-LET and low-LET radiation. As with studies of other types of exposure, caution needs to be attached to findings from small studies, and more weight should be given to well-designed large analyses. For example, Gundestrup and Storm [G22] drew attention to an excess incidence of AML in a cohort of Danish jet cockpit crew, albeit based on only 3 cases. A similar result had been reported previously for a study involving Canadian pilots [B32]. However, this finding was not replicated in a subsequent analysis based on a larger cohort of airline pilots in five Nordic countries [P21]. Analyses of leukaemia mortality in larger cohorts of aircrew from a wider range of European countries have generally provided little evidence of raised leukaemia risks relative to national rates with duration of employment (for more than 44,000 cabin crew [Z4]) or with estimated cumulative dose (for around 19,000 male pilots [L48]). However, even in large analyses such as these, the numbers of leukaemias have been small, so making inferences is difficult. Furthermore, when dose–response analyses have been conducted, the high- and low-LET components of dose have not been separated [L48].

### *(c) Internal low-LET exposures*

518. Two recent studies have considered leukaemia rates among people who lived near the Techa River in the Southern Urals in the Russian Federation, and who received protracted internal exposures (mainly due to $^{90}Sr$) and external exposures as a consequence of releases from the Mayak complex. Krestinina et al. [K50] conducted a study of leukaemia mortality based on a cohort of about 30,000 people born before 1950 who lived near the river sometime between 1950 and 1960. As of the start of 2000, about half the cohort was known to have died, and the cause of death was known in 85% of these instances. Although it was stated that about 16% of residents were lost to follow-up, the date of migration from the study area was known in many cases, and this allowed a more accurate determination of the number of person-years at risk. Krestinina et al. [K50] estimated that the ERR (low-LET) was 4.2 (95% CI: 1.2, 13) $Gy^{-1}$ for all leukaemias and 6.5 (95% CI: 1.8, 24) $Gy^{-1}$ for non-CLL leukaemia. However, they stressed caution in interpreting these values because of uncertainties in the dose estimates. In particular, this risk analysis incorporated "individualized" dose estimates—summed over internal and external exposures—that used age-dependent parameters and detailed residential histories, but did not take account of the precise location of individual residences within villages or of detailed lifestyle patterns. This is likely to give rise to Berkson measurement errors in the doses. These measurement errors may not have biased the estimates of any dose–response relationship, but would imply that confidence intervals for estimated trends in risk with dose are too narrow. Further work to improve the dosimetry and the follow-up of this population is in progress.

519. The other recent analysis of the Techa River population was a case-control study of leukaemia incidence, nested within essentially the same cohort as above [O13]. Leukaemia cases arising within the study region were identified from medical records of the leading haematological clinic in that area. Controls were selected randomly from the cohort and individually matched to the cases on the basis of the individual's age at the time of diagnosis, the individual's sex, and whether or not they moved into the area after the period of peak exposures. The dose estimates used in this analysis pre-dated those used by Krestinina et al. [K50]. However, the findings were broadly similar. The EOR (low-LET), based on both internal and external exposures, was 3.5 (95% CI: 1.5, 8.1) $Gy^{-1}$ for all leukaemias and 4.6 (95% CI: 1.7, 12.3) $Gy^{-1}$ for non-CLL leukaemia [O13]. Based solely on the cumulative internal dose at the time of diagnosis, the EOR (low-LET) for non-CLL leukaemia was little changed: specifically it was 5.4 (95% CI: 1.1, 27.2) $Gy^{-1}$. Adjustment for level of education, occupation and any history of tumours had little impact on these results. There was a weak suggestion that the estimated risk per unit dose might have been greater for persons younger than 26 years of age at around the time of peak exposures and for those diagnosed before 1970, but these findings were not statistically significant. There were a somewhat larger number of cases (83) than in the recent mortality data [K50] (49 non-CLL and 12 CLL), although only 50 of these were of known cell type, and 20 of these cases were CLL. Nevertheless, it should be recognized that both analyses are based on essentially the same cohort. Consequently, precise

quantification of risks is difficult for the same reasons as those mentioned earlier, particularly owing to the uncertainties in dosimetry.

520. Some other studies have examined the incidence of leukaemia in children in relation to radiation exposures arising from the Chernobyl accident in 1986. An updated follow-up of childhood leukaemia in Belarus continued to show no increase in rates [G19], as did an analysis in the Bryansk region of the Russian Federation [I32], whereas an analysis in Ukraine indicated a raised risk among children born in 1986 [N5]. Further afield, an analysis of childhood leukaemia in Hungary did not show a statistically significant increase in relation to the accident [T46] and, while it had been suggested that infant leukaemia was increased in Scotland and Wales as a result of the accident [B6], a wider analysis of data from the United Kingdom did not confirm an association [C28]. These analyses were "ecological studies", which did not take account of individual exposures. In contrast, a case-control study of leukaemia in young people has been conducted in Ukraine in which individual doses were estimated [N6]. This study indicated a raised risk among those with doses due to the accident of 10 mSv or more relative to those with doses of less than 2 mSv (RR = 2.5; 95% CI: 1.1, 5.4). However, a key limitation was the low proportion of eligible subjects who were included in the study, therefore raising the possibility of bias. A larger case-control study of leukaemia in young people was conducted in parts of Belarus, the Russian Federation and Ukraine [D52]. Only a small subset of the cases in this study was included in the earlier study [N6], while participation rates appeared to be higher in the three-country study. There was a statistically significant trend in leukaemia risk with estimated bone marrow dose, but interpretation of this finding was complicated by differences in the estimated dose response between the three countries [D52]. In particular, most of the evidence for a raised risk came from Ukraine, even though the mean dose for controls here was lower than the corresponding values for the regions of Belarus and the Russian Federation that were included in the study. Furthermore, all of these mean doses were low; the highest value was 11.74 mSv for the regions studied in Belarus.

521. There is little new information on leukaemia risks for those who might have received environmental exposures in adulthood as a consequence of the Chernobyl accident. An "ecological study" in northern Sweden did not show a clear excess of leukaemia [T47], although some aspects of the methodology (e.g. the exclusion of deaths when calculating disease rates during the 1986–1987 reference period) were questionable. Given these and the "ecological" design of the study, which is known to be susceptible to bias [L68, L69], little weight should be attached to the null findings of this study.

522. Further studies have been conducted in recent years around nuclear installations in other countries. A study of childhood leukaemia cases around the 29 nuclear installations in France found no evidence of a generally increased risk [W24]. While there was a weak suggestion of a raised rate of the incidence of ALL at ages younger than 10 years within 10 km of the La Hague reprocessing plant in France during 1978–1998, this finding was based on only 4 cases. Furthermore, an assessment based on a radioecological study conducted around this plant estimated that the expected number of radiation-induced leukaemias in young people due to releases from local nuclear installations would be less than 0.002 [L70, R50]. Likewise, there was little evidence of excess risk around French nuclear sites when using a geographical zoning based on gaseous discharge dose estimates [E13]. A study in the United Kingdom found no excess of childhood leukaemia during the period 1969–1993 around nuclear power plants and, aside from the raised rates previously reported around sites such as Sellafield and Dounreay, there was generally no new evidence of excesses around other nuclear sites [C7]. A study in Japan indicated a raised rate of leukaemia mortality summed over all ages in municipalities that contained a nuclear installation; however, there was no increase among young people [Y9]. An updated analysis of mortality rates around the Three Mile Island nuclear power plant in the United States did not indicate clear patterns in leukaemia risks [T45]. Overall, while there are a few nuclear installations around which raised leukaemia risks have previously been observed, there is very little evidence of raised rates around nuclear sites generally [L56]. This is not surprising in view of the very low radiation exposures of those living near most sites.

523. With regard to environmental exposures due to atmospheric nuclear weapons testing, Abylkassimova et al. [A23] gave brief details of a leukaemia case-control study conducted in Kazakhstan. This study was nested within a cohort of about 10,000 residents of settlements that were downwind from the Semipalatinsk nuclear test site. The risk among those with estimated doses of more than 2 Sv was about twice that among those whose doses were less than 0.5 Sv. However, this RR value was very imprecise, and the associated 95% confidence interval included 1, reflecting the small total number of cases of non-CLL leukaemia (i.e. 22). A study in French Polynesia reported higher rates of childhood leukaemia in the period 1985–1989 when compared with the period 1990–1995, although over the full study period of 1985–1995, rates were similar to those expected among New Zealand Maoris and natives of Hawaii [C5]. These data were not analysed specifically in relation to atmospheric nuclear weapons testing at the Mururoa and Fangataufa atolls. Extended follow-up of United Kingdom participants in the United Kingdom atmospheric nuclear weapons test programme provided some evidence of a raised risk of non-CLL leukaemia relative to a control group, although this might have been a chance finding in view of the low mortality observed in the controls relative to national rates [M35]. In a study of United States military personnel who took part in nuclear weapons tests in Nevada or the Pacific in the 1950s, mortality due to leukaemia was less than that expected from national rates, while the RR compared with a control group was slightly greater than, but consistent with, unity [I17].

524. A study of patients in France, Italy and Sweden who were treated with $^{131}$I for thyroid cancer has investigated the subsequent risk of various types of second cancers, including leukaemia [R38]. This study indicated a trend of increasing leukaemia risk with the cumulative $^{131}$I activity administered during the period two or more years previously. External irradiation as part of the treatment for thyroid cancer did not appear to influence this relationship. However, although this combined analysis has greater statistical power than the earlier studies conducted in each of the three countries [D18, D38, H2], detailed inferences about the relationship between administered activity and risk are not possible, because of the small total number of leukaemias (specifically 18). In addition, the risk of non-CLL leukaemia was not evaluated separately.

*(d) Internal high-LET exposures*

525. A combined analysis of patients in Denmark and Sweden who were injected with Thorotrast [T30] shows a substantial excess incidence rate of non-CLL leukaemia relative to both national rates and rates in an unexposed group of patients (see table 44). Leukaemia excesses have also been seen in recent analyses of patients injected with Thorotrast in the United States [T30] and Portugal [D27], although these were based on smaller numbers. Travis et al. [T30] noted that leukaemias were diagnosed throughout the more than 50 years of follow-up for the Danish and Swedish patients, which the authors considered to be due to the continual radiation exposure rather than an effect of the time since exposure. This analysis provided some suggestion of a higher incidence of CLL among irradiated than non-irradiated patients (with 6 and 1 cases observed, respectively, in similarly sized groups). However, this difference was not statistically significant and also appeared to be lower in magnitude than the corresponding difference for non-CLL leukaemia [T30]. In the Portuguese study, none of the leukaemias among irradiated patients was CLL, although the small numbers make inferences difficult [D27]. On the basis of earlier findings from studies on patients receiving Thorotrast and on survivors of the atomic bombings [U2], Harrison and Muirhead [H40] suggested that the relative biological effectiveness of alpha radiation might be around 2–3 times that of external low-LET radiation for the case of leukaemia, which would fit with associated animal data. However, Travis et al. [T30] noted that risk estimates based on Thorotrast data are subject to uncertainty, particularly with regard to dosimetry.

526. In a review published in 2001 of studies of radon exposure and leukaemia risks, Laurier et al. [L54] drew attention to the differences between findings from "ecological studies" and those from case-control studies involving individual assessments of exposures. This point, which was highlighted in the UNSCEAR 2000 Report [U2], has been reinforced by results from more recent studies of radon exposure and leukaemia risks. On the basis of data for 348 geographical units in France, Evrard et al. [E11] reported a trend of increasing risk of childhood acute leukaemia averaged over each of these areas with the average indoor radon concentration. This trend was of borderline statistical significance for all acute leukaemias ($p$ = 0.053), but was most apparent for AML ($p$ = 0.004) rather than for ALL ($p$ = 0.49). This conclusion was not modified by taking into account exposure to terrestrial and cosmic radiation [E1]. Attention has been drawn previously to the difficulties arising in interpreting such correlation studies, and greater weight would generally be placed on cohort and case-control studies [U2]. For example, a large case-control study in the United Kingdom found that, if anything, radon concentrations in the homes of childhood leukaemia cases may have been lower than those in the homes of the children in the control group [U16]. However, the similarity in findings seen across a range of childhood cancer types in this study suggests that differences in participation rates both between cases and controls and by level of deprivation might have led to some bias. Another large case-control study in the United Kingdom, this time focusing on incidence of acute leukaemia in adults, found no association with radon concentration as measured in the home occupied at the time of diagnosis [L55].

527. Recent reviews have considered the health risks [T31, T32], including leukaemia risks, in relation to exposure to uranium. These reviews have considered findings from studies of occupational exposures arising, for example, from the processing, manufacturing and milling of uranium. Studies of uranium miners have also been considered. In general, these studies have not indicated elevated risks of leukaemia in relation to uranium exposure. The Royal Society report [T32] concluded that any extra risk of death from leukaemia as a result of exposure to depleted uranium would be substantially lower than that from lung cancer, and that any raised leukaemia risk to persons exposed to depleted uranium is likely to be too small to be detectable. However, epidemiological studies of uranium exposures is limited by difficulties in assessing individual doses and in separating any effect due to radiation from that due to the chemical toxicity of uranium, as well as by the limited precision of individual studies and by the healthy worker effect [T31, T32]. For example, a recent study involving a cohort of uranium mill workers in the United States indicated that, if anything, leukaemia mortality was less than that expected from local rates (5 observed versus 6.51 expected), but the study was based on very small numbers [P25]. Studies of environmental exposures have also been conducted. In particular, a study of uranium and other natural radionuclides in drinking water in Finland did not indicate an association with leukaemia incidence, based on a total of 35 cases [A25]. Also, studies of populations living around some sites in the United States involved in uranium processing, manufacturing and milling did not show raised leukaemia risks [B29, B30, B31].

528. Of the roughly 21,500 workers at the Mayak plant in the Russian Federation who were studied by Shilnikova et al. [S28], 25% had been monitored for their exposure to plutonium. Although detailed estimates of plutonium

exposures were not available, analysis based on a surrogate measure of plutonium exposure did not indicate an association with rates of mortality due to non-CLL leukaemia [S28]. In a small study of radiation workers in the United States, Ritz et al. [R1] reported some weak evidence of a trend of increasing rates of mortality due to haematopoietic and lymphopoietic cancers (of which most were leukaemias) with internal dose, based on low- and high-LET radiation exposure from a mixture of radionuclides. However, not only was this finding based on only 10 deaths, but also the dose estimates were specific to the lung rather than the bone marrow. Other recent studies of radiation workers exposed internally to high-LET radiation have not reported results for leukaemia and/or they lacked detailed measures of exposure (e.g. [W22]).

### 4. Summary

529. New findings for leukaemia mortality in the cohort of Japanese survivors of the atomic bombings based on an extended follow-up show similar age and time patterns in radiation risks to those seen previously in this group. Furthermore, the use of the new DS02 dosimetry system has little impact either on the level of risk estimated for this cohort or on the evidence for a curvilinear dose–response relationship, such that the excess risk per unit dose decreases with decreasing dose.

530. A few recent studies have provided extra information on leukaemia risks among groups exposed for medical reasons. However, the studies of this type that were reviewed in the UNSCEAR 2000 Report and are also considered in Section II of this annex are generally more informative. In particular, these studies and also those of occupational exposures provide far stronger evidence of an association between non-CLL leukaemia risks and radiation exposure than is the case for CLL risks. Moreover, in view of the clinical and aetiological links between CLL and lymphomas, the conclusions reached elsewhere in this annex concerning radiation exposure and lymphoma risk should also apply to CLL risk.

531. New analyses of radiologists, radiologic technologists and other X-ray workers have confirmed higher risks of leukaemia among those exposed many years ago, when occupational doses are likely to have been higher than those received in recent years. In contrast, there is little evidence of increased risks for people receiving X-ray exposures more recently. However, more detailed inferences are precluded by the general lack of individual dosimetric data for these groups. Follow-up of workers at the Mayak plant in the Russian Federation who received a wide range of external and internal doses over a protracted period shows a raised risk of leukaemia in relation to external gamma dose, but not in relation to a measure of plutonium exposure. While precise quantification of the level of risk for these workers is difficult, the findings appear to be consistent with those from the studies of the Japanese survivors of the atomic bombings. Other recent analyses of radiation workers, including a large study based on data for workers in 15 countries, considered groups whose cumulative doses tended to be much lower than those of Mayak workers. The findings from these studies are largely consistent with extrapolation from the atomic bombing survivor data, but because of their generally low statistical precision, these studies are also consistent with a range of risks both lower and higher than this.

532. Several analyses have been conducted recently of aircrew exposed to external high-LET and low-LET radiation. In general, these studies have tended not to show raised risks of leukaemia. However, even analyses based on large cohorts have been limited by the relatively small numbers of leukaemias involved, as well as by the low doses received and by the general lack of individual dose estimates.

533. New information on leukaemia risks for groups exposed to internal low-LET radiation, as well as to external low-LET radiation, has become available from studies in the former Soviet Union. Cohort and case-control studies of Techa River residents have indicated dose-related trends in leukaemia risk that are reasonably consistent with estimates from studies of the Japanese survivors of the atomic bombings, but which are still somewhat uncertain. At much lower doses, a recent case-control study in Belarus, the Russian Federation and Ukraine of exposures due to the Chernobyl accident reported a dose-related increase in leukaemia in young people, but heterogeneity in the findings between the countries makes interpretation difficult. Recent studies of people living around nuclear installations in other countries have generally not shown raised risks, while findings for groups exposed as a consequence of atmospheric nuclear weapons testing have been mixed and generally do not provide strong evidence of an increased risk of leukaemia. A combined analysis of patients from three countries who were treated for thyroid cancer indicates a trend of increasing leukaemia risk with cumulative intake of $^{131}$I, but the number of cases studied was small.

534. Further data on patients injected with Thorotrast continue to show raised risks of leukaemia associated with this type of exposure. Comparison of these and earlier findings with those for the Japanese survivors of the atomic bombings provide some indication that, in this instance, the relative biological effectiveness of alpha radiation for leukaemia induction might be around 2–3. However, this estimate is subject to various sources of uncertainty, particularly relating to Thorotrast dosimetry.

535. Studies of radon exposure and leukaemia risks published since the UNSCEAR 2000 Report have continued to provide differing findings, according to whether they are based on an “ecological design” or on the collection of individual exposure information as part of case-control or cohort studies. While some of the case-control studies have had methodological limitations, the lack of any indication

from these and earlier case-control and cohort studies of a trend of increasing leukaemia risk with increasing individually assessed radon exposures is notable. In view of the generally low doses to the bone marrow arising from exposure to radon in dwellings, it is unlikely that risks of the order predicted from current radiation risk estimates for leukaemia could have been observed.

536. Studies of groups exposed to uranium or plutonium have generally provided little indication, if any, of raised leukaemia risks. Many of these studies have been limited by the relatively small numbers of cases and a general lack of detailed dosimetric data. However, it would appear that any increase in leukaemia associated with these exposures would be very small.

# IV. LIFETIME RISK FOR TOTAL CANCER

## A. Methods and assumptions of calculations

537. As noted in the Introduction to this annex and as further discussed in both section I.G and appendix B, the Committee has evaluated four commonly used measures of population cancer risk, derived from risk models fitted to the LSS mortality data, using the latest DS02 dosimetry and follow-up [P10]. Lifetime population cancer risks have been calculated for China, Japan, Puerto Rico, the United States and the United Kingdom. Mortality risk estimates are presented for solid cancers and leukaemia separately, these being the only malignant disease end points yet available for analysis in the latest version of the LSS mortality data using the updated DS02 dosimetry [P10]. The Committee has also evaluated risks of cancer for oesophageal, stomach, colon, liver, lung, bone, non-melanoma skin, female breast, urinary bladder, central nervous system, thyroid and all other solid cancers in the latest version of the LSS incidence data using the updated DS02 dosimetry [P48]. There were 100 or more cases for all these cancer sites with the exception of bone cancer, and a statistically significant (2-sided $p < 0.05$) dose response (see appendix A). Although there were only 19 cases of bone cancer, risks have nevertheless been assessed. The results of fitting models to the mortality rate and cancer incidence rate data using classical likelihood-based methods (with adjustment for dosimetric error) are presented; these methods are described in more detail in appendices C and D. Models have also been fitted to the DS02 mortality data using Bayesian methods, as outlined in appendix E. As discussed in section I.D, the main advantage of the Bayesian approach is that dosimetric and other uncertainties are better reflected in the variability of the model parameters. The analysis employs the two-step method recently used to evaluate the effects of dose uncertainties on model parameters and to propagate these into uncertainties in population cancer risk estimates [B18, L17].

538. Risks are calculated at three test doses, $D_t$, of 0.01 Sv, 0.1 Sv and 1 Sv. It is implicitly assumed that these doses are whole-body doses, uniformly irradiating the tissues under consideration. The results depend on the following factors, which are discussed briefly below:

- The exposed population for which risk estimates are developed, and the models used to describe the excess risks to this population;
- The models used to describe risk at low doses;
- The method used to extend the excess risk models beyond the period of observation of the population from which these models were developed;
- The cause-specific incidence and mortality rates and the age structure of the population to which the rates are applied;
- The methods used to transfer estimates of excess cancer risk based on models for one population to another population;
- The method used to allow for dose fractionation or dose-rate effects.

### 1. Risk models

539. As in the previous UNSCEAR reports [U2, U4], the Committee's risk estimates are based on recent data from the follow-up of the LSS of the survivors of the atomic bombings in Japan. The recent analysis by Preston et al. [P10] of LSS mortality data based on mortality follow-up from October 1950 to December 2000 is employed, as well as the latest analysis of the solid cancer incidence data based on follow-up from January 1958 to December 1998 [P48]. The Committee's analysis of the LSS data is the first to use the recently revised DS02 dosimetry [C13]. As noted in the Introduction, for some time it was thought that the neutron dose estimates for the survivors of the bombing of Hiroshima using the previous (DS86) dosimetry were systematic underestimates, particularly for survivors from beyond 1000 m from the hypocentre [R20, S39]. This led to substantial multinational efforts to develop a new dose assessment system, the DS02 dosimetry [C13, R12]. Recent analysis of all the data, including those on fast-neutron activation products, suggests that there are no appreciable systematic errors in the DS86 estimates of neutron doses for survivors of the bombing of Hiroshima [C13, R12, S41]. The DS02 dosimetry differs slightly from the DS86 system, for both neutron and gamma doses, by amounts generally of no more than 20% in the range up to 1,500 m from the two hypocentres, where survivors received the greatest doses [C13, R12]. Analyses of the Radiation Effects Research Foundation (RERF) epidemiological data using the new dosimetry indicate that cancer risk estimates might decrease by about 8% as a result, with no appreciable change in the shape of the dose response or in the age and time patterns of excess risk [P10].

540. The cancer risk models that are fitted to this data set for the purposes for deriving population risk estimates were developed specifically for the Committee. Radiation risks are often described by models for cause-specific death rates or "hazard functions". The hazard function, $h(a)$, for mor-

tality at age $a$ is defined as the probability of dying in a short interval $[a,a+\delta]$ divided by the probability of surviving up to age $a$ and the length of the interval $\delta$, in the limit that $\delta \to 0$, or more formally,

$$h(a) = \lim_{\delta \downarrow 0+} \frac{P[\text{time of death} \in [a, a+\delta)]}{\delta \cdot P[\text{time of death} \geq a]}$$

Similar definitions for the hazard function can be derived for deaths from some specific cause, or indeed for the occurrence of any specific type of event, e.g. the occurrence of cancer. Quite often the hazard function, $h(a)$, will depend on variables other than only age, for example sex, $s$, calendar period, $y$, and exogenous exposures, for instance to a dose of ionizing radiation $D$ delivered at age $e$, so that one may write the hazard function as $h = h(a,y,s,D,e)$.

541. In modelling the effect of some exposure, in particular that to ionizing radiation, it is usual to consider the difference between the instantaneous cancer death rate, or hazard function, when there has been exposure, $h(a,y,s,D,e)$, and what the instantaneous death rate, or hazard function, would have been without that exposure, $h_0(a,y,s,e) = h(a,y,s,0,e)$, the "baseline" hazard function. This difference is the excess absolute risk (EAR):

$$EAR(a,y,s,D,e) = h(a,y,s,D,e) - h(a,y,s,0,e) \quad (7)$$

An essential element of such models is the associated model for the baseline hazard function, which is often of simple parametric form, for example:

$$h_0(a,y,s,e,c) = \exp[\pi_0 \cdot 1_{c=Nagasaki} + \pi_1 \cdot 1_{s=female} + \pi_2 \cdot \ln[a] + \pi_3 \cdot [\ln[a]]^2 + \pi_4 \cdot e] \quad (8)$$

where $c$ refers to the city of residence at the time of the bombings (Hiroshima or Nagasaki), $s$ is the sex, $a$ is attained age, $e$ is age at exposure, and $\pi_0,\pi_1,\pi_2,\pi_3,\pi_4$ are the model parameters (which are often determined by fitting to the data).

542. Another commonly used measure is the excess relative risk (ERR), which is given by the EAR divided by the baseline hazard:

$$ERR(a,y,s,D,e) = EAR(a,y,s,D,e) / h(a,y,s,0,e) = [h(a,y,s,D,e) - h(a,y,s,0,e)] / h(a,y,s,0,e) \quad (9)$$

Again, an essential element in the specification of such models is the baseline hazard function, $h_0(a,s) = h(a,y,s,0,e)$, which is again often assumed to have a simple parametric form, for example along the lines of expression (8).

543. Corresponding to these methods for decomposing the hazard function are two much used models of radiation-induced cancer risk. Until the late 1980s, two fairly simple models for describing radiation-induced cancer risks were used by the Committee [U6] and by other national and international committees, such as the BEIR committee [C33] and the ICRP [I11]. These are empirical models, which do not depend on assumptions about specific mechanisms of carcinogenesis. The first is the "time-constant absolute (or additive) risk projection model", which assumes that, after some "latent period", the annual excess cancer risk is constant. This results in the cancer rate following exposure to a dose of radiation being given by:

$$h_0(a,s) + F(D) \quad (10)$$

where $h_0(a,s)$ is the baseline cancer hazard function in the absence of exposure to radiation, i.e. the underlying cancer rate at age $a$ and for sex $s$. $F(D)$ is the function describing the dose dependency of the cancer risk, which is often of the linear–quadratic form $F(D) = \alpha \cdot D + \beta \cdot D^2$. In the UNSCEAR 1988 Report [U6], a model of this form was used for describing the risk of leukaemia. The second model is the "time-constant relative (or multiplicative) risk projection model", which assumes that, after some latent period following an exposure to radiation, the annual cancer rate rises in a manner proportional to the underlying annual cancer risk. This results in the cancer rate following exposure to a dose $D$ of radiation being given by:

$$h_0(a,s) \cdot [1 + F(D)] \quad (11)$$

where again $F(D)$ is the function determining the dose dependency of the cancer risk, which again is often of the form $F(D) = \alpha \cdot D + \beta \cdot D^2$.

544. In the UNSCEAR 1988 Report [U6], a model of this form (with linear dose response) was used for modelling solid cancer risks. Until the late 1980s, both models were used for the purposes of estimating cancer risks. Largely as a result of extra years of follow-up of the survivors of the atomic bombings, it became clear that the RR model fitted most solid cancer data much better than the absolute risk model. For this reason, the ICRP [I11] and most other scientific committees [C35] tend to use the RR model rather than the absolute risk model for projecting solid cancer risks to the end of life.

545. While the RR model is the most useful for the purpose of modelling cancer risks, it is the absolute risk that is often of most interest to an exposed individual or population. This is readily derived from the calculated RR when the baseline risk is known.

546. It is well known that, for all cancer subtypes (including leukaemia), the ERR diminishes with increasing age at exposure [L51, L52, U2]. For those irradiated in childhood, there is evidence of a reduction in the ERR of solid cancer 25 or more years after exposure [L16, L53, P9, T1]. Therefore, even for solid cancers, various factors have to be employed to adjust the ERR. For many solid cancers, a

"generalized excess relative risk model" is commonly used, in which the cancer rate at *t* years after exposure, for sex *s*, following exposure at age *e* to a dose *D* of radiation is given by:

$$h_0(a,s)\cdot[1+F(D)\cdot\phi(t,e,s)] = h_0(a,s)\cdot [1+ERR(D,t,e,s)] \quad (12)$$

where as before $h_0(a,s)$ is the baseline cancer rate, $a = t + e$ is the age at observation (attained age) of the person and $F(D)$ is the function determining the dose dependency of the cancer risk, which is often of the form $F(D) = \alpha \cdot D + \beta \cdot D^2$. The expression $\phi(t,e,s)$ describes the adjustment to the ERR, $F(D)$, as a function of time since exposure *t*, age at exposure *e* and sex *s*.

547. For leukaemia, neither the time-constant EAR model nor the time-constant ERR model fits well. For reasons largely of ease of interpretation, Preston et al. [P4] present most of their analyses of the LSS leukaemia incidence data set using a "generalized excess absolute risk model", from which the cancer rate *t* years after exposure, for sex *s*, following exposure at age *e* to a dose *D* of radiation is given by:

$$h_0(a,s)+F(D)\cdot\psi(t,e,s) = h_0(a,s)+EAR(D,t,e,s) \quad (13)$$

The expression $\psi(t,e,s)$ describes the adjustment to the EAR, $F(D)$, as a function of time since exposure *t*, age at exposure *e* and for sex *s*. As above, very frequently a linear–quadratic form, $F(D) = \alpha \cdot D + \beta \cdot D^2$, is assumed for the dose response.

548. Given appropriate forms of the adjusting or modifying functions $\phi(t,e,s)$ and $\psi(t,e,s)$ of the relative and absolute risk, respectively, equivalently good fits to the leukaemia incidence data set were achieved using both generalized ERR and generalized EAR models [P4]. It is to some extent arbitrary which of these two models is used. However, models with equivalent fits to the data can yield somewhat different estimates of population cancer risks. The reason for this is that about half the LSS cohort are still alive [P10], so that population risk estimations based on this data set (and used by many scientific committees [C33, C35, I11, U2, U4, U6]) crucially depend on extrapolating the current mortality and incidence follow-up of this group to the end of life. Uncertainties due to risk projection are greatest for solid cancers, because the radiation-associated excess risk as seen by the LSS is still increasing [P9, P10]. For leukaemia, the excess risk is decreasing over time [P4], and most models used predict very few radiation-associated leukaemia deaths or cases in the future.

549. In modelling solid cancer and leukaemia mortality for the latest follow-up of mortality of the survivors of the atomic bombings [P10], the Committee has used generalized ERR and EAR models. For solid cancer mortality, the following generalized ERR model was used, in which the cancer mortality rate for age *a*, age at exposure *e*, city *c*, sex *s* and "true" colon dose *D* is given by:

$$h_0(a,e,c,s)\cdot\left[1+(\alpha\cdot D+\beta\cdot D^2)\cdot\exp[\kappa_1\cdot 1_{s=female} + \kappa_2\cdot\ln[a-e]+\kappa_3\cdot\ln[a]]\right] \quad (14)$$

This is a generalized ERR model that is linear in dose and that incorporates adjustment to the ERR for sex, *s*, attained age, *a*, and time since exposure, $a - e$. For purposes of comparison with models previously fitted by the Committee, the following generalized ERR model was also used, in which the cancer mortality rate is given by:

$$h_0(a,e,c,s)\cdot\left[1+(\alpha\cdot D+\beta\cdot D^2)\cdot\exp[\kappa_1\cdot 1_{s=female} + \kappa_2\cdot\ln[e]]\right] \quad (15)$$

This is a generalized ERR model that is linear in dose, and that incorporates adjustment to the ERR for sex, *s*, and age at exposure, *e*.

550. A generalized EAR model was also fitted in which the mortality rate is given by:

$$h_0(a,e,c,s)+(\alpha\cdot D+\beta\cdot D^2)\cdot\exp[\kappa_1\cdot\ln[a-e] + \kappa_2\cdot\ln[a]] \quad (16)$$

This is a generalized EAR model that is linear–quadratic in dose, and that incorporates adjustment to the EAR for attained age, *a*, and time since exposure, $a - e$. The parameters associated with the fits of these two models to the LSS DS02 solid cancer mortality data [P10] are given in table 45. The associated analysis of statistical deviance is given in tables D1 and D2 in appendix D. Table D17 in appendix D gives details of the specific form of the baseline rate, $h_0(a,e,c,s)$, used in model fitting.

551. Likewise, for leukaemia mortality the following generalized ERR model was used, in which the leukaemia mortality rate for age *a*, age at exposure *e*, city *c*, sex *s* and "true" colon dose *D* is given by:

$$h_0(a,e,c,s)\cdot\left[1+(\alpha\cdot D+\beta\cdot D^2)\cdot\exp[\kappa_1\cdot\ln[a]]\right] \quad (17)$$

This is a generalized ERR model that is linear–quadratic in dose, and that incorporates adjustment to the ERR for attained age, *a*. The Committee also fitted a generalized EAR model in which the leukaemia mortality rate is given by:

$$h_0(a,e,c,s)+(\alpha\cdot D+\beta\cdot D^2)\cdot\exp[\kappa_1\cdot 1_{s=female} + \kappa_2\cdot\ln[a-e]] \quad (18)$$

This is a generalized EAR model that is linear–quadratic in dose, and that incorporates adjustment to the absolute risk for sex, *s*, and time since exposure, $a - e$. The parameters associated with the fits of these two models to the LSS DS02 leukaemia mortality data [P10] are given in table 46. The associated analysis of deviance is given in tables D3 and D4 in appendix D. Table D17 in appendix D gives details of the specific form of the baseline rate, $h_0(a,e,c,s)$, used in model fitting.

552. In modelling the incidence of specific types of solid cancer for the latest follow-up of the survivors of the atomic bombings [P48], the Committee again used generalized ERR and EAR models. For solid cancer incidence, the following generalized ERR model was used, in which the cancer rate for age *a*, age at exposure *e*, city *c*, sex *s* and "true" colon dose *D* is given by:

$$h_0(a,e,c,s)\cdot\left[1+(\alpha\cdot D+\beta\cdot D^2)\cdot\exp[\gamma\cdot D]\cdot\exp[\kappa_1\cdot 1_{s=female}+\kappa_2\cdot\ln[a-e]+\kappa_3\cdot\ln[a]+\kappa_4\cdot\ln[e]]\right] \quad (19)$$

This is a generalized ERR model that is linear–quadratic–exponential in dose, and that incorporates adjustment to the ERR for sex, *s*, attained age, *a*, time since exposure, $a - e$, and age at exposure, *e*. For specific solid cancer subtypes, various coefficients are set to zero. In particular, for all cancers except non-melanoma skin cancer, the cell sterilization parameter, $\gamma$, is set to zero.

553. Likewise, the following generalized EAR model was used, in which the cancer rate for age *a*, age at exposure *e*, city *c*, sex *s* and "true" colon dose *D* is given by:

$$h_0(a,e,c,s)+(\alpha\cdot D+\beta\cdot D^2)\cdot\exp[\gamma\cdot D]\cdot\exp[\kappa_1\cdot 1_{s=female}+\kappa_2\cdot\ln[a-e]+\kappa_3\cdot\ln[a]+\kappa_4\cdot\ln[e]] \quad (20)$$

This is a generalized EAR model that is linear–quadratic–exponential in dose, and that incorporates adjustment to the EAR for sex, *s*, attained age, *a*, time since exposure, $a - e$, and age at exposure, *e*. Again, for specific solid cancer subtypes, various coefficients are set to zero. In particular, for all cancers except non-melanoma skin cancer, the cell sterilization parameter, $\gamma$, is set to zero. The parameters associated with the fits of these models to the DS02 cancer incidence data [P48] are given in tables 47–58. The associated analyses of deviance are given in tables D5–D16 in appendix D. Table D17 gives details of the specific forms of the underlying rate, $h_0(a,e,c,s)$, used in model fitting to data on each solid cancer type.

### 2. Low-dose response, fractionation and dose-rate effects

554. As noted above, it has been customary to model the dose–response function $F(D)$ that appears in expressions (10)–(13) in fits to biological [U5] and epidemiological [U2] data by the linear–quadratic expression:

$$F(D)=\alpha\cdot D+\beta\cdot D^2 \quad (21)$$

While this formulation can be drawn from knowledge of chromosome repair (e.g. [K54]), on a more heuristic basis, it represents the second-order Taylor series expansion of the dose response. There is significant curvilinearity in the dose response for leukaemia in the LSS [L29, L33, L34, L35, L37, P11], although for solid cancers, apart from non-melanoma skin cancer [L30, T1] and bone cancer [R27, T26], there has until recently generally been little evidence for anything other than a linear dose–response relationship for the Japanese cohort [L29, L33, L34, L35, L37, P11, P12] or for any other group [U2]. This issue is discussed at greater length in section I.J. However, the most recent follow-up of the survivors of the atomic bombings exhibits a pronounced and statistically significant upward curvature in the low dose (less than 2 Sv) region [P10], as will be discussed at greater length below.

555. It should be noted that, as well as differences in the effectiveness (per unit dose) relating to the total dose received, there are also possible variations in effectiveness as a result of dose fractionation (i.e. the splitting of a given dose into a number of smaller doses suitably separated in time) and dose rate [U5]. This is not surprising from a radiobiological point of view. If a given dose is administered at progressively lower dose rates (i.e. giving the same total dose over longer periods of time), or is split into many fractions, the biological system has time to repair the damage, so that the total damage induced will be less [U5]. Therefore, although for cancers other than leukaemia there is generally little justification for assuming anything other than a linear dose–response relationship, i.e. $\beta = 0$ in Eq. (21), it may nevertheless be justifiable to employ a dose and dose-rate effectiveness factor (DDREF) other than 1. (The DDREF is the factor by which one divides risks for high-dose and high-dose-rate exposures to obtain risks for low-dose and low-dose-rate exposures.) The ICRP [I11] recommended that a DDREF of 2 be used together with linear dose–response models for all cancer sites, largely on the basis of observations from various epidemiological data sets. The UNSCEAR 1993 Report [U5] recommended that a DDREF of no more than 3 be used in conjunction with these linear models. The BEIR VII Committee [C37] estimated what it termed an "LSS DDREF" to be 1.5 (95% CI: 1.1, 2.3) on the basis of estimates of curvature derived from data from animal experiments and from the latest LSS solid cancer incidence data. The BEIR VII Committee also conducted a detailed review of the experimental literature, and documented substantial DDREF values that had been found for chromosome aberrations and cell mutation (for

example at the HPRT locus), and for carcinogenesis in animals [C37]. DDREF values in excess of 2 were seen for many cellular systems; most of the animal cancer studies—the experimental end point nearest to cancer in humans—yield "[DDREF] estimates on the order of 2 to 6, with most values in the range 4–5" [C37]. The BEIR committee stated that their analysis was sensitive to the particular studies they chose to include and, perhaps more importantly, that the DDREF should not be mistakenly thought of as a universal low-dose correction factor. There is further discussion of the DDREF in section I.J.

556. Another form to represent dose response, perhaps less commonly used, slightly generalizes Eq. (21):

$$F(D) = (\alpha \cdot D + \beta \cdot D^2) \cdot \exp(\gamma \cdot D) \qquad (22)$$

This has been employed in fits to biological data [U5] and to epidemiological data [B5, L29, L30, L31, T21, W2]. The $\alpha \cdot D + \beta \cdot D^2$ component represents the effect of (carcinogenic) mutation induction, while the $\exp(\gamma \cdot D)$ term represents the effect of cell sterilization or killing. In general, the cell sterilization coefficient $\gamma$ is less than zero. Essentially this expresses the idea that there is a competing mechanism due to cell killing, which is more effective at higher radiation doses. A dead cell cannot proliferate and become the focus of a malignant clone. Variant forms of the cell-sterilization term $\exp(\gamma \cdot D)$ that incorporate higher powers of dose $D$, i.e. $\exp(\gamma \cdot D^k)$ for $k > 1$, are sometimes employed [L30, U5].

557. Although it is generally assumed that protraction of radiation dose results in a reduction of effect (i.e. DDREF > 1), largely as a result of the extra time that protraction allows for cellular repair processes to operate, there are biological mechanisms that could increase the effect when dose is protracted (i.e. DDREF < 1). Bystander effects, whereby cells that are not directly exposed to radiation exhibit adverse biological effects, have been observed in a number of experimental systems in vitro and in vivo [M49, M61]. The bystander effect implies that the dose response after broad-beam irradiation could be highly concave at low doses because of saturation of the bystander effect at high doses. This would mean that linear extrapolation from data for high-dose exposures would lead to substantial underestimates of effects at low doses. Recently, Brenner et al. [B25] proposed a model for the bystander effect based on the oncogenic transformation data of Sawant et al. [S43] and Miller et al. [M41] for in vitro exposure of C3H 10T½ cells to alpha particles. Brenner et al. [B25] discussed evidence from experimental systems consistent with concluding that the linear extrapolation of high-dose effects to low doses underestimates oncogenic transformation rates by a factor of between 60 and 3,000. However, Little and Wakeford [L46] assessed the ratio of the lung cancer risk for persons exposed to low (residential) doses of radon daughters to that for persons (underground miners) exposed to high doses of radon daughters; the ratio lay in the range 2–4 (95% CI: <1, ~14). This implies that low-dose-rate lung cancer risks associated with alpha particle exposure are not seriously underestimated by extrapolation from the high-dose miner data; it also implies that the bystander effect observed in the C3H 10T½ cell system cannot play a large part in the process of lung carcinogenesis in humans due to radon exposure [L46]. The bystander effect and other "non-targeted" effects are discussed at greater length in annex C of the UNSCEAR 2006 Report, "Non-targeted and delayed effects of exposure to ionizing radiation".

558. As noted above, in the latest follow-up of the survivors of the atomic bombings there has emerged evidence of a statistically significant ($p < 0.05$) upward curvature in the dose response for solid cancer mortality in the low dose range (colon dose less than 2 Sv) [P10, W20], although this is not observed over the full dose range (0–4 Sv). Similar findings have not as yet been observed in the solid cancer incidence data [P12, T1], so caution is advised in interpretation of this finding. As shown in appendix D, in general there are only weak indications of curvature in the dose response for particular solid cancer sites in the latest cancer incidence data [P48], with the possible exception of bone cancer and non-melanoma skin cancer. Nevertheless, it is important to explore the implications of this curvature in the low-dose response for solid cancer risk estimates. For this reason, models (14) and (16) were separately fitted to the mortality data [P10], assuming both a purely linear dose–response relationship (with the quadratic coefficient, $\beta$, set to zero) and a linear–quadratic dose response.

559. For leukaemia in the low dose range (bone marrow dose less than 2 Sv), comparison of the linear–quadratic and purely quadratic models suggests that the linear term does not statistically significantly improve the fit of the pure quadratic model ($p > 0.50$), although the linear–quadratic model fits statistically significantly better than the purely linear model ($p = 0.003$). This suggests that in this low dose region, a purely quadratic dose response may best describe the leukaemia induction curve. For solid cancers, similar findings have not as yet been observed in the incidence data [L29, P4], so caution is advised in interpretation of this finding. Nevertheless, it is important to explore the implications of this curvature in the low-dose leukaemia response for cancer risk estimates. For this reason, models of the form of Eqs (17) and (18)—assuming both a purely quadratic dose response (with the linear coefficient, $\alpha$, set to zero) and a linear–quadratic dose response—were separately fitted to the mortality data [P10].

560. As discussed in section I.D, measurement error can substantially alter the shape of the dose–response relationship and hence the derived population risk estimates [T17]. The problem of dosimetric error for the RERF data has been investigated by Jablon [J3], Gilbert [G17], and subsequently in a series of papers by Pierce et al. [P2, P11, P16] and Little et al. [B18, L17, L29, L32, L33, L35, L37, L49]. Because of the marked effect of adjusting for dosimetric errors on the shape of the dose–response curve, all the analyses presented in this annex employ such dosimetric adjust-

ments, using the regression calibration methodology developed by Pierce et al. [P2, P11, P16] and Little et al. [L29, L32, L33, L35, L37, L49]. Jablon [J3] investigated the errors in the dosimetry for the survivors of the atomic bombings and found that the errors were most likely to be log-normally distributed, with a geometric standard deviation (GSD) of about 30%. The analyses of this report employ the "central" estimate of 35% for GSD. This is the same central estimate as used by Pierce et al. [P2] and assumed by Little et al. [L29, L32, L33, L35, L37, L49]. Details on the methods for fitting the extended Weibull distribution to the LSS mortality data are given in appendix C.

### 3. Projection methods

561. In the UNSCEAR 2000 Report [U2], some use has been made of generalized ERR models for solid cancer incorporating adjustment for attained age and sex, and also such models with adjustment for age at exposure and sex. However, it is clear from the data on solid cancer incidence [L16, L21, T1], as also from the latest data on mortality [P10], that these models are not optimal. Detailed comparison of models with various sorts of adjustment (all combinations of logarithmic adjustment for attained age, age at exposure, time since exposure, sex and city) in the latest follow-up of the solid cancer mortality data [P10] suggested that, as indicated by the form of model (14) above, the optimal generalized ERR model was one with adjustment for sex, time since exposure and attained age. Among generalized EAR models for solid cancer mortality with these sorts of adjustment (all combinations of logarithmic adjustment for attained age, age at exposure, time since exposure, sex and city), as indicated by the form of model (16) above, again the optimal model was one with adjustment for the time since exposure and attained age. There was little to choose between the fits of these two classes of model (generalized ERR and generalized EAR). This annex therefore uses both models to project cancer risk over time. For purposes of comparison with the risk models used previously [U2], the risks calculated using model (15), with adjustment to the ERR for age at exposure and sex, are also presented. The mortality risks for these three models are presented in tables 59–62. In table 72, summary risk values from table 59 are presented together with various other recent estimations of population cancer mortality risks. Mortality risks estimated using Bayesian Markov Chain Monte Carlo (MCMC) methods are given in tables 63 and 64.

562. In previous UNSCEAR reports, a variety of methods were used to project leukaemia risk over time, including a time-constant EAR model for the UNSCEAR 1988 Report [U6] and the generalized EAR models developed by Preston et al. [P4] from the LSS incidence data for the UNSCEAR 1994 [U4] and 2000 [U2] Reports. As noted above, the EAR for leukaemia is generally declining over time, so projection of risk is not such an issue as for solid cancers. Detailed comparison of models with various sorts of adjustment (all combinations of logarithmic adjustment for attained age, age at exposure, time since exposure, sex and city) in the latest follow-up of the leukaemia mortality data [P10] suggested that, as indicated by the form of model (17) above, the optimal generalized ERR model was one with adjustment for attained age. Although the optimal generalized ERR model is one with logarithmic adjustment for attained age, a model with adjustment for time since exposure and age at exposure fitted nearly as well. However, the risks predicted by these two models are close, so for simplicity, the risk values presented here are only those calculated using the model with adjustment for attained age. Among generalized EAR models for leukaemia mortality with these sorts of adjustment (all combinations of logarithmic adjustment for attained age, age at exposure, time since exposure, sex and city), the optimal model was one with adjustment for sex and time since exposure, as indicated by the form of model (18) above. There was little to choose between the fits of these two classes of model (generalized ERR and generalized EAR). Therefore both models have been used to project cancer risk over time. Mortality risks for these two models are presented in tables 65–67. In table 72, summary risk values from table 65 are presented together with various other recent estimations of population mortality risks due to leukaemia. Mortality risks estimated using Bayesian MCMC methods are given in tables 68 and 69.

563. In the UNSCEAR 2000 Report [U2], similar models were employed for projection of the risk for solid cancer incidence as of the risk for solid cancer mortality. In particular, generalized ERR models with adjustment for powers of attained age or powers of age at exposure were used in the UNSCEAR 2000 Report [U2]. In the current report, a general framework for risk projection is used for the generalized ERR and EAR models expressed in Eqs (19) and (20). The details of the particular ERR and EAR models used for each cancer site are given in tables 47–58. Appendix D gives more details on the model fitting and the detailed justification of the form of each model (see particularly tables D5–D16). Tables 70 and 71 present risk estimates for solid cancer incidence calculated using the generalized ERR and EAR models separately for each of the five populations considered (China, Japan, Puerto Rico, the United States and the United Kingdom). Table 73 presents summary risk values from table 70, together with various other recent estimations of population risks for solid cancer.

564. As detailed in appendix B, the four measures of population risk relevant to mortality were estimated, namely: excess cancer deaths (ECD), risk of exposure-induced death (REID), years of life lost (YLL) per unit dose, and years of life lost per radiation-induced cancer death (YLLRIC). For cancer incidence, the measure of risk expressed as exposure-induced cancer incidence (REIC) is used. Persons are assumed capable of surviving in principle up to the age of $y_T$ (121 years here), at which point they are assumed to die instantaneously (i.e. the population is truncated at that age). It was assumed that there are no excess solid cancer cases or deaths in the first 5 years after exposure, and no

excess leukaemia deaths in the first 2 years after exposure. Otherwise the temporal expression of risk, in particular the projection of risk to the end of life, is as predicted by the fitted models expressed as Eqs (14)–(20).

#### 4. Populations, mortality rates and cancer incidence

565. Risks are calculated separately for populations having the population structure, cancer incidence and mortality rates of current Chinese, Japanese, Puerto Rican, United States and United Kingdom populations. For China, Japan, Puerto Rico and the United States, the mortality rates and population structure were derived from a database maintained by the World Health Organization (WHO) [W38]. These correspond to a 1999 Chinese population (a combined urban and rural sample), a 1994 Japanese population, a 1992 Puerto Rican population and a 1998 United States population. For the United Kingdom, mortality rates of the 2003 England and Wales population were used [O8]. Current cancer incidence rates were tabulated from reference [P19] for China (1993–1997), Japan (1993–1997) and Puerto Rico (1992–1993) (using rates from the Shanghai registry for China and from the Osaka registry for Japan). For the United States, rates for 2002 from the nine SEER registries (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco–Oakland, Seattle–Puget Sound and Utah) were used [S83]; and for non-melanoma skin cancer, rates (for basal and squamous cell carcinoma) for eight areas in 1977–1978 were used [S38]. For the United Kingdom, the cancer incidence rates for England in 2001 were employed [O12]. For the purposes of calculating cancer mortality risks in the United Kingdom population, "solid cancer" is defined to be any cause of death with an International Classification of Diseases (10th revision) (ICD10) code of C00–C80 or C97; "leukaemia" is defined as any cause of death with ICD10 code C91–C95 excluding C91.1, i.e. all leukaemias excluding CLL. CLL is excluded from the calculations of leukaemia risk here because there is little evidence that it is radiogenic [U2]. Similar definitions, in some cases based on ICD9 codes, were used for the other populations. The populations are assumed to be in equilibrium prior to radiation exposure, an assumption commonly made in such calculations [B18, L15, L16, L17]. All high-dose-rate risks are evaluated using models expressed by Eqs (14)–(20) fitted to the various LSS mortality and cancer incidence data sets [P10, P48].

#### 5. Transfer of risk estimates between populations

566. Risks of cancer and cancer mortality were transferred by means appropriate for each of the two sorts of model (generalized ERR and generalized EAR). Therefore, for generalized ERR models (time-, age- and sex-specific), ERR was assumed to be invariant between populations, whereas for generalized EAR models (time-, age- and sex-specific), EAR was assumed to be invariant. So, for example, if the age- and sex-specific solid cancer rates for the population being considered are given (from published tabulations, such as [O8, O12, P19, S38, S83, W38]) by $\lambda(a,s)$, then, when using the generalized ERR model (14), the cancer rate following a dose $D$ incurred at age $e$ will be:

$$\lambda(a,s)\cdot\left[1+(\alpha\cdot D+\beta\cdot D^2)\cdot\exp[\kappa_1\cdot 1_{s=\,female}+\kappa_2\cdot\ln[a-e]+\kappa_3\cdot\ln[a]]\right] \quad (23)$$

whereas if the generalized EAR model (16) is being used, the cancer rate is:

$$\lambda(a,s)+(\alpha\cdot D+\beta\cdot D^2)\cdot\exp[\kappa_1\cdot\ln[a-e]+\kappa_2\cdot\ln[a]] \quad (24)$$

where again the underlying cancer or cancer mortality rate $\lambda(a,s)$ is estimated from the published tabulations [O8, O12, P19, S38, S83, W38].

### B. Lifetime risk estimates

567. Table 59 presents the risks for various models fitted to the solid cancer mortality data. Risks are calculated assuming a number of test doses—0.01, 0.1 or 1.0 Sv. There is not much variation in any of the risk measures by test dose for the linear models, but as would be expected for the linear–quadratic models, which exhibit upward curvature (table 59), risks (for all measures except YLLRIC) are somewhat less, by about 20% at low doses (0.01 Sv) compared with high doses (1.0 Sv). For the linear models in general, the reverse effect is observed, whereby risks per unit dose are slightly higher (by about 5%) at lower test doses (0.01 Sv) compared with higher test doses (1.0 Sv). This is a consequence of the saturation of the solid cancer induction curve as a function of dose.

568. Most measures of risk (all except YLLRIC) that are estimated for the generalized ERR model, which assumes only variation of ERR with age at exposure (as used in previous UNSCEAR risk evaluations [U2]), are somewhat higher than risks estimated for the other four models. For example, for the United Kingdom population, this model predicts a low-dose (test dose = 0.1 Sv) REID of 11.5% $Sv^{-1}$, compared with REID in the range 4.5–7.4% $Sv^{-1}$ for the other four models. This is because this model assumes that the RR is constant over time to the end of life, whereas the other four models predict an ERR that will decrease with increasing follow-up (from now onwards), particularly for the groups for which this assumption is most critical, namely those exposed in childhood. In general, most measures of risks are fairly similar for generalized EAR models and generalized ERR models, although there is a tendency for most measures of risk (all except YLLRIC) under the two EAR models to be somewhat lower than under any of the three generalized ERR models. For example, for the United Kingdom population, the two generalized EAR

models predict a value for low-dose (test dose = 0.1 Sv) REID of 4.5–6.9% $Sv^{-1}$, compared with REID in the range 5.3–11.5% $Sv^{-1}$ from the generalized ERR models.

569. Not too much should be made of the magnitude of variation of risk estimates between the various models, at least at high doses. Apart from the age-at-exposure model, for all populations at a test dose of 0.1 Sv, the estimated excess cancer deaths are 3.1–6.4% $Sv^{-1}$, REID is in the range 3.6–7.7% $Sv^{-1}$, YLL is in the range 0.5–1.1 years per sievert and YLLRIC is in the range 13.8–15.2 years.

570. Table 60 shows that, in general, the values for all four measures of risk for women are higher than for men, irrespective of the models used. For example, for the United Kingdom, the REID for men is in the range 4.1–8.7% $Sv^{-1}$, while for women the REID is in the range 4.9–14.2% $Sv^{-1}$.

571. Table 61 shows that, in general, the values for all measures of risk decrease with increasing age at exposure. For example, for the United Kingdom, the REID for persons exposed under the age of 10 is in the range 8.4–38.3% $Sv^{-1}$, but the REID rapidly decreases with age at exposure, so that for those exposed over the age of 70, the REID is in the range 0.5–2.2% $Sv^{-1}$. This also highlights the substantial uncertainties in relation to risk estimates for those exposed in childhood, which are greater because, at least in the LSS cohort, risk estimates for this age group are much more dependent on extrapolation to the end of life than they are for those exposed in adulthood. Of those exposed under the age of 10 in the LSS cohort, 92% are still alive, as are 87% of those aged between 10 and 20 at exposure [P10].

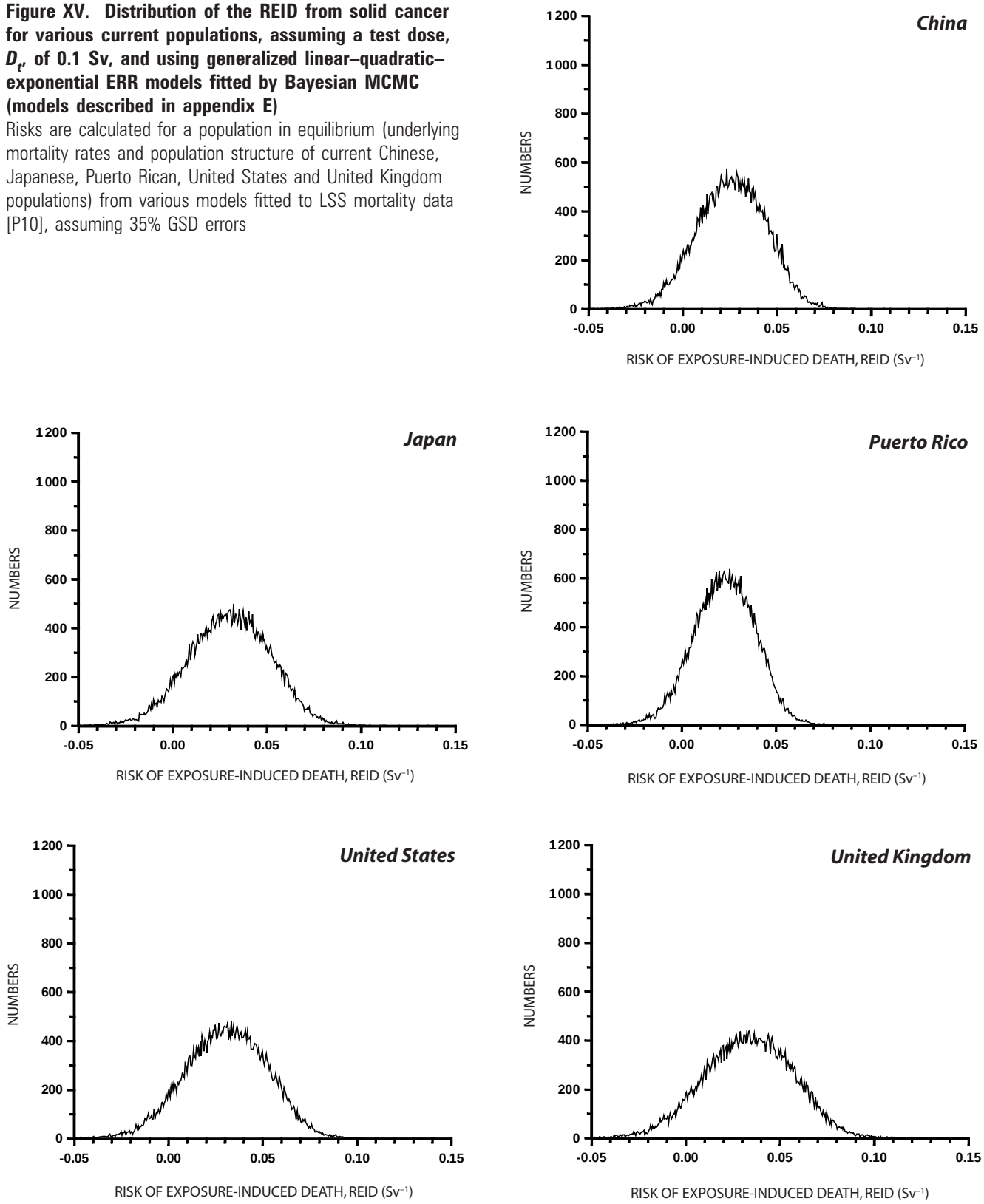
572. Table 62 demonstrates the difference made by use of the latest DS02 dosimetry, by the choice of risk models and by the period of fit for the risk models. The Committee has fitted models to data corresponding to the period 1950–2000, the full period of follow-up in the current mortality data [P10], as well as over 1950–1990, corresponding to the period available for the LSS mortality data [P1] evaluated in the UNSCEAR 2000 Report [U2]. For illustrative purposes, the Committee considers two linear generalized ERR risk models: one with adjustment to the ERR for age at exposure only (corresponding to one of the models used in the UNSCEAR 2000 Report [U2]); and one with adjustment to the ERR for attained age and time since exposure, which the Committee regards as more nearly optimal for the current follow-up (see table D1 in appendix D). The form of both models (if not the fitted parameter values) is described above, and also in table 45. As can be seen from table 62, in general, use of DS02 versus DS86 dosimetry leads to the REID value decreasing by 9.9–10.8%. For example, for the model of ERR with adjustment for age and years since exposure fitted for the period 1950–2000, the risk estimate decreases from 8.2% $Sv^{-1}$ with DS86 to 7.4% $Sv^{-1}$ with DS02, a reduction of 10.8%. Changing the interval over which models are fitted (1950–2000 versus 1950–1990) reduces the value for REID by 2.8–6.9%. For example, for the model of ERR with adjustment for age and time since exposure, using DS02 dose estimates and fitting for the period 1950–1990, the risk value is 7.6% $Sv^{-1}$, and over 1950–2000, the risk value is 7.4% $Sv^{-1}$, a reduction of 3.1%. The most substantial difference is made by the choice of risk model. The newer optimal model, with modification of ERR for age and time since exposure, generally predicts REID values of 35.8–38.3% lower than those predicted by the older model (with adjustment of ERR for age at exposure only). For example, using DS02 dose estimates and fitting over the period 1950–2000, the REID value calculated using the older model (adjusted for age at exposure) is 11.5% $Sv^{-1}$, while using the newer model (adjusted for age and years since exposure) it is 7.14% $Sv^{-1}$, a reduction of 35.8%.

573. Tables 63 and 64 and figures XV and XVI illustrate the distribution of risk predicted by the optimal linear–quadratic and linear–quadratic–exponential models fitted to the solid cancer mortality data using Bayesian techniques. For a United Kingdom population, using a test dose of 0.1 Sv, the mean REID value using the linear–quadratic–exponential model is 3.3% (90% CI: –0.6, 7.0) $Sv^{-1}$. However, when a higher test dose is used, risks increase appreciably for the linear–quadratic–exponential model: the REID value at 1 Sv is 7.1% (90% CI: 5.6, 8.7) $Sv^{-1}$. The reason for this can be seen from table E.1 in appendix E, which shows that the quadratic coefficient, $\beta$, is about four times larger than the linear coefficient, $\alpha$; the crossover value for the dose at which the linear and quadratic terms are of equal magnitude is 0.24 Sv. For a United Kingdom population, using a test dose of 0.1 Sv, the mean REID value using the linear–quadratic model is 5.4% (90% CI: 3.1, 8.0) $Sv^{-1}$. When a higher test dose of 1 Sv is used, the REID value increases to 6.7% (90% CI: 5.3, 8.1) $Sv^{-1}$, a figure very much in line with that predicted by the linear–quadratic –exponential model. The generally lower risk values produced by the linear–quadratic–exponential model (at least at low test doses) is perhaps remarkable, and is a result of the incorporation of an exponential term representing cell sterilization, $\exp[\gamma \cdot D]$, in the dose response, as detailed in Appendix E. Although the value for the cell sterilization coefficient, $\gamma$, is not statistically significant, its effect on the linear and quadratic coefficients is profound, resulting in the linear term becoming smaller (and generally not statistically significant) and the quadratic term becoming much larger (and generally statistically significant) (see table E.1). These effects are also observed in the fitting of similar models by maximum-likelihood techniques, which produce very similar central estimates of risk.

574. Table 65 presents the risk estimates using various models fitted to the leukaemia mortality data. As for solid cancers, risks are calculated assuming a number of test doses—0.01, 0.1 or 1.0 Sv. There is substantial variation with test dose in the values for all of the risk measures except YLLRIC; as would be expected, this variation is particularly marked for the purely quadratic models. Even for the linear–quadratic models, the risk values (for all measures except YLLRIC) are somewhat less, by about a factor

**Figure XV. Distribution of the REID from solid cancer for various current populations, assuming a test dose, $D_t$, of 0.1 Sv, and using generalized linear–quadratic–exponential ERR models fitted by Bayesian MCMC (models described in appendix E)**

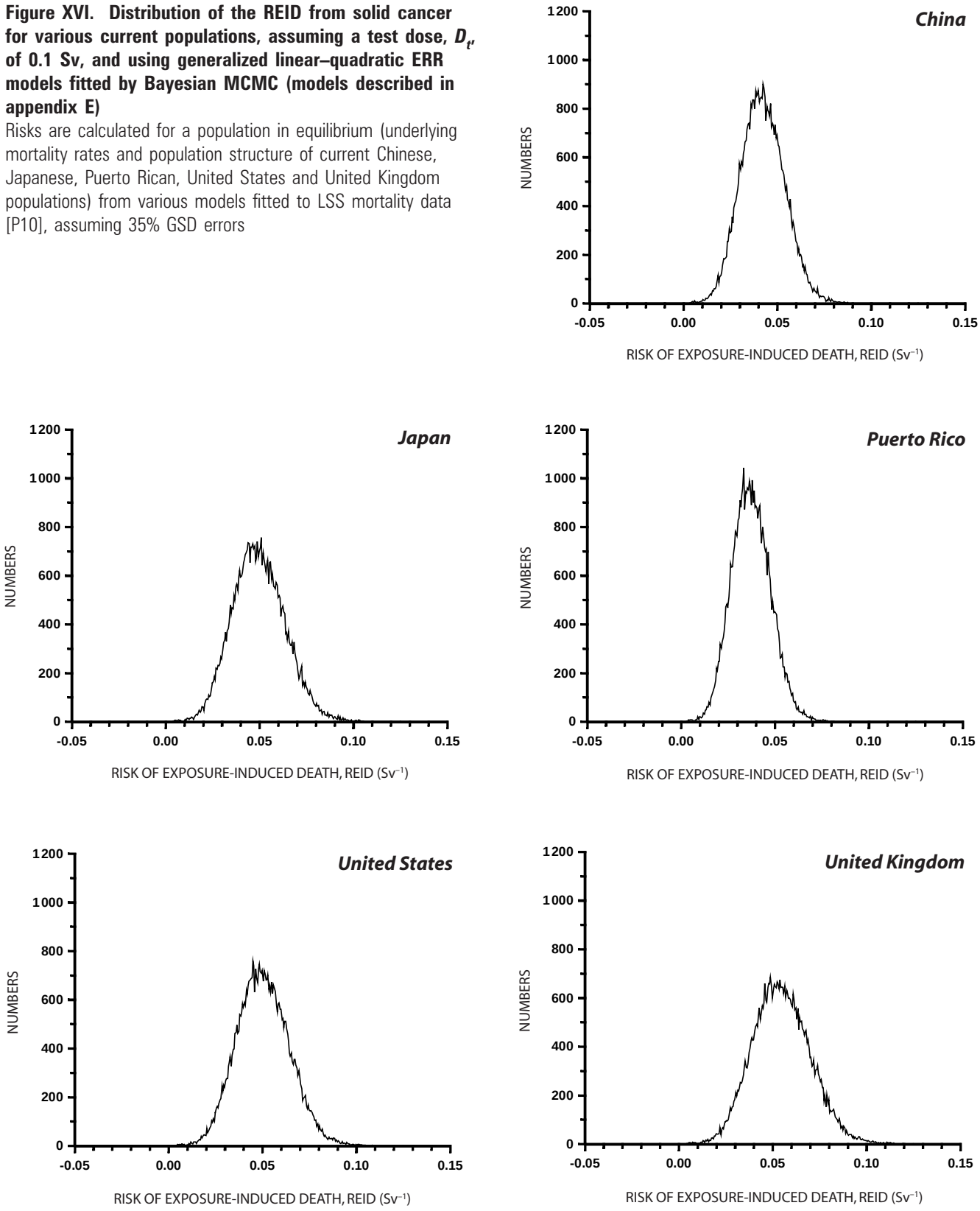
Risks are calculated for a population in equilibrium (underlying mortality rates and population structure of current Chinese, Japanese, Puerto Rican, United States and United Kingdom populations) from various models fitted to LSS mortality data [P10], assuming 35% GSD errors




of 2 at low doses (0.01 Sv) compared with those at high doses (1.0 Sv). For all measures of risk except YLLRIC, risks are generally slightly higher when generalized EAR models are employed than when generalized ERR models are employed. However, not too much should be made of the magnitude of variation of risk between the various models, at least at high doses. At a test dose of 1 Sv, when using the linear–quadratic models, the values for REID and excess leukaemia deaths for all five populations are in the range 0.4–1.0% $Sv^{-1}$, values for YLL are in the range 0.1–0.3 years per sievert and values for YLLRIC are between 18.8 and 38.8 years.

**Figure XVI. Distribution of the REID from solid cancer for various current populations, assuming a test dose, $D_t$, of 0.1 Sv, and using generalized linear–quadratic ERR models fitted by Bayesian MCMC (models described in appendix E)**

Risks are calculated for a population in equilibrium (underlying mortality rates and population structure of current Chinese, Japanese, Puerto Rican, United States and United Kingdom populations) from various models fitted to LSS mortality data [P10], assuming 35% GSD errors




575. Table 66 shows that, in general, values for all measures of leukaemia risk (except YLLRIC) are higher for men than for women, irrespective of the models used. For example, for the United Kingdom, the REID at 0.1 Sv for men is in the range 0.08–0.58% $Sv^{-1}$, while for women it is in the range 0.05–0.35% $Sv^{-1}$.

576. Table 67 shows that, in general, values for all measures of leukaemia risk decrease with increasing age at exposure. For example, for the United Kingdom, the REID for persons exposed under the age of 10 (calculated using the linear–quadratic models) is in the range 0.70–0.74% $Sv^{-1}$, but the REID rapidly decreases with increasing age at

exposure, so that for those exposed over the age of 70, the REID is in the range 0.16–0.17% $Sv^{-1}$.

577. Tables 68 and 69 and figures XVII and XVIII illustrate the distribution of risk predicted by the optimal linear–quadratic and linear–quadratic–exponential models fitted to the leukaemia mortality data using Bayesian techniques. For a United Kingdom population, using a test dose of 0.1 Sv, the mean REID value using the linear–quadratic–exponential model is 0.19% (90% CI: –0.27, 0.81) $Sv^{-1}$. However, when a higher test dose is used, risks increase appreciably: the REID value at 1 Sv is 1.28% (90% CI: 0.85, 1.84) $Sv^{-1}$. The reason for this can be seen from table E.1 in appendix E, which shows that the quadratic coefficient, $\beta$, is positive and the linear coefficient, $\alpha$, negative and much smaller in absolute value. The crossover value for the dose at which the linear and quadratic terms are of equal magnitude is about 0.02 Sv. For a United Kingdom population, using a test dose of 0.1 Sv, the mean value for REID using the linear–quadratic model is 0.58% (90% CI: 0.13, 1.15) $Sv^{-1}$. When a higher test dose of 1 Sv is used, the value for REID increases to 1.14% (90% CI: 0.74, 1.73) $Sv^{-1}$, a figure very much in line with that predicted by the linear–quadratic–exponential model. The slightly lower risk values produced by the linear–quadratic–exponential model (at least at low test doses) is perhaps remarkable, and is a result of the incorporation of an exponential cell sterilization term, $\exp[\gamma \cdot D]$, in the dose response, as detailed in appendix E. Although the value for the cell sterilization coefficient, $\gamma$, is not statistically significant, its effect on the linear and quadratic coefficients is profound, resulting in the linear term becoming smaller, indeed even negative (but generally not statistically significantly different from zero) and the quadratic term becoming much larger (and generally statistically significant) (see table E.1). These effects are also observed in the fitting of similar models using maximum-likelihood techniques, which produce very similar central estimates of risk.

578. Crucial to determining which of these sets of Bayesian risk estimates is best—those using the linear–quadratic–exponential or those employing the linear–quadratic models—is not straightforward, and it is not simply a statistical question. One justification for fitting a linear–quadratic–exponential model is that it allows more flexibility in the shape of the dose response. Because there are indications of a reduction in cancer risk at high doses in both the solid cancer and the leukaemia dose response in the LSS data (see figures VII and IX), arguably this flexibility is necessary. Both models are plausible from a radiobiological point of view, and the estimates derived for the cell sterilization term, $\delta$, of –0.41 $Sv^{-1}$ for solid cancers and –0.47 $Sv^{-1}$ for leukaemia (appendix E, table E1) are not inconsistent with experimentally derived "inactivation" coefficients. For a variety of fibroblastic and other human cell lines, these range from –1.72 to –0.30 $Gy^{-1}$, with a median of –0.65 $Gy^{-1}$ [D54]. Growth-factor-stimulated CD34+ cells (haemopoietic stem cells) have inactivation coefficients of between –2.44 $Gy^{-1}$ and –0.45 $Gy^{-1}$ [Z12]. Although cell sterilization is biologically plausible, its effect may be largely negated by cellular repopulation after radiation exposure. Crucial to determining risk is the balance between repopulation in normal stem cells and in pre-initiated cells [S84]. There are indications of relatively efficient repopulation of cells in damaged tissue for certain solid cancers [S84], although perhaps rather less for leukaemia [L91].

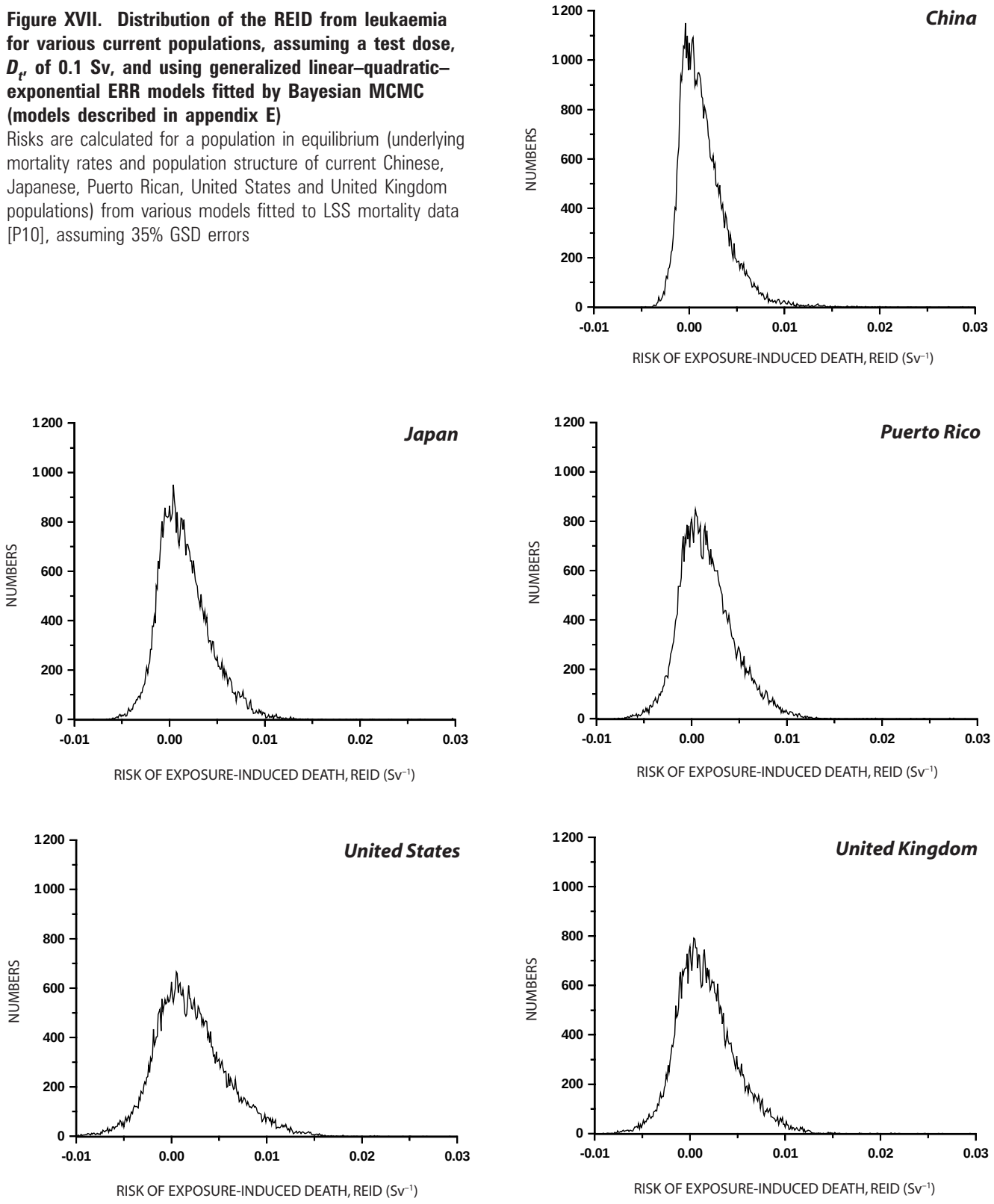
579. Table 70 presents risks of solid cancer (REIC) for the five populations being considered. Risks are calculated assuming a number of test doses—0.01, 0.1 or 1.0 Sv. For most cancer sites, there is not much variation in any of the risk measures by test dose. The only exceptions to this are for the sites that one would expect, i.e. bone cancer and non-melanoma skin cancer, for both of which non-linear dose–response relationships are assumed (see tables 52 and 53). For these two sites, the risks per unit dose strongly increase with increasing test dose. On aggregate, values of REIC per unit dose do not vary much with test dose. For example, for the United Kingdom, the values for REIC range between 15.7 and 23.1% per sievert for the generalized ERR models, and between 10.8 and 11.8% $Sv^{-1}$ for the generalized EAR models, for test doses between 0.01 Sv and 1.0 Sv. The value for non-melanoma skin cancer accounts for the somewhat larger risk values for the United Kingdom and United States than for the other populations at high test doses (1 Sv). At low to moderate doses (0.01 Sv, 0.1 Sv), it contributes much less (a consequence of the quadratic–exponential dose response assumed), and indeed for these dose levels, the United Kingdom and United States risk values are on aggregate much more in line with those for the other three populations.

580. The choice of risk model (generalized ERR versus generalized EAR) has somewhat greater impact depending on the cancer sites and population considered. For the United States and the United Kingdom, REICs can vary by an order of magnitude or more for sites such as stomach cancer and non-melanoma skin cancer (table 70). However, the aggregate REIC does not vary by as much as this. The variation is most substantial for the United States and the United Kingdom, where, as indicated above, the aggregate REIC value may differ by a factor of 2 for the two sets of models. For other populations, the REIC values predicted by the two sets of models (generalized ERR and generalized EAR) are generally within 20% of each other.

581. Table 71 shows that, in general, for all five populations, the aggregate REICs for women are higher than for men, irrespective of the models used. These differences between the REIC for each sex are most marked for the United States and the United Kingdom. For example, for the United Kingdom, the REIC for men is in the range 8.6–12.9% $Sv^{-1}$, while for women it is in the range 14.8–20.8% $Sv^{-1}$. However, for certain solid cancer sites and models, the reverse situation is true. For example, risk values for stomach cancer using the generalized ERR model are higher for men than for women in all five populations, although using the generalized EAR models the reverse is the case.

**Figure XVII. Distribution of the REID from leukaemia for various current populations, assuming a test dose, $D_t$, of 0.1 Sv, and using generalized linear–quadratic–exponential ERR models fitted by Bayesian MCMC (models described in appendix E)**

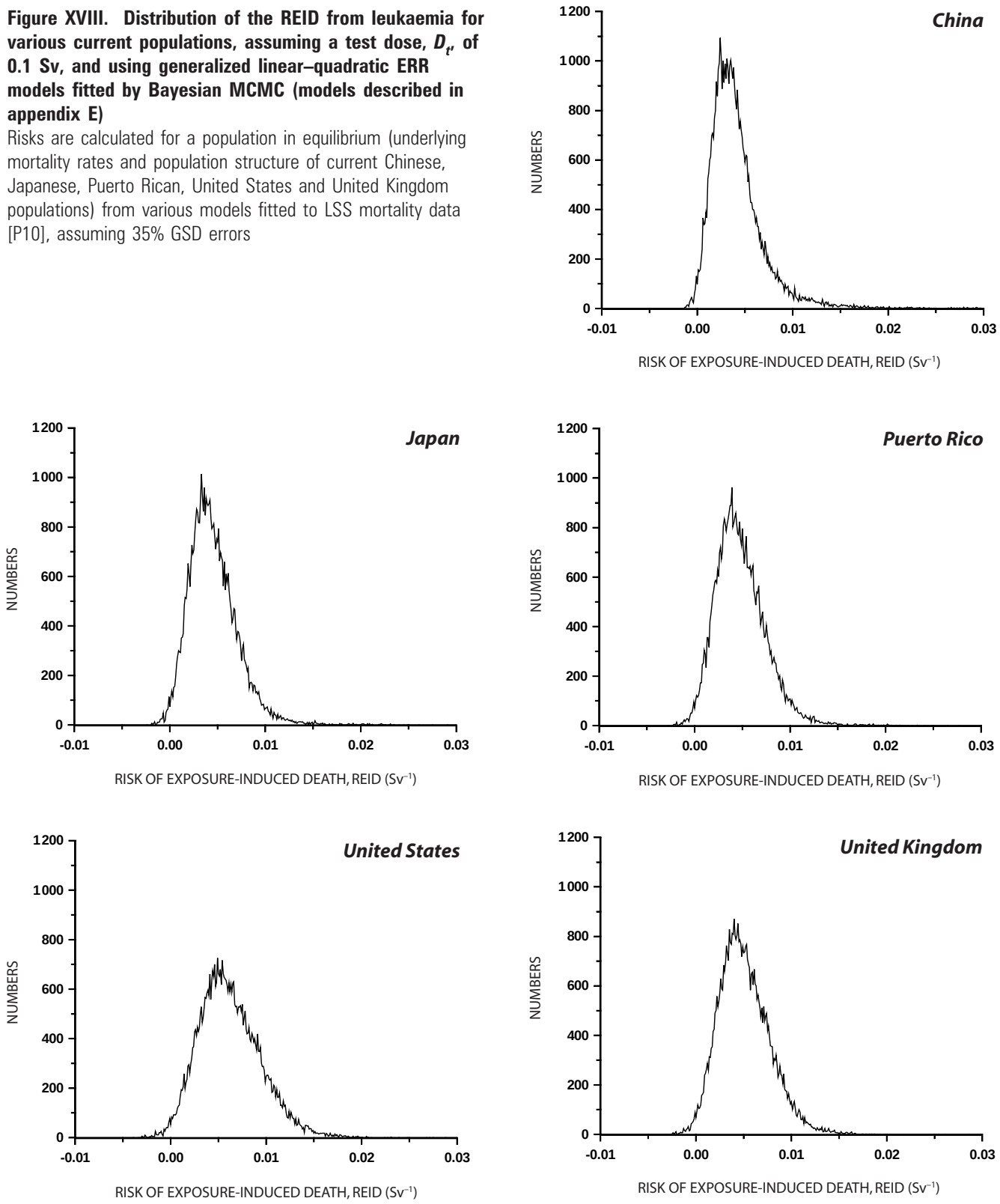
Risks are calculated for a population in equilibrium (underlying mortality rates and population structure of current Chinese, Japanese, Puerto Rican, United States and United Kingdom populations) from various models fitted to LSS mortality data [P10], assuming 35% GSD errors




582. Table 72 presents the mortality risks calculated here against some previous estimates of risk, for all four measures of risk employed. As can be seen, the solid cancer risk estimates (particularly excess cancer deaths, REID) are generally somewhat lower, by factors of up to 2, compared with some previous estimates; this is true irrespective of the population considered or the assumed test dose. For example, for a United Kingdom population, this report estimates a value for REID at 0.1 Sv of 3.3–5.4% $Sv^{-1}$ (depending on the projection/transfer model used), whereas the UNSCEAR 2000 Report [U2] estimated a value for a similar population of 7.9–14.4% $Sv^{-1}$ (again depending on the projection/transfer model used) (table 72).

**Figure XVIII. Distribution of the REID from leukaemia for various current populations, assuming a test dose, $D_t$, of 0.1 Sv, and using generalized linear–quadratic ERR models fitted by Bayesian MCMC (models described in appendix E)**

Risks are calculated for a population in equilibrium (underlying mortality rates and population structure of current Chinese, Japanese, Puerto Rican, United States and United Kingdom populations) from various models fitted to LSS mortality data [P10], assuming 35% GSD errors




583. For a United States population, the Committee estimates a value for REID at 0.1 Sv of 3.0–5.0% $Sv^{-1}$ (depending on the projection/transfer model used), whereas the recent BEIR VII report estimates a value at this dose of 7.4% (95% CI: 3.7, 15.0) $Sv^{-1}$ [C37] (table 72). A possible reason for this slight discrepancy is that BEIR VII assumed an adjustment to the ERR and EAR that was proportional to a power of attained age and an exponential function of min (age at exposure, 30), i.e. the variation of ERR or EAR with exposure age disappears above age 30 (see appendix D for more details). As shown in appendix D, there is no strong evidence from the LSS data for such a discontinuity in adjustment for age at exposure. The result of assuming such a variation of ERR or EAR would

be to inflate risks for those exposed above this age. However, one should not overemphasize this discrepancy in view of the other uncertainties, as implied by the uncertainty interval for the BEIR estimate, as well as by the uncertainty interval for the Bayesian risk calculations performed here.

584. Leukaemia risk estimates are more similar, although even in this case the risks estimated here tend to be smaller than previous estimates, by 20–30% (but in some cases by much more than this). For example, for a United Kingdom population, this report estimates a value for REID at 1.0 Sv of 0.8–0.9% $Sv^{-1}$ (depending on the projection/transfer model used), whereas the UNSCEAR 2000 Report estimated a value for a similar population and dose of 1.0% $Sv^{-1}$ (table 72). For a United States population, this report estimates a value for REID at 0.1 Sv of 0.2–0.7% $Sv^{-1}$, whereas the recent BEIR VII report estimates a value at this dose of 0.6 % $Sv^{-1}$ [C37] (table 72).

585. Table 73 presents the risks of solid cancer (REIC) calculated here against some previous estimates of risk. As can be seen, aggregate values for solid cancer REIC are generally similar to those previously estimated, although there is a substantial spread in the risk estimates, depending on the projection/transfer model used. For example, for a United Kingdom population, this report estimates an aggregate value for REIC at 1.0 Sv of 10.8–23.1% $Sv^{-1}$ (depending on the projection/transfer model used), whereas the UNSCEAR 2000 Report estimated an aggregate value of 17.0–19.3% $Sv^{-1}$ (again depending on the projection/transfer model used). For a United States population, this report estimates an aggregate value for REIC at 0.1 Sv of 11.6–24.1% $Sv^{-1}$ (depending on the projection/transfer model used), whereas the recent BEIR VII report estimates a value at this dose of 16.9–18.6% $Sv^{-1}$ (depending on the projection/transfer model used) [C37] (tables 70 and 73). It may be thought remarkable that risks of solid cancer are not vastly dissimilar from those assessed in the UNSCEAR 2000 Report [U2], in contrast to the much lower mortality risks compared with those previously derived. However, as shown by the analysis of table 62, a major part of the reduction in the risk estimates for solid cancer mortality is driven by the use of different optimal risk models, with a much smaller part of the reduction due to alterations in the interval for follow-up and to changes in dosimetry. Models for solid cancer incidence are generally of a different form from models for solid cancer mortality, and much more heterogeneous, as can be seen from tables 45 and 47–58, so it is not unexpected that they should produce changes in risk values of the same magnitude.

586. The risk estimates derived here using linear models are nominally exposure risks for high dose rates, and take no account of possible effects due to dose rate or fractionation. As discussed in section I.J (see also table 8), a DDREF of about 2 may be applied to obtain cancer risks at low doses and low dose rates. However, those models in which a linear–quadratic or more general (linear–quadratic–exponential) dose response is assumed (in particular the Bayesian MCMC model fits) implicitly take account of extrapolation of dose (if not dose rate), so that to some extent they take account of DDREF. As can be seen from tables 59, 63 and 64, these models predict solid cancer mortality risks (REID) per unit dose at high dose (1 Sv) that are between 20% and 185% larger than those at low doses (0.01 Sv). Likewise it is seen from tables 65, 68 and 69 that the leukaemia mortality risks (REID) per unit dose at high dose (1 Sv) are at least 100% larger than those at low doses (0.01 Sv).

# CONCLUSIONS

587. Since the Committee's assessment of the risks of radiation-induced cancer in the UNSCEAR 2000 Report [U2], more information has become available from epidemiological studies of radiation-exposed groups. There have been substantive updates to the follow-up of the survivors of the atomic bombings at Hiroshima and Nagasaki, both for solid cancer morbidity [P48] and for all cancer mortality [P10]; both of these reports incorporate the recently revised (DS02) dose estimates [R12]. The latest mortality analysis [P10] extended follow-up of the LSS cohort another 10 years, to the end of 2000, from the 1990 follow-up available in the previous report [P1]. As of December 2000, 45% of the cohort of 86,611 survivors were still alive. Out of the 10,127 deaths due to solid cancer, some 479 would be estimated to be associated with the radiation exposure incurred from either bomb detonation; and some 93 leukaemia deaths out of 296 would be estimated to be associated with radiation exposure [P10]. Analyses of the RERF epidemiological data using the new DS02 dosimetry indicate that values for cancer risk factors might decrease by about 8% as a result, with no appreciable change in the shape of the dose response or in the age–time patterns of excess risk [P10]. The reanalysis of the solid cancer incidence data using the DS02 dosimetry [P48] extends the follow-up to 1998 from 1994 (the year to which data had previously been followed up [P12]), resulting in a total of 18,645 cases of cancer, 13,454 of these within 10 km of either hypocentre at the time of the bombings and with a DS02 dose estimate. It is sometimes forgotten that, despite the high doses received by some survivors (in excess of 4 Sv), this is fundamentally a moderate dose cohort, for which the average colon dose is about 0.21 Sv.

588. Both these studies and further follow-up of patients who were medically exposed to radiation have provided additional data on cancer risks at long times after 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. For example, 92% of those exposed under the age of 10 in the LSS are still alive, as are 87% of those aged between 10 and 20 at exposure [P10].

589. The increased statistical precision associated with the longer follow-up and the resulting larger number of cancer cases observed in the above studies have also been useful in the examination of dose–response relationships, particularly at lower doses. For example, the most recent data for the survivors of the atomic bombings 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 survivors of the atomic bombings should hopefully provide more information at low doses. However, epidemiology alone will not be able to resolve the issue of whether there are dose thresholds for risk. In particular, the inability to detect increased risk at very low doses using epidemiological methods does not mean that the underlying cancer risks are not elevated. However, the high-dose radiotherapy studies of patients indicate that, for some cancers, e.g. bone, connective tissue, rectum, uterus and small intestine, any risks at doses of below several grays, if they exist, are small.

590. New findings have also been published from analyses of fractionated or chronic low-dose exposure to low-LET radiation, in particular the IARC 15-country nuclear worker study [C41] (although the statistical precision of these studies is low in comparison with the results from the survivors of the atomic bombings, exposed at high dose rates). There have also been major new analyses of the Techa River [K49, K50] and Semipalatinsk [B58] data sets. As noted in section II.E, there are concerns about bias in all three studies, which may explain why solid cancer risks are substantially elevated in comparison with those seen in the LSS cohort, although at least for the 15-country and Techa River studies, the confidence intervals for the risk estimates are wide [C41, K50] and overlap with findings from the studies of the survivors of the atomic bombings. However, these studies are potentially informative about risks following chronic exposure to moderate doses, once the various problems can be resolved. Further work to improve dosimetry and follow-up in all three cohorts would improve the interpretation of the studies' findings.

591. Particular attention has been paid in this report to risks for specific cancer sites. Again, the information that has become available in recent years has helped in the examination of risks. Risks have been assessed for cancer of the salivary gland, oesophagus, stomach, small intestine (including duodenum), colon, rectum, liver, pancreas, lung, bone and connective tissue, female breast, uterus, ovary, prostate, urinary bladder, kidney, brain and central nervous system, and thyroid, as well as for cutaneous melanoma, non-melanoma skin cancer, non-Hodgkin's lymphoma, Hodgkin's disease,

multiple myeloma and leukaemia. Of these, cancers of the salivary gland, small intestine, rectum, pancreas, uterus, ovary and kidney, as well as cutaneous melanoma, were not considered in the UNSCEAR 2000 Report [U2]. 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 sex. 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 between populations. An exception is breast cancer, where a comparison of data on the survivors of the atomic bombings and on women with medical exposures in North America indicates 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. chronic lymphocytic leukaemia, pancreatic cancer, prostate cancer, cervical cancer, testicular cancer, uterine cancer, non-Hodgkin's lymphoma, Hodgkin's disease and multiple myeloma), and others where excess risks have only been seen following very high (radiotherapeutic) doses (e.g. cancers of the small intestine, rectum, uterus and kidney). 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. Despite the statistical problems posed by considering particular cancer sites, there are indications of differences in the shape of dose response; in particular, the more substantial upward curvature in the dose response for bone cancer, non-melanoma skin cancer and leukaemia should be noted.

592. The results presented in tables 59–73 illustrate the sensitivity of the lifetime risk estimates to variations in underlying rates. These findings suggest that this variability can lead to differences that are comparable with the variations associated with the transfer method or method of risk projection. Issues of uncertainty in lifetime risk estimates are discussed in more detail in Report No. 126 of the National Council on Radiation Protection and Measurements [N17] and in the recent BEIR VII report [C37]. 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.

593. Despite these difficulties, risk estimates are of considerable value for use in characterizing the health impact of exposure of a population to radiation. In the UNSCEAR 2000 Report [U2], models with variation of relative risk according to age at exposure or attained age were emphasized for risk projection purposes. With the increased follow-up, it has become clear that those models do not fit well. The preferred models for solid cancer mortality imply that relative or absolute excess risk is proportional to a product of powers of the time since exposure and attained age, with linear, linear–quadratic or linear–quadratic–exponential dose response. The preferred models for leukaemia mortality imply that relative excess risk is proportional to a power of the attained age, and that absolute excess risk is proportional to a power of the time since exposure, with in both cases a linear–quadratic or linear–quadratic–exponential dose response. When these models are applied to any of five specific populations (China, Japan, Puerto Rico, United States or United Kingdom) of all ages, the lifetime risk of exposure-induced death due to all solid cancers combined following an acute dose of 0.1 Sv is estimated to be about 3.6–7.7% $Sv^{-1}$ averaged over both sexes, and at 1 Sv the risk is about 4.3–7.2% $Sv^{-1}$. When Bayesian models are used, the range of mean risks is 2.3–5.4% $Sv^{-1}$ following an acute dose of 0.1 Sv, and at 1 Sv the mean risk range is 4.6–7.1% $Sv^{-1}$. Leukaemia mortality risks at a dose of 0.1 Sv are estimated to be about 0.3–0.5% $Sv^{-1}$ averaged over both sexes, and at 1 Sv the risk is 0.6–1.0% $Sv^{-1}$. When Bayesian models are used, the range of mean risks is 0.2–0.7% $Sv^{-1}$ following an acute dose of 0.1 Sv, and at 1 Sv the mean risk range is 1.1–1.5% $Sv^{-1}$. The calculations in this report show that these values can vary for different populations and with different risk models. These cancer risk estimates are somewhat lower, although not much lower, than those previously estimated by UNSCEAR [U2], as well as those previously estimated by other bodies, e.g. [C35, C37]. A reduction of about 10% in the solid cancer risk estimate may be due to the new atomic bombings dosimetry, and a relatively small reduction of 3–7% may be due to increased follow-up [P10]. However, there is a relatively large reduction of 35–40% due to the different risk projection and transfer models used. The statistical uncertainties in the above estimates may be of the order of a factor of 2 higher, and the lower bounds include zero. These estimates, particularly those based on linear–quadratic or linear–quadratic–exponential models, implicitly adjust for extrapolation to low doses, so that no extra adjustment for chronic exposure (i.e. application of a DDREF) is needed. Values of DDREF of about 2, recommended by others [I11], are consistent with the dose protraction effects predicted by these models and with a large body of epidemiological and experimental data. Lifetime solid cancer risk estimates for those exposed as children might be factors of 2–3 times higher than the estimates for the general population. For certain cancer sites (e.g. thyroid and breast), the variation of risk with age at exposure would be expected to be greater than implied by this. Continued follow-up of existing irradiated cohorts will be important in determining lifetime risks. The experience of studies of the survivors of the atomic bombings 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 of risk following an acute dose of 1 Sv 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 2000 Report [U2].

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# TABLES

**Table 1 Lung cancer risks associated with cigarette smoking and radiation exposure for the survivors of the atomic bombings in Japan** [P17]

| *Relative risk due to cigarette smoking*[a] | | | *Relative risk due to radiation exposure*[b] |
|---|---|---|---|
| 1–15 cigarettes per day | 16–25 cigarettes per day | >25 cigarettes per day | 1 Sv |
| 4.9 | 8 | 13.3 | 2.2 |

[a] Relative risk adjusted for radiation exposure, age at exposure 30, attained age 60–70.
[b] Relative risk adjusted for smoking, attained age 60–70.

**Table 2 Illustrative scenarios showing the impact of dose level on the width of the confidence interval**
The scenarios assume two groups (one exposed, one unexposed) and an ERR of 1 $Gy^{-1}$

| *Scenario* | *Dose (Gy)* | *Total number of cancer cases* | *Proportion of person-years in exposed group (%)* | *Cancers expected in each group*[a] | | *Estimated*[b] *ERR (95% CI)*[c] *($Gy^{-1}$)* |
|---|---|---|---|---|---|---|
| | | | | *Exposed* | *Unexposed* | |
| A | 1 | 50 | 50 | 33 | 17 | 0.94 (0.10, 2.56) |
| B | 1 | 100 | 50 | 67 | 33 | 1.03 (0.35, 2.12) |
| C | 1 | 200 | 50 | 133 | 67 | 0.99 (0.49, 1.68) |
| D | 1 | 400 | 50 | 267 | 133 | 1.01 (0.63, 1.48) |
| E | 1 | 800 | 50 | 533 | 267 | 1.00 (0.73, 1.32) |
| F | 0.05 | 50 | 50 | 26 | 24 | 1.67 (–7.58, 17.95) |
| G | 0.05 | 100 | 50 | 51 | 49 | 0.82 (–5.95, 10.86) |
| H | 0.05 | 200 | 50 | 102 | 98 | 0.82 (–4.23, 7.49) |
| I | 0.05 | 400 | 50 | 205 | 195 | 1.03 (–2.72, 5.59) |
| J | 0.05 | 800 | 50 | 410 | 390 | 1.03 (–1.70, 4.16) |
| K | 1 | 50 | 10 | 9 | 41 | 0.98 (–0.10, 2.88) |
| L | 1 | 100 | 10 | 18 | 82 | 0.98 (0.15, 2.21) |
| M | 1 | 200 | 10 | 36 | 164 | 0.98 (0.36, 1.80) |
| N | 1 | 400 | 10 | 73 | 327 | 1.01 (0.55, 1.57) |
| O | 1 | 800 | 10 | 145 | 655 | 0.99 (0.66, 1.38) |
| P | 0.05 | 50 | 10 | 5 | 45 | 0.00 (–13.07, 25.77) |
| Q | 0.05 | 100 | 10 | 10 | 90 | 0.00 (–10.24, 16.55) |
| R | 0.05 | 200 | 10 | 21 | 179 | 1.12 (–6.95, 12.38) |
| S | 0.05 | 400 | 10 | 42 | 358 | 1.12 (–4.88, 8.71) |
| T | 0.05 | 800 | 10 | 84 | 716 | 1.12 (–3.27, 6.30) |

[a] Assumed to be distributed according to the underlying ERR and to the distribution of person-years, rounded to the nearest whole number.
[b] Maximum-likelihood value.
[c] Profile-likelihood-based confidence intervals.

**Table 3 Probabilities of various numbers of statistically significant results occurring by chance when various numbers of independent comparisons are made**

| *Number of statistically significant results (at $p = 0.05$)* | *Number of independent comparisons or tests made* | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 100 |
| 1 | 20.4% | 31.5% | 36.6% | 37.7% | 33.9% | 27.1% | 20.2% | 3.1% |
| 2 | 2.1% | 7.5% | 13.5% | 18.9% | 25.9% | 27.8% | 26.1% | 8.1% |
| 3 | 0.1% | 1.0% | 3.1% | 6.0% | 12.7% | 18.5% | 22.0% | 14.0% |
| 4 | 0.0% | 0.1% | 0.5% | 1.3% | 4.5% | 9.0% | 13.6% | 17.8% |
| 5 | 0.0% | 0.0% | 0.1% | 0.2% | 1.2% | 3.4% | 6.6% | 18.0% |
| 6 | – | 0.0% | 0.0% | 0.0% | 0.3% | 1.0% | 2.6% | 15.0% |
| Probability of 1 or more | 22.6% | 40.1% | 53.7% | 64.2% | 78.5% | 87.1% | 92.3% | 99.4% |
| Probability of 2 or more | 2.3% | 8.6% | 17.1% | 26.4% | 44.6% | 60.1% | 72.1% | 96.3% |

**Table 4 Excess relative risk of a second cancer occurring, according to whether or not the patient has another condition (bilateral retinoblastoma, a cancer-prone disorder)** [L9]

| *Second cancer* | *Study* | *First condition* | *ERR estimate (95% CI) ($Gy^{-1}$)* |
|---|---|---|---|
| Bone | [T10] | First cancer | |
| | | Non-retinoblastoma | 0.08 (0.02, 0.26) |
| | | Retinoblastoma | 0.05 (0.00, 0.27) |
| | | Total | 0.08 (0.03, 0.18) |
| Brain | [L24] | Cancer-prone disorder | |
| | | No | 0.28 (0.05, 1.40) |
| | | Yes | –0.01 (–0.04, 0.08)[a] |
| | | Total | 0.19 (0.03, 0.85) |

[a] Wald-based CI (likelihood bounds did not converge).

**Table 5 Multiplier of the risk of a second cancer occurring after treatment with radiotherapy for a first cancer, according to whether the first cancer is heritable or non-heritable retinoblastoma** [L9, W11]

| *First cancer* | *Treatment* | *Observed* | *Expected* | *Observed/Expected* | *Multiplier of radiosensitivity in heritable radioblastoma group = $\theta$* |
|---|---|---|---|---|---|
| Non-heritable retinoblastoma | Unirradiated | 6 | 4.48 | 1.3 (0.5, 2.9) | n.a. |
| | Irradiated | 3 | 1.11 | 2.7 (0.6, 7.9) | |
| Heritable retinoblastoma | Unirradiated | 10 | 1.37 | 7.3 (3.5, 13.4) | 1.62 (0.70, >10 000) |
| | Irradiated | 180 | 4.91 | 36.7 (31.6, 42.5) | |

**Table 6 Criteria for defining the low dose range for assessing cancer risks due to low-LET radiation exposure**

| *Source* | *Basis of estimation* | *Upper value of low dose range (mGy)* |
|---|---|---|
| UNSCEAR 1993 Report [U5] | Linear term dominant in fits to LSS data | 200 |
| UNSCEAR 2000 Report [U2] | Linear term dominant in fits to LSS data | 200 |
| UNSCEAR 2000 Report [U2] | Linear term dominant in fits to peripheral blood lymphocyte chromosome aberration data | 20–40 |
| UNSCEAR 2000 Report [U2] | Microdosimetric analysis of multitrack coincidences | 0.8 |
| BEIR VII report [C37] | – | 100 |
| This report | Linear term dominant in fits to LSS data | 100 |

**Table 7 Criteria for defining the range for low dose rates for assessing cancer risks due to low-LET radiation exposure**

| *Source* | *Basis of estimation* | *Upper value of range of low dose rate (mGy/min)* |
|---|---|---|
| UNSCEAR 1986 Report [U7] | Data from dose-rate studies with experimental animals | 0.05 |
| UNSCEAR 1993 Report [U5] | Data from dose-rate studies with experimental animals and other biophysical data | 0.1[a] |
| UNSCEAR 2000 Report [U2] | Data from dose-rate studies with experimental animals | 0.06 |
| UNSCEAR 2000 Report [U2] | Microdosimetric analysis of multitrack coincidences, based on lifetime exposure of cell and no repair | $10^{-8}$ |
| UNSCEAR 2000 Report [U2] | Microdosimetric analysis of multitrack coincidences, assuming DNA repair | $10^{-3}$ |
| BEIR VII report [C37] | – | 0.01 |

[a] Averaged over about an hour.

**Table 8 Values of dose and dose-rate effectiveness factors (DDREFs) used to assess cancer risks due to low-LET radiation exposure**

| *Source* | *Basis of estimation* | *DDREF (95% CI)* |
|---|---|---|
| ICRP [I11] | Mainly LSS and other epidemiological data | 2 |
| UNSCEAR 1993 Report [U5] | Data from dose-rate studies with experimental animals and other biophysical data | <3 |
| Pierce and Vaeth [P11] | LSS leukaemia mortality data | 1.8 (1.0, 6.0)[a] |
| | LSS solid cancer mortality data | 1.2 (<1, 3.4)[a] |
| Little and Muirhead [L37] | LSS leukaemia incidence data fitted to 0–4 Gy | 2.47 (1.24, >1 000)[a] |
| | LSS leukaemia incidence data fitted to 0–2 Gy | 1.73 (<1, 147.67)[a] |
| | LSS solid cancer incidence data fitted to 0–4 Gy | 1.06 (<1, 1.62)[a] |
| | LSS solid cancer incidence data fitted to 0–2 Gy | 1.21 (<1, 2.45)[a] |
| BEIR VII report [C37] | Estimates of curvature from selected data on tumours and lifespan shortening in experimental animals, data on chromosomal aberrations in human lymphocytes, and LSS solid cancer incidence data | 1.5 (1.1, 2.3) |

[a] Low-dose extrapolation factor, representing the ratio of the linear dose coefficient in the fit of a linear model and the linear dose coefficient in the fit of a linear–quadratic model.

**Table 9 Excess relative risks of lung cancer in moderate- and low-dose-rate radiation therapy studies and in matched subsets of the survivors of the atomic bombings in Japan** [L20]

Subsets are matched for sex, age at exposure and years of follow-up; values with 95% CI

| *Study* | *Nature of exposure* | *End point* | *Age at exposure (years)* | *Follow-up (years)* | *Average dose (and range) (Sv)* | *Cases or deaths* | *LSS cases or deaths* | *ERR estimate ($Sv^{-1}$)* | *LSS ERR estimate ($Sv^{-1}$)* |
|---|---|---|---|---|---|---|---|---|---|
| [M3] | 170–175 kVp therapeutic X-rays; small number of high-dose-rate fractions | Cancer | 8–74 (median 40) | 5–61 (mean 27) | 0.75 (0.00–8.98) | 19 | 364 | 0.38 (<0, 0.60) | 1.85 (1.14, 2.75)[a, e] |
| [D4] | Repeated chest fluoroscopy (90 kVp X-rays) in many low-dose fractions (each of about 10 mGy) | Mortality | <24–>38 (mean 33) | 0–50 (mean 25) | 0.84 (0.0–>8) | 69 | 936 | –0.16 (–0.32, 0.08)[b] | 0.59 (0.33, 0.91)[c, e] |
| [G6] | Mostly 200–250 kVp X-rays in a small number of moderate-dose fractions | Mortality | <35–>55 (mean 49) | 1–51 (mean 21.5) | 1.17(0–1.17) | 162 | 750 | 0.60 (0.17, 1.20) | 0.69 (0.37, 1.09)[d] |
| [H7] | Repeated chest fluoroscopy (90 kVp X-rays) in many low-dose fractions(each of about 10 mGy) | Mortality | <10–>50 (mean 28) | 10–57 (mean 37) | 1.02 (0–24.2) | 1 178 | 936 | 0.00 (–0.06, 0.07) | 0.59 (0.33, 0.91)[c, e] |

[a] Calculation based on lung dose, females.
[b] Calculation incorporates adjustment to underlying rate for age at exposure (<30 versus >30).
[c] Calculation based on lung dose.
[d] Calculation based on lung dose, age at exposure >30 years.
[e] LSS and radiation therapy ERR statistically inconsistent ($p < 0.001$).

**Table 10 Excess relative risks of breast cancer in moderate- and low-dose-rate radiation therapy studies and in matched subsets of the survivors of the atomic bombings in Japan** [L20]

Subsets are matched for sex, age at exposure and years of follow-up; ERR estimates with 95% CI

| *Study* | *Nature of exposure* | *End point* | *Age at exposure (years)* | *Follow-up (years)* | *Average dose (and range) (Sv)* | *Cases or deaths* | *LSS cases or deaths* | *ERR estimate ($Sv^{-1}$)* | *LSS ERR estimate ($Sv^{-1}$)* |
|---|---|---|---|---|---|---|---|---|---|
| [S30] | Repeated chest fluoroscopy (90 kVp X-rays) in many low-dose fractions (each of about 10 mGy) | Cancer incidence | <20–>60 | <10–>40 (mean 30) | 0.27 (0–2.74) | 89 | 330 | –0.00 (–0.43, 0.94) | 0.90 (0.47, 1.48)[a] |
| [G6] | Mostly 200–250 kVp X-rays in small number of moderate-dose fractions | Cancer mortality | <35–>55 (mean 49) | 1–51 (mean 21.5) | Unknown (0–0.17) | 16 | 100 | 6.07 (–3.70, 39.26) | 0.74 (0.08, 1.87)[b] |
| [H9] | Repeated chest fluoroscopy (90 kVp X-rays) in many low-dose fractions (each of about 10 mGy) | Cancer mortality | <10–>50 (mean 26) | 5–57 (mean 39) | 0.89 (0–18.40) | 688 | 151 | 0.90 (0.55, 1.39)[c] | 1.56 (0.41, 3.53)[c] |
| [D17] | Multiple low-dose (<10 mGy) X-rays | Cancer mortality | 0–19 (mean 10.1) | 0–>70 (mean 40.1) | 0.11 (0.00–1.70) | 77 | 67 | 2.7 (–0.2, 9.3)[d] | 2.62 (1.09, 5.31)[e] |

[a] Calculation based on breast dose, age at exposure >20 years.
[b] Calculation based on breast dose, age at exposure >30 years.
[c] Modelled ERR adjusted for age at exposure 15 years.
[d] Calculation based on women who received at least one radiographic examination.
[e] Calculation based on breast dose, age at exposure <20 years.

**Table 11 Risk estimates for radiation-induced breast cancer** [P3]
From epidemiological studies where the mean breast dose was acute/high-dose, or the doses were fractionated or protracted

| *Study* | *Nature of exposure* | *Mean breast dose (and range) (Sv)* | *Cases* | *Person-years of follow-up* | *ERR (95% CI) ($Sv^{-1}$)* | *EAR (95% CI) ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|
| **High-dose-rate studies** | | | | | | |
| Survivors of the atomic bombings | Single acute exposure, mixed whole-body gamma and neutron irradiation, predominantly high-energy (>1 MeV) | 0.3 (0.02–5) | 707 | 1 182 306 | 2.10 (1.6, 2.8)[a] | 11.6 (7.3, 17)[b] |
| Rochester thymus irradiation | 80–250 kVp therapeutic X-rays; small number of high-dose, high-dose-rate fractions | 0.7 (0.02–7.5) | 34 | 59 222 | 0.74 (0.4, 1.2)[a] | 30 (7.7, 71)[c] |
| Acute post-partum mastitis | 175–250 kVp therapeutic X-rays; small number of high-dose, high-dose-rate fractions | 3.8 (0.6–14) | 114 | 35 585 | 0.56 (0.3, 0.9)[d] | 18.8 (8.1, 37)[b] |
| **Low-dose-rate studies** | | | | | | |
| Gothenburg and Stockholm haemangioma | External, mainly protracted low-dose-rate gamma rays from $^{226}$Ra applicators | 0.37 (0.02–35)[e] | 226 | 415 877 | 0.34 (0.1, 0.7)[d] | 20 (6, 124)[c] |
| Massachusetts TB fluoroscopy cohorts | Repeated chest fluoroscopy (90 kVp X-rays) in many low-dose fractions (each of about 10 mGy) | 0.8 (0.02–6)[f] | 211 | 90 026 | 0.74 (0.4, 1.2)[a] | 5.7 (0.7, 16)[b] |

[a] Risk estimate based on relative risk model with adjustment for attained age, adjusted to age 50 years, taken from Preston et al. [P3].
[b] Risk estimate based on absolute risk model with adjustment for age at exposure and attained age, adjusted to age at exposure 25 years, attained age 50 years, taken from Preston et al. [P3].
[c] Risk estimate based on absolute risk model with adjustment for attained age, adjusted to attained age 50 years, taken from Preston et al. [P3].
[d] Risk estimate based on unadjusted relative risk model, taken from Preston et al. [P3].
[e] Total average dose derived from individual averages in each subcohort (Gothenburg, Stockholm) weighted by numbers of women in each subcohort.
[f] Total average dose derived from individual averages in each subcohort (adult, childhood) weighted by numbers of women in each subcohort.

**Table 12 Excess relative risks of leukaemia in moderate- and low-dose-rate radiation therapy studies and in matched subsets of the survivors of the atomic bombings in Japan** [L20]

Subsets are matched for sex, age at exposure and years of follow-up; ERR estimates with 95% CI

| *Study* | *Nature of exposure* | *End point* | *Age at exposure (years)* | *Follow-up (years)* | *Average dose (and range) (Sv)*[a] | *Cases or deaths* | *LSS cases or deaths*[b] | *ERR estimate ($Sv^{-1}$)*[a] | *LSS ERR estimate($Sv^{-1}$)*[b] |
|---|---|---|---|---|---|---|---|---|---|
| [A13] | Thorotrast exposure (protracted moderate-dose-rate exposure over many years) | Cancer incidence | 1–73 (mean 37.4) | 0–50 (median 21.0) | 26.8 (0–171.4) | 23 | 192 | 0.56 (>0, 5.50)[c] | 5.24 (3.58, 7.55)[d] |
| [H12] | $^{131}$I exposures (mean <2 treatments), protracted over a few days | Cancer incidence | 1–75 (mean 47) | 2–37 (mean 21) | 0.01 (0.01–2.22) | 130 | 192 | –1.04 (–3.44, 3.64) | 5.24 (3.58, 7.55)[d, k] |
| [D2] | Small number (3–6) of moderate doses of X-rays | Cancer incidence | <20–>70 (mean 53) | 0–>19.6 (mean 19.6) | 0.39 (<0.06–>1.04) | 61[e] | 91 | 0.70 (–0.43, 3.48)[e] | 6.49 (3.76, 10.99)[f, l] |
| [I1] | Mixture of brachytherapy (gamma rays from $^{226}$Ra applicators), radium, 200 kVp X-rays in small number of fractions (usually <10) | Cancer mortality | 13–89 (mean 46.5) | 0–59.9 (mean 24.9) | 1.19 (0–11) | 43[e] | 97 | 2.1 (0.19, 9.49)[e] | 3.62 (1.91, 6.29)[g] |
| [G6] | Mostly 200–250 kVp X-rays in small number of moderate-dose fractions | Cancer mortality | <35–>55 (mean 49) | 1–51 (mean 21.5) | 1.55 (0–1.55) | 11[h] | 136 | 1.13 (–0.19, 6.45)[h] | 3.14 (1.81, 5.07)[i] |
| [L6] | External, mainly protracted low-dose-rate gamma rays from $^{226}$Ra applicators | Cancer mortality | 0–1.5 (mean 0.5) | 0–>65 (mean 38.6) | 0.13 (<0.01–4.6) | 20 | 49 | 2.12 (–0.70, 10.18) | 14.16 (7.02, 29.12)[j, k] |

[a] Unless otherwise stated, all doses and risks are in terms of bone marrow dose.
[b] In all analyses of risks in the LSS incidence data, the three main radiogenic leukaemia subtypes (acute myeloid leukaemia, acute lymphoblastic leukaemia, chronic myeloid leukaemia) are analysed together, using bone marrow dose.
[c] 95% CIs are Wald-based (likelihood bounds did not converge).
[d] Calculation based on full cohort.
[e] Acute leukaemia and chronic myeloid leukaemia.
[f] Calculation based on age at exposure >20 years, time since exposure <30 years.
[g] Calculation based on females, age at exposure >15 years.
[h] Leukaemia excluding chronic lymphoblastic leukaemia.
[i] Calculation based on age at exposure >30 years.
[j] Calculation based on age at exposure <15 years.
[k] LSS and radiation therapy ERR statistically inconsistent ($p < 0.05$).
[l] LSS and radiation therapy ERR statistically inconsistent ($p < 0.01$).

**Table 13 Comparison of estimates (and 90% CI) of ERR per unit dose ($Sv^{-1}$) in the United Kingdom NRRW** [K27, M12]**, the IARC 3-country study** [C3]**, the IARC 15-country study** [C41] **and data on the survivors of the atomic bombings in Japan, adapted from references** [C3, C41, M12]

| | *Leukaemia excluding chronic lymphoblastic leukaemia* | *All malignant neoplasms excluding leukaemia* | *All malignant neoplasms excluding leukaemia and lung cancer* | *All malignant neoplasms* |
|---|---|---|---|---|
| Second NRRW analysis [M12] | 2.55 (–0.03, 7.16) | 0.09 (–0.28, 0.52) | 0.17 (–0.26, 0.70) | 0.09 (–0.27, 0.52) |
| First NRRW analysis [K27] | 4.28 (0.40, 13.6) | 0.41 (–0.17, 1.15) | 0.56 (–0.14, 1.48)[a] | 0.47 (–0.12, 1.20) |
| IARC 15-country study [C41] | 1.93 (<0, 8.47)[b] | 0.97 (0.14, 1.97)[b] | n.a. | n.a. |
| IARC 3-country study [C3] | 2.18 (0.13, 5.7) | –0.07 (–0.39, 0.30) | n.a. | –0.02 (–0.34, 0.35) |
| Atomic bombing survivor data [P9, P10][c] | 1.59 (0.03, 3.82)[d] | 0.25 (0.13, 0.37)[e] | 0.26 (0.12, 0.41)[f] | 0.31 (0.20, 0.44)[e] |
| Estimated ratio of risk coefficients from the second NRRW analysis [M12] and atomic bombing survivor data [P9, P10][g] | 1.60 (<0, 5.27) | 0.35 (<0, 2.10) | 0.67 (<0, 2.74) | 0.30 (<0, 1.67) |
| Estimated ratio of risk coefficients from IARC 15-country study [C41] and atomic bombing survivor data [P9, P10][g] | 1.21 (<0, 5.85)[b] | 3.93 (<0, 8.62)[b] | n.a. | n.a. |
| Estimated ratio of risk coefficients from IARC 3-country study [C3] and atomic bombing survivor data [P9, P10][g] | 1.37 (<0, 4.31) | <0 (<0, 1.22) | n.a. | n.a. |

[a] Also excluding pleural cancer.
[b] 95% CI.
[c] Japanese male atomic bombing survivors, aged between 20 and 60 at exposure, excluding survivors with >4 Gy shielded kerma, fitted to data of Preston et al. [P9, P10].
[d] Based on fitting a model of the format of BEIR [C35] to the data of Preston et al. [P10]. Values given are relevant to exposure at age >20 years, follow-up time 2–25 years and low doses.
[e] Based on fitting a time-constant relative risk model with a linear dose response to the data of Preston et al. [P10].
[f] Based on fitting a time-constant relative risk model with a linear dose response to the data of Preston et al. [P9].
[g] The upper (respectively lower) 90%/95% confidence limit is estimated from the length of the upper (respectively lower) part of the CI for the ERR for the relevant data sets in the upper part of the table.

**Table 14 Excess relative risk (and 95% CI) per unit dose ($Sv^{-1}$) as a function of dose range fitted to the DS02 LSS cancer mortality and incidence data**

The lowest dose range with a statistically significant trend (lower 97.5 centile for ERR > 0) is highlighted in boldface for each site[a]

| Colon dose range (Sv) | DS02 mortality | | DS02 incidence | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *All solid cancer*[b] | *Leukaemia*[c] | *All solid cancer*[b] | *Oesophageal cancer (ICD9 150)*[d] | *Stomach cancer (ICD9 151)* | *Colon cancer (ICD9 153)* | *Liver cancer (ICD9 155)* | *Lung cancer (ICD9 162)* | *Bone cancer (ICD9 170)*[e] | *Non-melanoma skin cancer (ICD9 173)* | *Female breast cancer (ICD9 174)* | *Urinary bladder cancer (ICD9 188)* | *CNS cancer (ICD9 191–192)*[f] | *Thyroid cancer (ICD9 193)* |
| 0–0.02 | 1.45 (–4.14, 7.38) | –12.01 (–36.51, 24.25) | –0.71 (–5.69, 4.53) | 0.47 (–29.33, 42.57) | 6.22 (–3.41, 16.82) | 0.06 (–16.15, 19.35) | –8.05 (–22.02, 8.50) | –0.75 (–14.81, 15.86) | –20.91 (<–20.91, 153.10) | –18.96 (<–18.96, 6.08) | –5.47 (–20.86, 13.51) | 11.76 (–19.21, 54.61) | –25.58 (<–25.58, 3.59) | 9.49 (–15.81, 43.78) |
| 0–0.04 | 0.61 (–1.94, 3.33) | 2.34 (–10.40, 21.39) | –2.13 (–4.37, 0.22) | –7.14 (–18.81, 10.26) | –1.15 (–5.31, 3.46) | –4.62 (–11.40, 3.58) | –7.08 (–13.00, 0.09) | 2.63 (–4.02, 10.55) | –19.66 (<–19.66, 20.23) | 1.13 (–8.85, 15.67) | –2.97 (–9.95, 5.81) | 10.14 (–5.18, 31.56) | –8.81 (–17.57, 5.01) | –11.08 (<–11.08, 1.28) |
| 0–0.06 | 0.45 (–1.14, 2.14) | –6.68 (–12.77, 2.88) | –0.53 (–1.94, 0.96) | –5.24 (–12.08, 4.95) | –1.26 (–3.78, 1.52) | –2.76 (–6.97, 2.30) | –2.97 (–6.76, 1.56) | 2.36 (–1.85, 7.33) | –14.08 (<–14.08, 6.66) | 0.41 (–5.87, 9.52) | –4.61 (–8.59, 0.44) | 5.62 (–3.75, 18.61) | –4.01 (–10.17, 5.33) | 2.77 (–4.27, 12.53) |
| 0–0.08 | 0.58 (–0.62, 1.87) | –3.44 (–8.08, 3.82) | –0.34 (–1.40, 0.78) | –2.48 (–7.93, 5.50) | –0.23 (–2.15, 1.88) | –0.85 (–4.14, 3.09) | –3.33 (–6.04, –0.07) | 0.99 (–2.12, 4.65) | –10.12 (<–10.12, 4.77) | 1.00 (–3.91, 8.11) | –2.90 (–5.89, 0.88) | 3.10 (–3.74, 12.58) | 0.14 (–5.32, 8.12) | 0.70 (–4.44, 7.76) |
| 0–0.10 | 0.52 (–0.44, 1.55) | –2.49 (–6.22, 3.28) | 0.26 (–0.60, 1.16) | 0.07 (–4.69, 6.93) | –0.54 (–2.03, 1.10) | 0.03 (–2.67, 3.25) | –1.07 (–3.35, 1.66) | 1.55 (–0.98, 4.53) | –7.81 (<–7.805, 3.90) | 2.19 (–2.02, 8.24) | –1.50 (–3.96, 1.60) | 1.46 (–3.72, 8.66) | 2.30 (–2.63, 9.38) | 3.83 (–0.84, 10.17) |
| 0–0.125 | 0.11 (–0.66, 0.93) | –0.09 (–3.60, 5.12) | 0.22 (–0.48, 0.95) | –0.58 (–4.37, 4.86) | –0.55 (–1.75, 0.77) | 0.96 (–1.33, 3.68) | –0.87 (–2.74, 1.37) | 0.46 (–1.51, 2.78) | –5.56 (<–5.56, 4.11) | 3.23 (–0.47, 8.49) | –0.43 (–2.54, 2.19) | 0.67 (–3.38, 6.30) | 1.56 (–2.49, 7.36) | 3.57 (–0.33, 8.83) |
| 0–0.15 | 0.48 (–0.18, 1.18) | –0.55 (–3.48, 3.79) | 0.36 (–0.23, 0.98) | 0.15 (–3.21, 4.91) | –0.14 (–1.15, 0.98) | 0.36 (–1.55, 2.62) | –0.26 (–1.91, 1.70) | 0.66 (–1.00, 2.62) | –5.41 (<–5.413, 2.48) | 1.20 (–1.64, 5.23) | –0.11 (–1.91, 2.13) | 0.35 (–2.98, 4.97) | 0.50 (–2.76, 5.18) | 2.23 (–0.93, 6.48) |
| 0–0.175 | 0.28 (–0.27, 0.87) | –1.65 (–3.93, 1.80) | 0.29 (–0.21, 0.81) | –0.05 (–2.91, 4.00) | –0.17 (–1.03, 0.77) | 0.84 (–0.82, 2.80) | –0.49 (–1.88, 1.17) | 0.30 (–1.09, 1.92) | –3.95 (<–3.952, 2.95) | 1.00 (–1.36, 4.34) | 0.36 (–1.21, 2.30) | 0.50 (–2.38, 4.46) | –0.12 (–2.73, 3.69) | 1.79 (–0.87, 5.36) |
| 0–0.20 | **0.53 (0.02, 1.07)** | –0.22 (–2.48, 3.14) | 0.43 (–0.03, 0.90) | 0.13 (–2.47, 3.82) | –0.43 (–1.19, 0.40) | 0.91 (–0.60, 2.69) | 0.36 (–0.97, 1.94) | 0.87 (–0.43, 2.40) | –3.50 (<–3.499, 2.62) | –0.13 (–2.06, 2.65) | 1.35 (–0.18, 3.22) | 2.63 (–0.30, 6.61) | –0.35 (–2.62, 2.98) | 0.90 (–1.38, 3.95) |
| 0–0.25 | 0.41 (–0.01, 0.86) | 0.82 (–1.29, 3.88) | **0.58 (0.20, 0.98)** | –0.89 (–2.83, 1.94) | 0.10 (–0.54, 0.80) | **1.49 (0.17, 3.05)** | –0.09 (–1.17, 1.19) | 1.06 (–0.04, 2.35) | –2.79 (<–2.793, 2.25) | –0.55 (–1.99, 1.59) | **1.55 (0.22, 3.17)** | 1.92 (–0.49, 5.17) | 0.07 (–1.85, 2.87) | 1.12 (–0.79, 3.70) |
| 0–0.30 | 0.53 (0.18, 0.91) | 0.88 (–0.94, 3.51) | 0.69 (0.37, 1.03) | 0.10 (–1.65, 2.59) | 0.19 (–0.34, 0.78) | 1.24 (0.13, 2.55) | 0.19 (–0.72, 1.28) | 1.33 (0.38, 2.44) | –2.31 (<–2.313, 2.00) | 0.25 (–1.03, 2.11) | 1.30 (0.17, 2.66) | 1.44 (–0.55, 4.12) | 1.59 (–0.32, 4.29) | **2.23 (0.44, 4.61)** |
| 0–0.50 | 0.36 (0.13, 0.60) | 1.37 (–0.02, 3.29) | 0.52 (0.31, 0.74) | 0.32 (–0.86, 1.97) | 0.22 (–0.14, 0.60) | 0.81 (0.09, 1.65) | 0.60 (–0.05, 1.35) | 0.56 (–0.02, 1.24) | –1.30 (<–1.296, 1.54) | –0.01 (–0.78, 1.11) | 1.65 (0.84, 2.62) | **1.51 (0.13, 3.35)** | 0.05 (–1.00, 1.57) | 2.18 (0.89, 3.84) |
| 0–0.75 | 0.31 (0.14, 0.48) | **2.29 (1.03, 4.00)** | 0.47 (0.32, 0.63) | –0.05 (–0.84, 1.09) | 0.12 (–0.13, 0.40) | 0.53 (0.02, 1.13) | **0.51 (0.04, 1.06)** | **0.44 (0.02, 0.93)** | –1.09 (<–1.09, 1.01) | 0.21 (–0.37, 1.05) | 1.46 (0.85, 2.19) | 1.61 (0.52, 3.02) | 0.71 (–0.15, 1.92) | 2.21 (1.18, 3.53) |
| 0–1.00 | 0.40 (0.26, 0.54) | 2.45 (1.31, 3.99) | 0.55 (0.42, 0.69) | 0.22 (–0.44, 1.16) | **0.25 (0.04, 0.48)** | 0.48 (0.07, 0.97) | 0.63 (0.23, 1.10) | 0.61 (0.25, 1.02) | –0.78 (<–0.7806, 0.92) | 0.48 (–0.06, 1.24) | 1.61 (1.07, 2.25) | 1.08 (0.24, 2.19) | **0.98 (0.20, 2.07)** | 1.86 (1.00, 2.96) |
| 0–1.25 | 0.41 (0.29, 0.54) | 3.16 (1.99, 4.72) | 0.59 (0.48, 0.71) | 0.31 (–0.27, 1.13) | 0.30 (0.12, 0.50) | 0.52 (0.16, 0.95) | 0.44 (0.11, 0.84) | 0.71 (0.38, 1.08) | –0.19 (<–0.1942, 2.46) | **0.63 (0.13, 1.32)** | 1.65 (1.15, 2.25) | 1.19 (0.43, 2.18) | 0.90 (0.19, 1.86) | 2.05 (1.24, 3.09) |
| 0–1.50 | 0.39 (0.28, 0.50) | 3.27 (2.13, 4.76) | 0.57 (0.46, 0.67) | 0.09 (–0.40, 0.79) | 0.33 (0.16, 0.51) | 0.63 (0.29, 1.02) | 0.35 (0.06, 0.70) | 0.65 (0.37, 0.99) | –0.28 (<–0.2784, 2.11) | 0.93 (0.41, 1.63) | 1.52 (1.06, 2.06) | 1.09 (0.41, 1.98) | 0.86 (0.22, 1.74) | 1.77 (1.05, 2.69) |
| 0–1.75 | 0.46 (0.36, 0.57) | 3.45 (2.32, 4.94) | 0.59 (0.49, 0.69) | 0.11 (–0.34, 0.77) | 0.34 (0.19, 0.52) | 0.54 (0.23, 0.91) | 0.46 (0.18, 0.80) | 0.80 (0.52, 1.13) | 0.48 (<0, 3.51) | 1.13 (0.59, 1.85) | 1.50 (1.07, 2.02) | 1.05 (0.41, 1.89) | 0.87 (0.26, 1.72) | 1.54 (0.87, 2.39) |
| 0–2.00 | 0.46 (0.37, 0.57) | 3.56 (2.43, 5.03) | 0.60 (0.50, 0.70) | 0.33 (–0.13, 1.00) | 0.35 (0.19, 0.51) | 0.49 (0.19, 0.83) | 0.50 (0.22, 0.81) | 0.78 (0.51, 1.10) | 1.12 (–0.18, 4.72) | 1.18 (0.65, 1.90) | 1.43 (1.01, 1.92) | 0.90 (0.30, 1.69) | 0.77 (0.19, 1.56) | 1.60 (0.95, 2.43) |
| 0–2.50 | 0.46 (0.37, 0.56) | 4.02 (2.86, 5.55) | 0.61 (0.53, 0.70) | **0.57 (0.11, 1.22)** | 0.33 (0.19, 0.48) | 0.56 (0.29, 0.88) | 0.45 (0.21, 0.74) | 0.74 (0.49, 1.03) | **1.64 (0.10, 5.58)** | 1.31 (0.79, 2.01) | 1.49 (1.09, 1.95) | 0.78 (0.24, 1.48) | 0.55 (0.04, 1.24) | 1.84 (1.20, 2.65) |
| 0–3.00 | 0.47 (0.38, 0.56) | 3.96 (2.81, 5.47) | 0.61 (0.53, 0.70) | 0.55 (0.11, 1.17) | 0.37 (0.24, 0.51) | 0.58 (0.32, 0.88) | 0.41 (0.19, 0.68) | 0.68 (0.45, 0.95) | 1.55 (0.08, 5.31) | 1.33 (0.82, 2.00) | 1.50 (1.12, 1.95) | 0.85 (0.33, 1.53) | 0.54 (0.06, 1.19) | 1.65 (1.06, 2.40) |

[a] Relative risks and profile-likelihood CIs obtained by fitting a linear relative risk model, stratifying on city, sex, age at exposure and attained age, using data from Preston et al. [P10]. All analyses use the relevant organ dose (except where indicated), adjusted for dosimetric errors (assumed 35% GSD), neutron RBE of 10. Those survivors "not-in-city" (>10 km from either hypocentre) were excluded from the incidence data; survivors with shielded kerma dose >4 Gy were excluded from the mortality data.

[b] Using colon dose.
[c] Using red bone marrow dose.
[d] Using stomach dose.
[e] Using skeletal dose.
[f] Using brain dose.

**Table 15 Cohort and case-control epidemiological studies of the carcinogenic effects of exposures to low-LET radiation**
Table is expanded from table 2 in annex I of the UNSCEAR 2000 Report [U2]

| *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** | | | | | | | | |
| LSS [P1] | Mortality | 50 113 exposed persons[c]<br>36 459 unexposed persons<br>55.5% females<br>Age: 0–>90 (28.4)[d] | Japan | 5–45 | 2 812 863<br>(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 CNS, lymphoma, myeloma* |
| LSS [P9] | Mortality | 49 114 exposed persons<br>(≥5 mSv)<br>37 458 unexposed persons<br>Age: 0–>90 | Japan | 5–52 | 3 062 046<br>(35.4) | Gamma and neutron radiation from nuclear explosions | Individual estimates derived from detailed shielding histories | Total solid cancer, oesophagus, stomach, colon, rectum, liver, gallbladder, pancreas, lung, breast, uterus, ovary, prostate, bladder, other solid tumours |
| LSS [P4, T1] | Incidence | 37 270 exposed persons[e]<br>42 702 unexposed persons<br>55.5% females<br>Age: 0–>90 (26.8) | Japan | 13–42[f] | 1 950 567[g]<br>(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*, CNS, thyroid* |
| Survivors of the atomic bombings (in utero) [D14, Y1] | Mortality/ incidence | 1 078 exposed persons[h]<br>2 211 unexposed persons<br>50.7% females<br>Exposure: in utero | Japan | 5–47 | n.a.[i] | Maternal exposure to gamma and neutron radiation at high dose rate | Estimated dose to uterus of mother | Leukaemia, all solid cancers |
| **Treatment of malignant disease** | | | | | | | | |
| Cervical cancer cohort [B11] | Incidence | 82 616 exposed women<br>99 424 unexposed women<br>Age: <30–>70 (26.8) | Canada<br>Denmark<br>Finland<br>Norway<br>Slovenia<br>Sweden<br>United Kingdom<br>United States | 1–>30 | 1 278 950<br>(7.0) | Radiotherapy, including external beam and intracavity 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 |

| *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 cohort [K1] | Incidence | 49 828 exposed women<br>16 713 unexposed women<br>Age: <40–>60 | Denmark<br>Finland<br>Norway<br>Sweden<br>Connecticut and Iowa (United States) SEER | 1–>30 | 532 740 (10.4) | Radiotherapy, external beam or brachytherapy | Data on typical range of estimates for specific organs and phantom measurements | Oesophagus, stomach, small intestine, colon, rectum, liver, pancreas, larynx, lung, breast, uterine corpus, vagina, vulva, ovary, kidney, bladder, thyroid, bone, connective tissue, non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, leukaemia (non-CLL), total |
| Lung cancer following breast cancer [I7] | Case-control<br>61 cases<br>120 controls from a cohort of 27 106 women | 38 exposed women<br>143 unexposed women<br>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 |
| Lung cancer following breast cancer [Z8] | Cohort<br>(111 lung cancers occurring in the ipsilateral breast ≥10 years after radiotherapy only) | 28 038 exposed women<br>166 943 unexposed women | United States (SEER) | 6 months to >15 years (only those with ≥10 years of follow-up) | n.a. | External radiotherapy | Not performed (used assessment given in reference [I7]) | Ipsilateral lung cancer |
| Cervical cancer case-control [B5, B7, B8] | Case-control<br>4 188 cases<br>6 880 controls | 10 286 exposed women<br>782 unexposed women<br>Age: <30–>70 (26.8) | Austria<br>Canada<br>Czech Rep.<br>Denmark<br>Finland<br>France<br>Germany<br>Iceland<br>Italy<br>Norway<br>Slovenia<br>Sweden<br>United Kingdom<br>United States | 0–>30 (7.0 years per case) | n.a. | Radiotherapy, including external beam and intracavity 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 [B10] | Case-control<br>655 cases<br>1 189 controls from a cohort of 41 109 women | 449 exposed women<br>1 395 unexposed women<br>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 [S20] | Case-control<br>529 cases<br>529 controls from a cohort of 56 540 women | 157 exposed women<br>901 unexposed women<br>Age: <45–>60 (51) | Denmark | 12–47 (~16 years per case) | n.a. | Radiotherapy | Individual doses from therapy records and experimental measurements | Contralateral breast |

| *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* | | | | | |
| Soft-tissue sarcoma following breast cancer [K18] | Case-control<br>107 cases<br>321 controls from a cohort of 122 991 women | 310 exposed women<br>86 unexposed women<br>32 women with unknown exposure status<br>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<br>90 cases<br>264 controls from a cohort of 82 700 women | 110 exposed women<br>244 unexposed women<br>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-lymphoblastic leukaemia and myelodysplastic syndrome*, chronic myelogenous leukaemia, acute lymphoblastic leukaemia |
| Leukaemia following cancer of the uterine corpus [C8] | Case-control<br>218 cases<br>775 controls from a cohort of 110 000 women | 612 exposed women<br>351 unexposed women<br>30 women with unknown exposure status<br>Age: <55–>75 (62) | Canada<br>Denmark<br>Finland<br>Norway<br>United States | 1–50 | n.a. | Radiotherapy | Individual doses from therapy records and experimental measurements | Leukaemia* |
| Leukaemia following testicular cancer [T24] | Case-control<br>36 cases<br>106 controls from a cohort of 18 567 men | 93 exposed men<br>49 unexposed men<br>Age: <30–>50 | Canada<br>Denmark<br>Finland<br>Netherlands<br>Sweden<br>United States | 1–>15 | n.a. | Radiotherapy | Individual doses from therapy records and experimental measurements | Leukaemia (other than CLL)* |
| Lung cancer following Hodgkin's disease (seven cancer registries) [T3] | Nested case-control<br>222 cases<br>444 controls | 150 exposed cases<br>256 exposed controls<br>Age: <30–>55 | Ontario (Canada)<br>Denmark<br>Finland<br>Netherlands<br>Sweden<br>Connecticut and Iowa (United States) | 1–>20 | n.a. | Radiotherapy (and chemotherapy for some) | Individual treatment information and experimental measurements | Lung cancer |
| Lung cancer following Hodgkin's disease [K9] | Case-control<br>98 cases<br>259 controls | 303 exposed persons<br>54 unexposed persons<br>15% female | Canada<br>Denmark<br>Finland<br>France<br>Norway<br>Slovenia<br>United Kingdom | 1–>10 | n.a. | Radiotherapy | Individual doses from therapy records and experimental measurements | Lung cancer |

| *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 [V2] | Case-control<br>30 cases<br>82 controls from a cohort of 1 939 patients | 101 exposed persons<br>11 unexposed persons<br>4% female<br>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 [H20] | Incidence/mortality | 855 exposed women<br>30 unexposed women<br>Age: 4–81 (28) | United States | 0–29 | 8 832<br>(10) | Radiotherapy | Individual doses from therapy records | Breast cancer* |
| Breast cancer following Hodgkin's disease [V8] | Case-control<br>48 cases<br>175 matched controls from a cohort of female patients | 650 exposed women<br>Age: <40 at radiotherapy | Netherlands | Median<br>17.8<br>(5 to >25) | n.a. | Radiotherapy (plus chemotherapy for some) | Individual dose reconstruction from therapy records | Breast cancer |
| Breast cancer following Hodgkin's disease [T25] | Case-control<br>105 cases<br>266 matched controls from a cohort of female patients | 3 817 exposed women<br>Age: ≤30 at radiotherapy | Canada<br>Denmark<br>Finland<br>Netherlands<br>Sweden<br>United States | Median<br>18.0<br>(7 to 30) | n.a. | Radiotherapy (plus chemotherapy for 35%) | Individual dose reconstruction to the specific breast location from therapy records | Breast cancer |
| Leukaemia following Hodgkin's disease [K20] | Case-control<br>163 cases<br>455 controls from a cohort of 29 552 patients | 36% exposed<br>35% females<br>Age: (40) | Canada<br>Denmark<br>Finland<br>France<br>Germany<br>Italy<br>Netherlands<br>Norway<br>Slovenia<br>United Kingdom | 1–>10 | n.a. | Radiotherapy | Individual doses from therapy records and experimental measurements | Leukaemia (non-CLL) |
| Leukaemia following non-Hodgkin's lymphoma [T6] | Case-control<br>35 cases<br>140 controls from a cohort of 11 386 women | 123 exposed persons<br>52 unexposed persons<br>Age: <50–70 | Canada<br>Netherlands<br>Sweden<br>United States | 2–25<br>(7.6 years per case) | n.a. | Radiotherapy | Individual doses from therapy records and experimental measurements | Leukaemia |
| Leukaemia following non-Hodgkin's lymphoma [T15] | Incidence | 61 exposed persons<br>50% females<br>Age: 18–70 (49.5) | United States | 2–22 | 590<br>(9.7) | Total-body irradiation | Individual doses from therapy records and experimental measurements | Acute non-lymphoblastic leukaemia*, all solid cancers |

| *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 [T5, T7, T10] | Case-control<br>23 thyroid cancers with 89 controls,<br>25 leukaemia with 90 controls,<br>64 bone cancers with 209 controls from a cohort of 9 170 members | 112 exposed persons<br>388 unexposed persons<br>45% females<br>Age: 0–18 (7) | Canada<br>France<br>Italy<br>Netherlands<br>United Kingdom<br>United States | 5–48 | 50 609<br>(5.5) | Adjuvant radiotherapy | Individual doses from therapy records and experimental measurements | Thyroid*, leukaemia, bone sarcoma* |
| Childhood cancers [D16, D19] | Incidence | 3 109 exposed persons<br>1 291 unexposed persons<br>45% females<br>Age: 0–16 (7) | France<br>United Kingdom | 3–48 | 66 000<br>(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 [H27] | Case-control<br>59 cases<br>220 controls, largely within a cohort of 13 175 members | 208 exposed persons<br>71 unexposed persons<br>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 [H21] | Case-control<br>26 cases<br>96 controls | 88 exposed persons<br>34 unexposed persons<br>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<br>642 unexposed persons<br>47% females<br>Age: 0–17 | United States | 1–>60 | n.a.<br>(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<br>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<br>8% unexposed<br>35% female<br>Age: 1–16 (median 11) | Canada<br>France<br>Italy<br>United Kingdom<br>United States | 0–37<br>(median 11.4) | 15 660<br>(11.3) | Radiotherapy | Individual doses from therapy records and experimental measure-ments | Leukaemia*, non-Hodgkin's lymphoma*, breast*, thyroid*, other solid cancers* |

| *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** | | | | | | | | |
| Childhood skin haemangioma: Stockholm [K15, L6, L7, L10, L12, L13] | Incidence/mortality | 14 351 exposed persons[j]<br>67% females<br>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 [K14, K15, L4, L12] | Incidence | 11 914 exposed persons<br>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*, CNS*, all other sites |
| Benign lesions in locomotor system [D2, J2] | Incidence/mortality | 20 024 exposed persons<br>49% females<br>Age: <20–>70 (53) | Sweden | Up to 38 | Incidence: 493 400 (24.6)<br>Mortality: 392 900 (19.6) | X-ray therapy | Individual red bone marrow doses from therapy records and phantom measurements | Leukaemia*, non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma |
| Ankylosing spondylitis [W2, W8][k] | Mortality | 13 914 exposed persons<br>16.5% females<br>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) |
| Tinea capitis [R5, R9, R16, R17] | Incidence/mortality | 10 834 exposed persons<br>16 226 unexposed persons<br>50% females<br>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<br>Mortality: head and neck*, leukaemia* |
| Tinea capitis: New York [S7, S15, S22, S68] | Incidence | 2 224 exposed persons<br>1 380 unexposed persons<br>12.8% females<br>Age: <1–19 (7.7) | United States<br>24% African-American | 10–>50 | 125 357 (35) | X-ray induced epilation | Representative doses based on standard treatment | Thyroid*, skin*, brain*, leukaemia, salivary gland |
| Acute post-partum mastitis: New York [S5, S22] | Incidence | 571 exposed women<br>993 unexposed women<br>Age: 14–>40 (27.8) | United States | 20–35 | 38 784 (25.1) | X-ray therapy | Individual doses from therapy records | Breast* |
| Thymic irradiation: Rochester [H10, H26, S18, S22] | Incidence | 2 657 exposed persons<br>4 833 unexposed persons<br>42% females<br>Age: 0–1 | United States | 23–>50 | 237 048 (31.6) | X-ray therapy | Individual doses from therapy records | Thyroid*, breast*, skin |
| Tonsil irradiation [S17, S21, S22, S74] | Incidence | 2 634 exposed persons[l]<br>40.7% females<br>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* |

| *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* | | | | | |
| Tonsil, thymus or acne irradiation [D9] | Incidence | 416 exposed persons<br>Age: (7.1) | United States | n.a. | 11 000<br>(26.4) | Radiotherapy | Individual doses from therapy records | Thyroid* |
| Benign breast disease [M3, M8, M17] | Incidence | 1 216 exposed women<br>1 874 unexposed women<br>Age: 10–>85 | Sweden | 5–60 | 56 900<br>(18) | X-ray therapy | Individual doses from therapy records and phantom measurements | Breast*, all other sites |
| Metropathia haemorrhagica [D7][m] | Mortality | 2 067 exposed women<br>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 |
| Benign gynaecological disorders [I1, I4] | Mortality | 4 153 exposed women<br>Age: 13–88 (46.6) | United States | 0–60 | 109 910<br>(26.5) | Intrauterine $^{226}$Ra | Individual doses from therapy records and phantom measurements | Leukaemia*, other haematolympho-poietic cancers, uterus*, bladder*, rectum*, other genital*, colon, bone (in pelvis), liver and gallbladder, stomach, kidney, pancreas* |
| Lymphoid hyperplasia screening [P5] | Incidence/prevalence | 1 195 exposed persons<br>1 063 unexposed persons<br>40% females<br>Age: 0–17 (6.9) | United States | 12–44 | 66 000<br>(29) | X-ray therapy | Individual doses from therapy records and phantom measurements | Thyroid nodular disease* |
| Peptic ulcer [C4, G6] | Mortality | 1 859 exposed persons<br>1 860 unexposed persons<br>19.8% females<br>Age: <35–>55 (49) | United States<br>6% non-white | 20–61 | 92 979<br>(25.0) | X-ray therapy | Individual doses from therapy records and experimental measurements | Stomach*, colon, pancreas*, lung*, leukaemia*, female breast, oesophagus, liver, bladder, prostate, kidney, thyroid, non-Hodgkin's lymphoma, myeloma, pancreas |
| **Diagnostic examinations** | | | | | | | | |
| TB fluoroscopy: Massachusetts [B3, S22] | Incidence | 2 367 exposed women<br>2 427 unexposed women<br>Age: 12–50 (26) | United States | 0–>50 | 54 609<br>(11.4) | Multiple X-ray chest fluoroscopies | Individual exposures from medical records and doses from phantom measurements and computer simulations | Breast*, skin |
| TB fluoroscopy: Massachusetts [D4] | Mortality | 6 285 exposed persons<br>7 100 unexposed persons<br>49% females<br>Age: 12–50 (26) | United States | 0–>50 | 331 206<br>(24.7) | Multiple X-ray chest fluoroscopies | Individual exposures from medical records and doses from phantom measurements and computer simulations | Breast*, oesophagus*, lung, leukaemia |

| *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* | | | | | |
| TB fluoroscopy [H7, H9] | Mortality | 25 007 exposed persons<br>39 165 unexposed persons<br>50% females<br>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 (United States health plans) [B17] | Case-control<br>565 leukaemia<br>318 non-Hodgkin's lymphoma<br>208 multiple myeloma<br>1390 controls | 2 203 exposed persons<br>278 unexposed persons<br>39% females<br>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 |
| Medical and dental X-rays: Los Angeles [P7] | Case-control<br>408 cases<br>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 [P6] | Case-control<br>130 cases<br>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 [I9] | Case-control<br>484 cases<br>484 controls | 736 exposed persons<br>232 unexposed persons<br>77% females<br>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 [D17] | Mortality | 4 822 exposed women<br>644 unexposed women<br>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 exposures** | | | | | | | | |
| Oxford Survey of Childhood Cancers [B12, M18, S11] | Case-control<br>14 491 cases<br>14 491 controls | 3 797 exposed persons<br>25 185 unexposed persons<br>56% females<br>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* |

| *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* | | | | | |
| Northeastern United States childhood cancers [M16] | Case-control<br>1 342 cases<br>14 292 controls | 1 506 exposed persons<br>14 130 unexposed persons<br>49.2% females<br>Exposure: in utero | United States | 20 (max.) | n.a. | Maternal X-rays during pregnancy | Number of exposures | Leukaemia*, solid tumours |
| Childhood acute lymphoblastic leukaemia [S67] | Case-control<br>1 811 cases<br>1 966 controls | 273 exposed persons<br>3 504 unexposed persons<br>45.3% females<br>Exposure: in utero | United States | 15 (max.) | n.a. | Maternal X-rays during pregnancy | Number of exposures | Acute lymphoblastic leukaemia |
| Sweden [N4] | Case-control<br>624 cases<br>624 controls | 234 exposed persons<br>1 014 unexposed persons<br>48.2% females<br>Exposure: in utero | Sweden | 16 (max.) | n.a. | Maternal X-rays during pregnancy | Number and type of X-rays, plus trimester and calendar period of exposure, abstracted blindly from medical records | All leukaemia, lymphoblastic leukaemia, myeloid leukaemia |
| **Occupational exposures** | | | | | | | | |
| 15-country nuclear worker study [C41] | Mortality | 407 391 workers<br>10% females | Australia<br>Belgium<br>Canada<br>Finland<br>France<br>Hungary<br>Japan<br>Korea (Rep. of)<br>Lithuania<br>Slovakia<br>Spain<br>Sweden<br>Switzerland<br>United Kingdom<br>United States | Up to 47 (but varied by country) | 5 192 710 (12.7) | Nuclear power plants, fuel cycle, defence, weapons production and research facilities | Recorded exposures to external radiation | Leukaemia, all other cancers combined* |
| Nuclear workers in Japan [I14] | Mortality | 175 939 men | Japan | Up to 12 (but up to >24 since first exposure) | ~1 390 000 (7.9) | Nuclear power plants, fuel processing and research facilities | Recorded exposures to external radiation | Leukaemia, all other tumours, oral/pharynx, oesophagus, stomach, colon, rectum, liver, gallbladder, pancreas, lung, prostate, bladder, kidney/other urinary, brain/CNS, non-Hodgkin's lymphoma, multiple myeloma |
| Nuclear workers in Canada, United Kingdom and United States [C3][n] | Mortality | 95 673 workers<br>15% females | Canada<br>United Kingdom<br>United States | Up to 43 | 2 124 526 (22.2) | Nuclear power plants, fuel processing and research facilities | Recorded exposures to external radiation | Leukaemia, all other cancers |

| *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* | | | | | |
| NRRW [M12][o] | Mortality | 124 743 monitored workers<br>9% females | United Kingdom | Up to 47 | 2 063 300 (16.5) | Nuclear power plants, fuel cycle, defence, weapons production and research facilities | Recorded exposures to external radiation | Leukaemia, all other cancers |
| Sellafield [C10, D11][p] | Mortality/incidence | 10 028 monitored workers<br>3 711 other workers<br>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 |
| United Kingdom Atomic Energy Authority [A22, C10, F8][p] | Mortality/incidence | 26 395 monitored workers<br>24 972 other workers<br>29% females | United Kingdom | Up to 51 | 1 371 153 (26.7) | Nuclear and reactor research and fuel processing | Recorded exposures to external radiation | Leukaemia, all other cancers |
| United Kingdom Atomic Weapons Establishment [B14, C10][p] | Mortality | 9 389 monitored workers<br>12 463 other workers<br>9% females | United Kingdom | Up to 37 | 216 000[q] (23) | Weapons research | Recorded exposures to external radiation | Leukaemia, all other cancers |
| Chapelcross workers [B15, M6] | Mortality/incidence | 2 209 monitored workers<br>419 other workers<br>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 |
| Capenhurst uranium facility [M4] | Mortality/incidence | 3 244 radiation workers<br>9 296 other workers<br>3% females | United Kingdom | Up to 46 | 61 190 (18.9) | Uranium enrichment plant | Recorded exposures to external radiation (alpha dose not assessed) | Leukaemia, all other cancers, stomach, colon, rectum, lung, pleura, melanoma, prostate, bladder, brain, non-Hodgkin's lymphoma, all lymphohaematopoietic cancers |
| Springfields uranium workers [M5] | Mortality/incidence | 13 960 radiation workers<br>5 489 other workers<br>4% females | United Kingdom | Up to 50 | 341 813 (24.5) | Uranium production facility | Recorded exposures to external radiation (alpha dose not assessed) | Leukaemia, all other cancers, mouth/pharynx, oesophagus, stomach, colon, liver, pancreas, larynx, lung, pleura, bone, connective tissue, melanoma, breast, uterus, ovary, prostate, testis, bladder, kidney, brain, thyroid, non-Hodgkin's lymphoma, Hodgkin's disease, myeloma |
| Canadian National Dose Registry [A8][r] | Mortality | 206 620 monitored workers<br>49% females | Canada | Up to 37 | 2 861 093 (13.8) | Dental, medical, industrial and nuclear power | Recorded exposures to external radiation | Leukaemia, all other cancers |
| Canadian National Dose Registry [S8] | Incidence | 191 333 monitored workers<br>50% females | Canada | Up to 38 | 2 667 903 (13.9) | Dental, medical, industrial and nuclear power | Recorded exposures to external radiation | Leukaemia, all other cancers |
| Atomic Energy of Canada Ltd. [C3, G9][s] | Mortality | 11 355 monitored workers<br>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 |

| *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* | | | | | |
| Spanish Nuclear Energy Board [A32] | Mortality | 5 657<br>17% females | Spain | Up to 39 | 89 946<br>(15.9) | Research, inspection of nuclear facilities, open pit mining | Recorded exposures to external radiation (alpha dose not assessed) | Total cancer, bone, lung, liver, stomach, nervous system |
| Hanford [G8, G10][t] | Mortality | 32 643 monitored workers<br>24% females | United States | Up to 43 | 633 511<br>(19.4) | 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. | Nuclear fuel cycle and research | Recorded exposures to external radiation | Leukaemia, all other cancers |
| Rocky Flats [G8, W12] | Mortality | 5 952 men | United States (white) | Up to 32 | 81 237<br>(13.6) | Nuclear fuel cycle and research | Recorded exposures to external radiation | Leukaemia, all other cancers |
| Portsmouth Naval Shipyard [S56, Y10] | Mortality | 13 468 monitored workers<br>24 385 other workers<br>13% females | United States | Up to 47 | 303 892[cc]<br>(22.6) | Work on overhauling and building nuclear submarines | Recorded exposures to external radiation | Leukaemia, oesophagus, pancreas, pharynx, larynx, lung, kidney, bladder and other urinary organs |
| Rocketdyne/Atomics International [R15] | Mortality | 4 563 monitored workers<br>6% females | United States | Up to 45 | 118 749<br>(26) | Nuclear research and production facility | Recorded exposures to external radiation | Leukaemia, all other cancers |
| Mound facility [W5] | Mortality | Males<br>3 229 monitored workers<br>953 other workers | United States (white) | Up to 33 | 78 600<br>(18.8) | Nuclear research and production facility | Recorded exposures to external radiation | Leukaemia, all other cancers |
| 5 rem study [F3] | Mortality/incidence | Males<br>2 392 workers with ≥50 mSv in a year | United States (white) | Up to 42 | 69 000<br>(20) | Department of Energy facilities or nuclear shipyards | Recorded exposures to external radiation | Leukaemia, digestive organs, colon, lung, lymphopoietic, all cancers combined |
| Multiple myeloma (Hanford, Oak Ridge, Savannah River, Los Alamos) [W7] | Case-control<br>98 cases<br>391 controls | 11% females<br>5% African-American | United States | n.a. | n.a. | Four Department of Energy facilities | Recorded exposures to external radiation; indications of monitoring for radionuclides | Multiple myeloma |
| Non-Hodgkin's lymphoma (Atlanta, Connecticut, Detroit, Iowa, Kansas, Miami, San Francisco, Seattle) [E10] | Case-control<br>1 056 cases<br>1 860 controls | Males<br>342 with reported occupational exposure<br>2 574 unexposed | United States | n.a. | n.a. | Various occupations | Self-reported occupational history, plus job exposure matrix | Non-Hodgkin's lymphoma |
| Chernobyl clean-up workers (cohort) [I5, I8][u] | Incidence | 114 504 male workers<br>Age: <20–≥61 | Russian Federation | 0–9 | 797 781<br>(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 (leukaemia case-control) [K3] | Case-control<br>41 cases<br>162 controls from a cohort of 162 684 men | Males<br>Age: <20–>55 | Russian Federation | 2–9 | n.a. | Emergency and recovery work in the vicinity of Chernobyl | Assessed external radiation dose | All leukaemia, non-CLL leukaemia |

| *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* | | | | | |
| Chernobyl clean-up workers [I10, R11, T13] | Mortality/incidence | 4 742 men<br>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 [S28] | Mortality | 21 557 workers<br>25% females[v] | Russian Federation | 0–50 | 720 000 | Nuclear fuel cycle and research | Recorded exposures to external radiation | Lung, liver and skeletal (combined)*, other solid cancers*, leukaemia* |
| Mayak workers: stomach cancer study [Z3] | Case-control<br>157 cases<br>346 controls | 40 persons with external doses of above 3 Gy<br>463 with lower doses<br>10% females | Russian Federation | Up to 37 | n.a. | Nuclear fuel cycle and research | Recorded exposures to external radiation and measurements of plutonium | Stomach* |
| Medical radiologic technologists [M10, M31, S29] | Mortality/incidence | 146 022<br>90 305<br>73% females<br>95% Caucasian American | United States | Up to 72 | Approx. 3 900 000 (26.7) | Medical diagnostic X-ray | Time and duration of radiation work | Total cancer, buccal/pharynx, oesophagus, stomach, colon, rectum, liver, pancreas, larynx, lung, skin, breast, cervix, uterus, prostate, bladder, kidney, brain/CNS, thyroid, non-Hodgkin's lymphoma, multiple myeloma, leukaemia |
| Radiological technologists [A3] | Mortality | 9 179 radiological technologists<br>(2 300 with recorded doses) | Japan | Up to 28 | n.a. | Radiology | Recorded exposures to external radiation | All cancers combined*, oesophagus, stomach, colorectal, lung |
| Radiotherapy staff [A6] | Incidence | 4 151 persons<br>Age: <20–≥50 | Denmark | Up to 32 | 49 553 (11.9) | Work in radiotherapy departments | Recorded exposures to external radiation | Leukaemia, prostate*, all other cancers |
| Nuclear workers [R54] | Mortality | 22 395 monitored persons<br>3.4% females | France | Up to 33 (average 11.7) | 261 418 | Reactor operation | Recorded exposures to external radiation | Leukaemia, all other cancers |
| **Natural sources of radiation** | | | | | | | | |
| Yangjiang [A11, S23, T12, T14, T16, Z2][w] | Mortality | 89 694 persons in high-background area<br>35 385 persons in control area<br>50% females<br>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 |
| Childhood Cancer Study [U17] | Case-control<br>Approx. 800 leukaemia cases, 160 non-Hodgkin's lymphoma cases, 70 Hodgkin's disease cases | Similar proportions of males and females<br>Age at diagnosis: 0–14<br>Mean annual absorbed dose for controls: 0.843 mGy | United Kingdom | n.a. | n.a. | Gamma radiation | Measurements in dwelling occupied for six months or more prior to diagnosis | Leukaemia, non-Hodgkin's lymphoma, Hodgkin's disease |

| *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* | | | | | |
| Sweden<br>[A24] | Case-control<br>312 cases<br>1 418 controls | Age at diagnosis: 0–19<br>% females unknown | Sweden | n.a. | n.a. | Gamma radiation | Measurements outside dwellings known to have been built from alum shale concrete | Acute lymphoblastic leukaemia |
| Central Italy<br>[F7] | Case-control<br>44 cases<br>211 controls | Males<br>Age at diagnosis: 35–80 (68)<br>76% with gamma dose rate above 300 nGy/h | Italy | 10 | n.a. | Gamma radiation<br>Radon | Measurements in last dwellings occupied and characteristics of dwellings | Acute myeloid leukaemia |
| **INTERNAL LOW-DOSE-RATE EXPOSURES** | | | | | | | | |
| **Medical exposures** | | | | | | | | |
| Diagnostic $^{131}$I<br>[D42, H8, H12, H14][x] | Incidence | 36 792 exposed persons<br>80% females<br>Age: 1–75 (43) | Sweden | 5–39 | 885 618<br>(26.1) | Diagnostic $^{131}$I | Individual values of activity administered; organ dose estimates for thyroid | Thyroid, leukaemia, all other sites |
| $^{131}$I hyperthyroidism<br>[H6, H24][y] | Incidence/mortality | 10 522 exposed persons<br>82% females<br>Age: 13–70 | Sweden | 1–26 | 139 018<br>(13.6) | Treatment of hyperthyroidism | Average administered activity (multiple treatments) | Stomach*, kidney*, brain*, all other sites[z] |
| Thyrotoxicosis patients<br>[D12, R3, S24][aa] | Incidence/mortality | 23 020 exposed persons<br>12 573 unexposed persons<br>79% females<br>Age: <10–80 | United States | 0–45 | 738 831<br>(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 CNS tumours, thyroid*, lymphoma, myeloma, leukaemia |
| $^{131}$I hyperthyroidism<br>[F1] | Incidence/mortality | 7 417 exposed persons<br>83% females<br>Age: ≤49–≥70 (57) | United Kingdom | 1–≥20 | 72 073<br>(9.7) | Treatment of hyperthyroidism | Individual values of activity administered | Thyroid*, bladder, uterus, small bowel*, all other sites |
| $^{131}$I thyroid cancer<br>[H2] | Incidence | 834 exposed persons<br>1 121 unexposed persons<br>75% females<br>Age: 5–75 (48) | Sweden | 2–34 | 25 830<br>(13.2) | Treatment of thyroid cancer | Individual values of activity administered | Leukaemia, salivary gland*, kidney*, all other sites |
| Therapeutic $^{131}$I<br>[D18] | Incidence | 846 persons with therapeutic exposures<br>501 persons with diagnostic exposures<br>274 unexposed persons<br>79% females<br>Age: 5–89 (40) | France | 2–37 | 14 615<br>(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 |

| *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* | | | | | |
| $^{131}$I thyroid cancer patients [R38] | Incidence | 6 676 patients<br>4 225 treated with $^{131}$I<br>1 194 treated with external beam radiotherapy<br>(9% received both types of treatment) | France<br>Italy<br>Sweden | 2–55 | n.a.<br>(13) | Treatment of thyroid cancer | Individual values of $^{131}$I activity administered | All solid cancers*, soft tissue and bone*, colorectal*, breast, leukaemia* |
| **Environmental exposures** | | | | | | | | |
| Extended Techa River Cohort [K49, K50] | Mortality | 29 873 residents<br>~60% females<br>Age: <20–>60 | Russian Federation (ethnic Russians and Tartars/ Bashkirs) | Up to 50 | 865 812 | 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*, all solid cancers other than bone* |
| Extended Techa River cohort: leukaemia case-control study [O13] | Case-control<br>83 cases<br>415 controls | 59% females<br>Age: 9–83 (54.3)[dd] | Russian Federation (ethnic Russians and Tartars/ Bashkirs) | Up to 47 | 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* |
| Chernobyl-related exposure in Belarus, Russian Federation and Ukraine [D52] | Case-control<br>421 cases<br>835 controls | 44% females<br>Age at exposure: in utero and 0–5<br>Age at diagnosis: 0–19 | Belarus, Russian Federation and Ukraine | Up to 14 | n.a. | Internal and external exposure in areas contaminated by the Chernobyl accident | Dose reconstruction based on environmental measurements and modelling of external and internal doses | Leukaemia* |
| Chernobyl-related exposure in Ukraine [N6] | Case-control<br>98 cases<br>151 controls | 44% females<br>Age: 0–20 | Ukraine | Up to 11 | n.a. | Internal and external exposure in areas contaminated by the Chernobyl accident | Dose reconstruction based on environmen-tal measurements and modelling of external and internal doses | Leukaemia* |
| Chernobyl-related exposure in Belarus [A10] | Case-control<br>107 cases<br>214 controls | 52% females<br>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, from contemporary thyroid radiation measure-ments, and from questionnaires and interviews | Thyroid* |
| Semipalatinsk: leukaemia case-control study [A23] | Case-control<br>22 cases, 132 controls from a cohort of ~10 000 persons | All ages, both sexes | Kazakhstan | Up to 49 | n.a. | Short-lived radionuclides from nuclear weapons tests | Based on residence histories and age at exposure | Non-CLL leukaemia |

| *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* | | | | | |
| Marshall Islands fallout [H25, R13] | Prevalence | 2 273 exposed persons<br>55% females<br>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 [K19] | Prevalence | 2 473 persons | United States | 12–17 and 32–33[bb] | n.a. | Fallout from nuclear weapons tests | Based on residence histories and fallout deposition records | Thyroid |
| Utah $^{131}$I fallout [S2] | Case-control | 92 persons with bone marrow doses of 6 mGy or more<br>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** | | | | | | | | |
| United Kingdom Atomic Energy Authority: prostate cancer [R14] | Case-control<br>136 cases<br>404 controls | Males<br>Age at diagnosis:<br><65–>75<br>14% of subjects with documented internal exposure | United Kingdom | n.a. | n.a. | 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 of above 0.01 Sv.
*i* Not available.
*j* Figures quoted in reference [L10].
*k* Figures quoted are for the leukaemia study [W2].
*l* Figures quoted in reference [S21].
*m* Significance tests based on 5-year survivors (2 years for leukaemia).
*n* Includes workers in studies [B14, C10, D11, F8, G8, G9, G10, W12, W16].
*o* Includes workers in studies [B14, B15, C10, D11, F8].
*p* Figures quoted are from reference [C10].
*q* Values for monitored workers only.
*r* Includes workers in study [G9].
*s* Figures quoted are from reference [C3].
*t* Figures quoted are from reference [G8].
*u* Figures quoted are from reference [I8].
*v* Figures quoted are from reference [K16].
*w* Figures quoted are from reference [T14, T16].
*x* Figures quoted are for the thyroid cancer study [H14].
*y* Figures quoted are for the incidence study [H6].
*z* Significance tests based on 10-year survivors.
*aa* Figures quoted are from reference [R3].
*bb* Periods of thyroid examinations, relative to the peak fallout in 1953 [K19].
*cc* Values for monitored workers only [Y10].
*dd* Values for controls.

**Table 16 Cohort and case-control epidemiological studies of carcinogenic 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* | | | | | |
| **Medical exposures** | | | | | | | | |
| $^{224}$Ra TB and ankylosing spondylitis patients [H53, N2, N3, S79] | Incidence | 899 exposed persons<br>31% females<br>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 [W9, W15] | Incidence | 1 577 exposed persons<br>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 |
| Cohort with cerebral angiography [T4, T30] | Mortality | 1 736 with Thorotrast<br>1 407 with non-radioactive agent<br>45% females<br>Age: <20–>60 (33.9) | Denmark (45%)<br>Sweden (29%)<br>United States (26%) | 2–>50 | 37 542 (26.6) | Thorotrast | Volume of Thorotrast injected (available on 80% of patients) × length of exposure | Total cancer, leukaemia, lung, pancreas, kidney |
| Cohort with cerebral angiography [N1] | Incidence | 432 with Thorotrast<br>44% females<br>Age: <20–>40 (34) | Sweden | 1–>40 | 7 284 (34) | Thorotrast | Injected volume of Thorotrast (available on 55%; number of injections used for remainder); mean injected volume: 3–52 mL (15.5) | Total cancer, stomach, small intestine, colon, rectum, liver, pancreas, respiratory, uterine corpus, ovary, prostate, kidney, bladder, skin (non-melanoma), brain/CNS, thyroid, connective tissue, sarcoma, leukaemia |
| Thorotrast patients [V1, V4] | Incidence | 2 326 exposed persons<br>1 890 unexposed persons<br>26% females | Germany | 3–>50 | n.a.[e] | Injection with Thorotrast | Hospital records of amounts injected; computerized tomography 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, lymphoblastic leukaemia, kidney, bladder, prostate, adrenal, brain, gastrointestinal tract |
| Cohort with mainly cerebral angiography [D27] | Mortality | 1 096 with Thorotrast<br>1 014 with non-radioactive agent<br>38% females<br>Age: <20–79 | Portugal | 0–>50 (22.2) | 13 283 (for >5 years after exposure) | Thorotrast | Volume of Thorotrast injected (available for 92% of the exposed patients) | Liver*, lung, bone, breast, brain, leukaemia*, all lymphoblastic and haematopoetic* |
| Early Thorotrast patients [M14, M19] | Mortality | 262 exposed persons<br>1 630 unexposed persons<br>Age: 20–39 | Japan | 18–68 | n.a. | Injection with Thorotrast | Amount injected | Liver*, lung, bone sarcoma, leukaemia* |

| *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* | | | | | |
| Later Thorotrast patients [K48, M14] | Mortality | 150 exposed persons<br>Age: 15–39 | Japan | 34–65 | n.a. | Injection with Thorotrast | Amount injected | Liver*, lung, leukaemia* |
| **Occupational exposures: radium** | | | | | | | | |
| Radium luminizers [C11, S12, S16, S25] | Incidence/mortality | 2 543 females | United States | 0–69.5 | 119 020 | 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 CNS tumours, leukaemia, multiple myeloma |
| Radium luminizers [B54, B55] | Mortality | 1 203 females | United Kingdom | 47 (max.) | 44 883 | Work with radium | Some measurements of body burdens<br>Assessments of external doses | Breast, leukaemia, osteosarcoma, all cancers combined |
| **Occupational exposures: plutonium** | | | | | | | | |
| Mayak workers as plutonium or radio-chemical workers: lung cancer study [K8] | Mortality | 1 669 men employed between 1948 and 1958, with plutonium bioassays<br>2 172 reactors workers exposed only to gamma rays | Russian Federation | Up to 46 (39.8) | 25 727 plutonium exposed; 85 151 gamma exposed | Plutonium, radiochemical or reactor work | Bioassays for plutonium and recorded dose due to external exposures | Lung |
| Mayak plutonium workers: liver cancer study [G2] | Mortality | 2 207 with detectable plutonium body burden<br>31% females | Russian Federation | Up to 49 | n.a. | Plutonium or radio-chemical work | Bioassays for plutonium and recorded dose due to external exposure | Liver |
| Sellafield plutonium workers [O1] | Incidence/mortality | 5 203 plutonium workers<br>4 609 of whom had plutonium dose assessed<br>5 179 other radiation workers<br>4 003 non-radiation workers<br>19% females | United Kingdom | Up to 46 for mortality (29);<br>Up to 40 for incidence | 415 432 (29) | 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 CNS tumours, ill-defined and secondary, non-Hodgkin's lymphoma, leukaemia |
| Rocky Flats workers [W12] | Mortality | 5 413 males with external and/or plutonium exposures | United States | Up to 28 | 52 772 (9.7) | Nuclear fuel cycle and research | Measurement of plutonium in urine, recorded exposures to external radiation | Buccal cavity and pharynx, oesophagus, stomach, colon, rectum, liver and gallbladder, pancreas, larynx, lung, bone, skin, prostate, bladder, kidney, brain and other CNS tumours, thyroid, non-Hodgkin's lymphoma, leukaemia, other lymphoblastic, benign and unspecified* |

| *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* | | | | | |
| Hanford workers [W22] | Mortality | 3 065 workers in jobs with routine potential for plutonium exposure<br>8 266 workers in jobs with non-routine or limited potential for plutonium exposure<br>15 058 workers in jobs with minimal potential for plutonium exposure<br>25% females | United States | Up to 50 | n.a. | Nuclear fuel cycle and research | Classification of jobs according to potential for plutonium exposure, number of years in such jobs | All cancers combined, digestive, lung, brain, lymphoma |
| Los Alamos workers [W6] | Mortality | 3 775 males with plutonium body burdens of 74 Bq or more<br>11 952 males with lower body burdens | United States | Up to 47 | 456 637 (29) | 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 CNS tumours, all lymphoblastic/haematopoietic cancers |
| **Occupational exposures: others (excluding radon in mines)** | | | | | | | | |
| Three industry workforces [C40] | Mortality | 17 605 workers monitored for radionuclide exposure<br>23 156 other radiation workers<br>8% females | United Kingdom | Up to 43 | 1 020 000 (25) | 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 [C6] | Mortality | Males<br>3 490 workers with internal exposure monitoring data<br>3 291 other workers<br>Age at entry: 16–64 | United States | 0–33 | 133 535 (19.7) | Nuclear fuel cycle and research | Urine measurements and whole-body monitoring of internally deposited uranium | Lung, brain and other CNS |
| Mound workers [W36] | Mortality | 4 402 males | United States (white) | Up to 40 | 104 326 (23.7) | 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 CNS tumours, thyroid, non-Hodgkin's lymphoma, Hodgkin's disease, leukaemia |
| Fernald workers [D43, R43] | Mortality | 4 014 males<br>Age at entry: (30.4) | United States | 0–49 | 124 177 (30.9) | Nuclear fuel cycle and research | Measurement of uranium, thorium and radium compounds in urine, plus environmental area sampling; recorded exposures to external radiation | Buccal cavity and pharynx, oesophagus, stomach, colon, rectum, liver, pancreas, larynx, lung, bone, skin, prostate, testis, bladder, kidney, eye, brain and other CNS tumours, thyroid, non-Hodgkin's lymphoma, Hodgkin's disease, leukaemia |

| *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* | | | | | |
| Florida phosphate workers [C39] | Mortality | 17 929 males<br>Age at entry: (median 25) | United States | Up to 44 | 545 867<br>(30.4) | Exposures in mining and chemical processing of phosphate ores | Assessment of cumulative exposures to alpha and gamma radiation based on job histories | Lung |
| Mill workers [P25] | Mortality | | United States | | | | | |
| Rocketdyne/Atomics International [R1] | Mortality | 2 297 workers<br>3% females<br>Age at entry: (34.5) | United States | Up to 45 | 58 837<br>(25.6) | Nuclear research and development | Measurement of uranium, mixed fission products, strontium, caesium and plutonium in urine and faeces, plus in vivo whole-body and lung counts; recorded exposures to external radiation | All cancers combined, all haematopoietic and lymphopoietic cancers, lung, upper aerodigestive tract cancers, bladder and kidney, prostate |
| Iron and steel workers [L86] | Mortality | Males<br>5 985 exposed<br>2 849 unexposed | China | Up to 17 | 111 286<br>(12.6) | Thorium-containing dust in an iron and steel company | Assessment of lung doses due to inhalation | Lung, leukaemia* |
| **Occupational exposures: radon in mines** | | | | | | | | |
| Uranium miners [T33] | Mortality | 5 002<br>All males | Czech Republic | Up to 48<br>(25.5) | 127 397 | Radon | Measurement data plus dose reconstruction | Lung |
| Uranium miners [R39] | Mortality | 4 134 exposed<br>All males | France | Up to 49<br>(26.2) | ~108 000 | Radon | Dose reconstruction before 1956, exposure records from 1956 on | Lung |
| **Exposures to radon in residences** | | | | | | | | |
| Iowa case-control study [F6, F12] | Incidence | 413<br>100% females | United States | n.a. | n.a. | Radon | Four 1-year alpha track detectors per home plus regional outdoor measurements | Lung |
| Cohort study [T38] | Mortality | 11 800 exposed<br>Female % n.a. | Czech Republic | (49.4) | 582 751 | Radon | Direct measurements in homes; village means | Lung |
| Acute lymphoblastic leukaemia study [L85] | Case-control<br>505 cases<br>443 controls | 48% females<br>Age at diagnosis: 0–14<br>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 |

| *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* | | | | | |
| Acute myeloid leukaemia study [S80] | Case-control<br>173 cases<br>254 controls | 51% females<br>Age at diagnosis: 0–17<br>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 subjects at time of diagnosis | Acute lymphoblastic leukaemia |
| West German childhood cancer [K47] | Case-control<br>82 leukaemia cases<br>82 solid tumour cases<br>209 controls | Age at diagnosis: 0–14<br>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 |
| Childhood Cancer Study [U16] | Case-control<br>805 leukaemia cases (1 306 controls)<br>166 non-Hodgkin's lymphoma cases (265 controls),<br>72 Hodgkin's disease cases (136 controls) | Similar proportions of males and females<br>Age at diagnosis: 0–14<br>2.8% of controls with radon concentrations of 100 Bq/m$^3$ or more | United Kingdom | n.a. | n.a. | Radon in homes | Measurements in homes occupied for six months or more<br>Characteristics of homes | Leukaemia, non-Hodgkin's lymphoma, Hodgkin's disease |
| Adult acute leukaemia [L55] | Case-control<br>578 cases<br>983 controls | Age at diagnosis: 16–69<br>5% with radon concentrations of 100 Bq/m$^3$ or more | United Kingdom | n.a. | n.a. | Radon in homes | Track-etch detector measurements in homes occupied by subjects at time of diagnosis | Acute leukaemia |
| Central Italy [F7] | Case-control<br>44 cases<br>211 controls | Males<br>Age at diagnosis: 35–80 (68)<br>75% with radon concentrations above 100 Bq/m$^3$ | Italy | 10 | n.a. | Radon and gamma radiation in homes | Measurements in last homes occupied and characteristics of homes | Acute myeloid leukaemia |
| Case-control [B41] | Case-control<br>486 cases<br>984 controls | Cases (under age 75) and controls selected from five university hospitals<br>43% of cases and 40% of controls with time-weighted average radon concentrations of 100 Bq/m$^3$ or more | France | n.a. | n.a. | Radon in homes | Radon measured in each home occupied for at least 1 year in last 5–30 years | Lung |
| **Uranium and other radionuclides in drinking water** | | | | | | | | |
| Case-cohort [A25] | Case-cohort<br>35 cases<br>Sample of 274 persons from larger cohort | 41% females | Finland | n.a. | n.a. | Uranium, $^{226}$Ra and radon in drinking water | Measurements of drinking water from drilled wells | Leukaemia |

*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 [N3].
*e* Not available.

**Table 17 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** | | |
| LSS [P1, P4, P9, P10, P48, T1] | Large population of all ages and both sexes, not selected because of disease or occupation<br>Wide range of doses<br>Comprehensive individual dosimetry<br>Survivors followed prospectively for up to 45 years<br>Complete mortality ascertainment<br>Cancer incidence ascertainment | Acute, high-dose-rate exposure that provides no direct information on effects of chronic low-dose-rate exposure<br>Restriction to 5-year survivors for mortality (13 years for incidence)<br>Possible contribution of neutrons somewhat uncertain<br>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<br>Reasonably accurate estimate of doses<br>Mortality follow-up relatively complete<br>Follow-up into adulthood | Small numbers of exposed individuals and cases<br>Cancer case determination may not be complete<br>Mechanical and thermal effects may have influenced results |
| **Treatment of malignant disease** | | |
| Cervical cancer cohort [B5, B7, B11] | Large-scale incidence study based on tumour registry records<br>Long-term follow-up<br>Relatively complete ascertainment of cancers<br>Unexposed comparison patients | Very large doses to some organs result in cell killing and tissue damage<br>Potential misclassification of metastatic disease for some organs<br>Potential misclassification of exposure<br>No individual dosimetry<br>Characteristics of patients with cervical cancer differ from general population |
| Cervical cancer case-control [B8] | Comprehensive individual dosimetry for many organs<br>Dose–response analyses<br>Other strengths as above [B5] | As above [B5], except that problems with individual dosimetry and comparison with general population now removed<br>Small number of unexposed cases<br>Partial-body and partial-organ dosimetry complex |
| Lung cancer following breast cancer [I7] | Individual estimates of radiation dose to different segments of the lungs<br>Large number of unirradiated patients<br>Most patients did not receive chemotherapy<br>Substantial proportion of patients with over 20 years of follow-up | Small number of lung cancers<br>Lack of data on individual smoking habits<br>Potential inaccuracies in partial-body dosimetry |
| Contralateral breast cancer [B10, S20] | Large numbers of cases within population-based tumour registries<br>Individual radiation dosimetry<br>Wide range of doses | Limited number of young women<br>Possibility of overmatching, resulting in some concordance of exposure between cases and controls<br>Possible misclassification of metastases or recurrence |
| Soft-tissue sarcoma following breast cancer [K18] | 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<br>Comprehensive ascertainment of treatment information to separate chemotherapy risk<br>Dose–response analyses | Very large high-dose partial-body exposure to chest wall, probably resulting in cell-killing |
| Leukaemia following cancer of the uterine corpus [C8] | Large number of cases within population-based cancer registries<br>Comprehensive individual dosimetry for bone marrow compartments<br>Attempt to adjust for chemotherapy<br>Large unirradiated comparison group<br>Dose–response analyses covering doses below 1.5 Gy as well as above 10 Gy | Effects of cell-killing at high doses<br>Potential inaccuracies in partial-body dosimetry |
| Leukaemia following testicular cancer [T24] | Cases within population-based cancer registries<br>Comprehensive individual dosimetry for bone marrow compartments<br>Attempt to adjust for chemotherapy<br>Dose–response analyses | Small number of leukaemias available to analyse the effects of age at exposure, time since exposure and interaction with chemotherapy |
| Lung cancer following Hodgkin's disease (international) [K9] | Individual estimates of radiation dose to the affected lung<br>Some data on individual smoking habits<br>Detailed information on chemotherapy<br>Relatively large number of cases | Smoking data limited, and reported more fully for cases than for controls<br>Follow-up period generally less than 10 years |

| *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<br>Individual data on smoking habits<br>Extensive data on doses from chemotherapy | Small number of cases<br>Limited follow-up (median 10 years)<br>Few females |
| Breast cancer following Hodgkin's disease [H20] | Individual assessment of doses<br>Analysis by age at exposure | Small number of cases<br>Limited follow-up<br>Mostly very high doses (>40 Gy) |
| Leukaemia following Hodgkin's disease (international) [K20] | Individual radiation dosimetry<br>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<br>Detailed information on chemotherapy | Small number of cases<br>No dose–response analysis, other than separation into two groups |
| Leukaemia following non-Hodgkin's lymphoma (United States) [T15] | Individual dosimetry for bone marrow<br>Detailed information on chemotherapy | Very small cohort, few cases<br>No comparison group of unexposed patients |
| Childhood cancers (international) [T5, T7, T10] | Comprehensive individual dosimetry to estimate organ doses<br>Attempt to adjust for drug exposure<br>Dose–response analyses | Only high-dose exposures<br>Potential for some overmatching since hospital-based<br>Complete dosimetry not always available |
| Childhood cancers (France, United Kingdom) [D16, D19] | Incidence follow-up<br>Doses from radiotherapy and chemotherapy estimated | Individual dose estimates generally not used in analyses<br>Lack of external comparison group<br>Small numbers for specific types of cancers |
| Bone cancer and leukaemia after childhood cancers (United Kingdom) [H21, H27] | Cancer case follow-up<br>Individual dosimetry<br>Information available on chemotherapy | Most of the findings concern doses of 5–10 Gy or more |
| Retinoblastoma [W11] | Long-term cancer case follow-up<br>Individual dose estimates for bone and soft-tissue sarcoma sites<br>Wide range of doses | Little information on chemotherapy<br>Most of the findings concern doses of 5 Gy or more |
| Thyroid cancer following childhood cancers [D20] | Cancer case follow-up<br>Individual organ dose estimates<br>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<br>Individual dosimetry<br>Information available on chemotherapy doses | Small number of cases<br>No formal modelling of dose response or of chemotherapy effects |
| **Treatment of benign disease** | | |
| Childhood skin haemangioma [K15, L4, L6, L7, L10, L12, L13] | Long-term and complete follow-up<br>Comprehensive individual dosimetry for many organs<br>Incidence ascertained<br>Protracted exposure to radium plaques | Relatively small numbers of specific cancers |
| Benign lesions in locomotor system [D2, J2] | Long-term and complete follow-up<br>Individual dose estimates<br>Incidence and mortality ascertained | Uncertainties in computing individual doses to sites, based upon a sample of records |
| Ankylosing spondylitis [W2, W8] | Large number of exposed patients<br>Long-term and complete mortality follow-up<br>Detailed dosimetry for leukaemia cases and sample of cohort<br>Small unexposed group evaluated for general reassurance that leukaemia risk was unrelated to underlying disease | Comparisons with general population<br>Underlying disease related to colon cancer and possibly other conditions<br>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<br>Two control groups<br>Ascertainment of cancer cases from hospital records and tumour registry<br>Individual dosimetry for many organs | Dosimetry for some sites (e.g. thyroid) uncertain, owing to possible patient movement or uncertainty in tumour location<br>Limited dose range |

| *Study* | *Strengths* | *Limitations* |
|---|---|---|
| New York tinea capitis [S7, S15, S22, S68] | Relatively good dose ascertainment for skin and other cancers | Small number of cancers<br>Few females |
| New York post-partum mastitis [S5, S22] | Individual estimates of breast dose from medical records<br>Breast cancer incidence ascertained<br>Dose–response analyses | All exposed women were parous, but comparison women were not (380 unexposed and sisters of both exposed and unexposed)<br>Inflamed and lactating breast might modify radiation effect |
| Rochester thymic irradiation [H10, H26, S18, S22] | Individual dosimetry for thyroid and some other sites<br>Sibling control group<br>Long follow-up<br>Fractionation effects could be evaluated<br>Dose–response analyses | Radiation treatment fields for newborns varied, and dosimetry uncertain for some sites<br>Adjustment in analysis for sibship size uncertain<br>Questionnaire follow-up may have resulted in underascertainment of cases |
| Tonsil irradiation [S17, S21, S22] | Individual dosimetry for thyroid and some other sites<br>Long follow-up<br>Large numbers of cases for certain sites<br>Dose–responses analyses | Effect of screening on ascertainment of thyroid cancer and nodules<br>No unexposed control group |
| Tonsil, thymus or acne irradiation [D9] | Long period between exposure and examination<br>Prospective as well as retrospective follow-up | Possible screening effect<br>Small cohort<br>No unexposed control group |
| Swedish benign breast disease [M3, M8, M17] | Incidence study with long-term follow-up<br>Individual dosimetry for many organs<br>Fractionated exposure<br>Unexposed control group | Lack of data on potential confounding factors<br>Small numbers for most cancer types other than breast |
| Benign gynaecological disorders [D7, I1, I4] | Large number of exposed women<br>Unexposed women with benign gynaecological disorders<br>Very long mortality follow-up<br>Individual dosimetry<br>Protracted exposures to radium implants (10–24 hours)<br>Dose–response analyses | Uncertainty in proportion of active bone marrow exposed<br>Small numbers of specific types of cancer<br>Misclassification of certain cancers on death certificates (e.g. pancreas) |
| Lymphoid hyperplasia screening [P5] | Individual dosimetry<br>Comparison of questionnaire and clinical examination results<br>Comparison group treated by surgery for the same condition | Apparent bias in questionnaire data, owing to self-selection of subjects<br>Clinical examinations provide data on prevalence rather than incidence<br>Study of thyroid nodules; cancer cases not confirmed |
| Peptic ulcer [C4, G6] | Individual dosimetry<br>Unexposed patients with peptic ulcer<br>Exceptionally long follow-up (>50 years)<br>Some risk factor information available in records | Standardized radiotherapy precluded dose–response analyses<br>Non-homogeneous dose distribution within organs, such that simple averaging may be misleading<br>Metastatic spread of stomach cancer probably misclassified as liver and pancreatic cancer on death certificates<br>Possible selection of somewhat unfit patients for radiotherapy rather than surgery |
| **Diagnostic examinations** | | |
| TB fluoroscopy (Massachusetts) [B3, D4, S22] | Incidence study with long-term follow-up (50 years)<br>Individual dosimetry based on patient records and measurements<br>Unexposed TB patients<br>Fractionated exposures occurred over many years<br>Dose–response analyses | Uncertainty in dose estimates related to fluoroscopic exposure time and patient orientation<br>Questionnaire response probably underascertained cancers<br>Debilitating effect of TB may have modified radiation effect for some sites, e.g. lung |
| Diagnostic X-rays (United States health plans) [B17] | Information on diagnostic X-rays abstracted from medical records<br>Surveillance bias unlikely, since cases and controls were at equal risk for having X-ray procedures recorded and malignancy diagnosed | Potential for ascertainment bias, for example through early diagnosis of a malignancy<br>Analyses based on number of X-ray procedures rather than actual doses |
| TB fluoroscopy (Canada) [H7, H9] | Large number of patients<br>Unexposed TB comparison group<br>Individual dosimetry for lung and female breast<br>Fractionated exposures occurred over many years<br>Dose–response analyses | Mortality limits comparisons with breast cancer incidence series, e.g. time response<br>Uncertainties in dosimetry limit precise quantification of risk<br>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 |
| Diagnostic medical and dental X-rays (Los Angeles) [P6, P7] | Dosimetry attempted on the basis of number and type of examinations | No available records of X-rays<br>Potential for recall bias in dose assessment<br>Doses likely to have been underestimated |

| *Study* | *Strengths* | *Limitations* |
|---|---|---|
| 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 [D17] | Adolescence possibly a vulnerable age for exposure<br>Dosimetry undertaken on the basis of number of films and breast exposure<br>Dose–response analysis | Comparison with general population potentially misleading, since scoliosis associated with several breast cancer risk factors (e.g. nulliparity)<br>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 [B12, M18, S11] | Very large numbers<br>Comprehensive evaluation of potential confounding<br>Early concerns over response bias and selection bias resolved | Uncertainty in foetal dose from obstetric X-ray examinations<br>Similar relative risks for leukaemia and other cancers may point to possible residual confounding |
| Northeastern United States childhood cancers [M16] | Large numbers<br>Reliance on obstetric records | Uncertainty in foetal dose |
| United States childhood acute lymphoblastic leukaemia [S67] | Large numbers of cancer cases<br>Information collected on potential confounding factors | Uncertainty in foetal dose – likely to be lower than in previous decades<br>Not possible to validate exposure data using medical records |
| Swedish childhood leukaemia [N4] | Population-based design with cancer cases<br>Reliance on medical records, which were ascertained for most potential study subjects | Uncertainty in foetal dose<br>Number of cases smaller than in some other studies |
| **Occupational exposures** | | |
| Nuclear workers | Often large numbers<br>Personal dosimetry<br>Low-dose fractionated exposures<br>Could provide useful information in future | Low doses make clear demonstration of radiation effect difficult<br>Possibly confounding influence of chemical and other toxic exposures in workplace<br>Healthy worker effect<br>Mortality follow-up<br>Lifestyle factors (e.g. smoking histories) generally not available |
| United States non-Hodgkin's lymphoma case-control [E10] | Large number of cases, identified from population-based cancer registries<br>Pathological review of cases<br>Low-dose fractionated exposures<br>Information on potential confounding factors | Reliance on self-reported occupational exposures<br>Low doses make clear demonstration of radiation effect difficult |
| Chernobyl clean-up workers | Often large numbers<br>Low-dose fractionated exposures<br>Could provide useful information in future | Difficulties in assessing individual exposures<br>Possible differences in cancer ascertainment relative to the general population<br>Short period of follow-up so far |
| Mayak workers [S28, Z3] | Wide range of exposures<br>Individual measurements of external gamma dose and plutonium body burden<br>Individual information on potential confounding factors in stomach cancer study | Possible uncertainties in assessment of exposures<br>Further details of ascertainment of stomach cancer cases and controls desirable |
| Medical workers | Often large numbers<br>Low-dose fractionated exposures over long periods | General lack of information on individual doses precludes usefulness to date |
| **Natural sources of radiation** | | |
| Yangjiang [A11, S23, T12, T14, T16, Z2] | Large cohorts in high-background and control areas<br>Stable population<br>Extensive dosimetry for region<br>Assessment of potential confounding factors | Mortality follow-up<br>Small numbers for some cancer types<br>Low doses |
| United Kingdom Childhood Cancer Study [U17] | Large numbers of cases ascertained within a population-based study<br>Individual measurements of domestic gamma radiation dose rates | Gamma radiation dose rates generally low and did not vary greatly |
| Sweden [A24] | Cancer cases within population-based registry | Possible misclassification of exposures, owing to absence of measurements for dwellings not known to have been built from alum shale concrete<br>Low doses |

| *Study* | *Strengths* | *Limitations* |
|---|---|---|
| Central Italy [F7] | Individual measurements of domestic gamma radiation and radon | Small number of cases<br>Mortality data only<br>Measurements only in last home<br>Low doses |
| **INTERNAL LOW-DOSE-RATE EXPOSURES** | | |
| **Medical exposures** | | |
| Swedish $^{131}$I thyroid cancer [H6, H24] | Large numbers<br>Nearly complete cancer case ascertainment<br>Administered activities of $^{131}$I known | Comparison with general population<br>Dose–response not based on organ doses<br>High-dose cell-killing probably reduced possible thyroid effect<br>Patients selected for treatment |
| Diagnostic $^{131}$I [H8, H12, H14] | Large numbers<br>Unbiased and nearly complete ascertainment of cancers through linkage with cancer registry<br>Administered activities of $^{131}$I known for each patient<br>Organ doses to the thyroid computed with some precision<br>Dose–response analyses for thyroid cancer and leukaemia, based on wide range of doses<br>Low-dose-rate exposure | Comparison with general population only, except for thyroid cancer and leukaemia<br>Reason for some examinations related to high detection of thyroid cancers, i.e. suspicion of thyroid tumour was often correct<br>Doses to organs other than thyroid very low<br>Population under surveillance |
| United States thyrotoxicosis patients [D12, R3, S24] | Large numbers of patients treated with $^{131}$I<br>Large unexposed comparison groups<br>Comprehensive follow-up effort<br>Administered activities of $^{131}$I known | Individual doses computed only for certain organs<br>Mortality follow-up<br>Few patients irradiated at young ages<br>Possibility of selection bias by treatment |
| Thyroid cancer patients [D18, H2, R38] | Cancer case follow-up<br>Administered activities of $^{131}$I known<br>Unexposed group | Individual doses not computed<br>Small numbers for some specific cancer types<br>Few patients irradiated at young ages<br>Possibility of selection bias by treatment |
| French therapeutic $^{131}$I [D18] | Cancer case follow-up<br>Administered activities of $^{131}$I known<br>Exclusion of patients who received external radiotherapy<br>Unexposed group | Individual doses not computed<br>Small numbers for specific cancer types<br>Few patients irradiated at young ages<br>Possibility of selection bias by treatment |
| **Environmental exposures** | | |
| Techa River population [K4, K13, K49, K50, O2] | Large numbers with relatively long follow-up<br>Wide range of estimated doses<br>Unselected population; attempted use of local population rates for comparison<br>Possible to examine ethnic differences in cancer risk<br>Potential for future | Dosimetry difficult and not individual<br>Mixture of internal and external exposures complicates dosimetry<br>Follow-up and cancer case ascertainment uncertain<br>Contribution of chemical exposures not evaluated |
| Chernobyl-related exposure [A10, D52, N6] | Large numbers exposed<br>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<br>Possible differences in cancer ascertainment relative to the general population<br>Fairly short period of follow-up so far<br>Generally low doses to bone marrow<br>Low participation rates in Ukrainian leukaemia study [N6] |
| Marshall Islands fallout [H25, R13] | Population unselected for exposure<br>Comprehensive long-term medical follow-up<br>Individual dosimetry attempted | Mixture of radioiodines and gamma radiation precludes accurate dose estimation<br>Surgery and hormonal therapy probably influenced subsequent occurrence of thyroid neoplasms<br>Small numbers |
| Utah $^{131}$I fallout: thyroid disease [K19] | Comprehensive dosimetry attempted<br>Protracted exposures at low rate | Possible recall bias in consumption data used for risk estimation<br>Possible underascertainment of disease in low-dose subjects<br>Small number of thyroid cancers |
| Utah $^{131}$I fallout [S2] | Comprehensive dosimetry attempted<br>Large number of leukaemia deaths<br>Protracted exposures at low rate | Uncertainty in estimating bone marrow doses<br>Estimated cumulative doses lower than from natural background radiation |
| **Occupational exposures** | | |
| United Kingdom Atomic Energy Authority: prostate cancer [R14] | Information abstracted for study subjects on socio-demographic factors, exposures to radionuclides, external doses and other substances in the workplace<br>Cases and controls selected from an existing cohort | Exposures to some radionuclides tended to be simultaneous, making it difficult to study them individually |

**Table 18 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<br>Long-term follow-up<br>Substantial proportion of patients treated in childhood or adolescence | Uncertainties in organ doses for individual patients<br>Other aspects of treatment may be relevant (e.g. X-rays)<br>Comparison group constructed only recently for the Spiess study [S79] |
| **Diagnostic examinations** | | |
| Thorotrast patients | Large number of excess cancers<br>Long-term follow-up | Uncertainties in organ doses for individual patients<br>Chemical attributes of Thorotrast might influence risks |
| **Occupational exposures** | | |
| Radium luminizers | Protracted exposures from $^{226}$Ra<br>Large numbers of excess cancers in United States study | Potential inaccuracies in estimating radium intakes<br>Distribution of radium in bone may be non-uniform<br>External irradiation may be relevant for breast cancers |
| Mayak workers | Wide range of exposures<br>Individual measurements of plutonium body burden and external gamma dose<br>Information on smoking and other potential confounding factors in the lung cancer case-control study | Possible uncertainties in assessment of exposures<br>Further details of the ascertainment of subjects in the lung cancer case-control study [T9] 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 confounding factors<br>Possible uncertainties in assessment of internal exposures |
| Florida phosphate workers [C39] | Relatively large number of person-years<br>Assessment of exposures to other agents (e.g. silica and acid mists) | Not possible to obtain direct quantitative estimates of exposure levels<br>Absence of data on smoking habits for lung cancer analysis |
| Chinese iron and steel workers [L86] | Assessments made of lung doses due to inhalation of thorium<br>Information available on smoking habits | Lung doses generally low<br>Small numbers of deaths for specific cancer types |
| Radon-exposed underground miners | Large numbers<br>Protracted exposures over several years<br>Wide range of cumulative exposures<br>Exposure–response analyses | Uncertainties in assessment of early exposures (e.g. [R8, W10, X2], but applies to other studies considered in reference [L8])<br>Possible modifying effect of other types of exposure (e.g. arsenic)<br>Smoking histories limited or not available |
| **Environmental exposures** | | |
| Residential radon | Large numbers in most studies<br>Protracted exposures over many years<br>Individual data on radon and smoking | Uncertainties in assessing exposures (measurement error, mobility between dwellings, structural changes to dwellings)<br>Radon concentrations low for many subjects |

**Table 19 Risk estimates for cancer incidence and mortality from studies of radiation exposure: total solid cancers (or all cancers apart from leukaemia when noted)**

The number of observed and expected cases as well as the mean dose and number of person-years for cohort studies are computed throughout this table for exposed persons only. In the LSS the exposed group included survivors with doses of 0.005 Sv or more (weighted colon dose) for incidence or mortality. The studies listed are those for which quantitative estimates of risk could be made

| *Study* | | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|---|
| **EXTERNAL LOW-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| LSS [P48] | | | | | | | |
| Sex | Males | 3 433 | 3 192.2[d] | 0.21 | 436 180 | 0.43 (0.35, 0.53) | 14.57 (10.68, 18.88) |
| | Females | 4 418 | 3 836.0[d] | 0.20 | 729 607 | 0.81 (0.71, 0.92) | 31.52 (27.40, 35.83) |
| Age at exposure | <20 years | 2 120 | 1 758.3[d] | 0.21 | 586 255 | 1.00 (0.86, 1.15) | 20.65 (17.26, 24.25) |
| | 20–40 years | 3 093 | 2 832.8[d] | 0.21 | 378 204 | 0.50 (0.39, 0.61) | 29.67 (23.47, 36.24) |
| | >40 years | 2 638 | 2 472.9[d] | 0.19 | 201 329 | 0.36 (0.25, 0.48) | 37.28 (25.23, 50.11) |
| Time since exposure | 12–15 years | 389 | 348.3[d] | 0.21 | 119 774 | 0.44 (0.16, 0.78) | 9.68 (5.42, 15.16) |
| | 15–30 years | 2 492 | 2 218.5[d] | 0.21 | 514 582 | 0.58 (0.46, 0.71) | 16.87 (13.39, 20.63) |
| | >30 years | 4 970 | 4 476.9[d] | 0.20 | 531 432 | 0.64 (0.55, 0.73) | 46.84 (40.69, 53.24) |
| All | | 7 851 | 7 036.4 | 0.21 | 1 165 787 | 0.62 (0.55, 0.69) | 24.54 (21.53, 27.68) |
| Canadian National Dose Registry [S8][b] | | 2 030 | n.a. | 0.066 4 | 2 667 903 | 2.3 (1.1, 3.9)[g] | n.a. |
| Capenhurst uranium facility, United Kingdom [M4][b] | | 177 | 215.83 | 0.098 5 | 40 933 | –0.67 (<–1.72, 4.32)[i] | n.a. |
| Springfields uranium workers, United Kingdom [M5][b] | | 901 | 1 115.79 | 0.022 8 | 190 795 | 1.77 (–0.06, 4.02)[i] | n.a. |
| United Kingdom Chapelcross workers [M6][b] | | 131 | 149.44 | 0.083 6 | 39 210 | 1.28 (–0.38, 3.79)[i] | n.a. |
| **Mortality** | | | | | | | |
| LSS [P10] | | | | | | | |
| Sex | Males | 2 711 | 2 564.2[d] | 0.20 | 682 048 | 0.34 (0.24, 0.45) | 2.74 (1.20, 4.67) |
| | Females | 3 090 | 2 745.7[d] | 0.19 | 1 075 919 | 0.65 (0.52,0.78) | 7.10 (5.19, 9.17) |
| Age at exposure | <20 years | 1 185 | 998.6[d] | 0.20 | 916 830 | 0.80 (0.62,1.00) | 3.42 (2.09, 4.93) |
| | 20–40 years | 2 138 | 1 968.4[d] | 0.20 | 520 263 | 0.49 (0.36, 0.63) | 9.50 (6.13, 13.21) |
| | >40 years | 2 478 | 2 353.6[d] | 0.18 | 320 873 | 0.28 (0.17, 0.41) | 17.14 (10.01, 24.84) |
| Time since exposure | 12–15 years | 762 | 719.2[d] | 0.20 | 465 730 | 0.26 (0.07, 0.48) | 0.92 (0.04, 2.16) |
| | 15–30 years | 1 625 | 1 480.3[d] | 0.20 | 586 804 | 0.44 (0.29, 0.60) | 4.48 (2.60, 6.68) |
| | >30 years | 3 414 | 3 116.9[d] | 0.19 | 705 432 | 0.54 (0.44, 0.65) | 17.95 (14.48, 21.63) |
| All | | 5 801 | 5 313.2[d] | 0.20 | 1 757 966 | 0.48 (0.40, 0.57) | 5.16 (3.80, 6.63) |
| Nuclear workers in Canada, United Kingdom and United States [C3][b] | | 3 830 | n.a. | 0.040 2 | 2 124 526 | –0.07 (–0.39, 0.30) | n.a. |
| United Kingdom NRRW [M12][b] | | 3 020 | n.a. | 0.030 5 | 2 063 300 | 0.09 (–0.28, 0.52) | n.a. |
| Nuclear power industry workers in the United States [H44] | | 368 | 564.3 | 0.026 | 698 041 | 0.51 (–2.01, 4.64)[c] | n.a. |
| Extended Techa River cohort [K50] | | 1 842 | n.a. | 0.03[e] | 865 812 | 0.92 (0.2, 1.7)[c, e] | 70.5 (25, 118)[c, e, f] |
| IARC 15-country nuclear worker study [C41] | | 6 519 | n.a. | 0.019 4 | 5 192 710 | 0.97 (0.14, 1.97)[c] | n.a. |

| *Study* | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|
| **INTERNAL LOW-LET EXPOSURES** | | | | | | |
| **Mortality** | | | | | | |
| Semipalatinsk study [B58] | 889 | n.a. | 0.63 | 582 750 | 0.81 (0.46, 1.33)[c, h] | n.a. |

[a] 90% CI in parentheses derived from fitting models (4) and (5) for the LSS, and derived from published data for other studies unless otherwise stated.
[b] All cancers except leukaemia.
[c] 95% CI in parentheses.
[d] All expected numbers calculated by means of fitted relative risk model (4), evaluated at zero dose.
[e] Based on stomach dose, which is predominantly (75%) due to external exposure [K50].
[f] Estimated at age 70.
[g] Tabulation and analysis with a 10-year lag. Risk estimate based on a dose–response analysis.
[h] Based on a dose–response analysis, restricted to the exposed group only.
[i] Males only.

**Table 20 Risk estimates for cancer incidence and mortality from studies of radiation exposure: salivary gland 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 LSS of cancer incidence the exposed group included survivors with organ (brain) doses of 0.005 Sv or more. The studies listed are those for which quantitative estimates of risk could be made

| *Study* | | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|---|
| **EXTERNAL LOW-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| LSS [P48][e] | | | | | | | |
| Sex | Males | 17 | 7.1[b] | 0.26 | 436 180 | 4.50 (1.32, 12.68) | <0 (<0, 105.57) |
| | Females | 6 | 6.9[b] | 0.24 | 729 608 | 0.95 (<0, 4.09) | <0 (<0, 46.27) |
| Age at exposure | <20 years | 13 | 3.2[b] | 0.25 | 586 255 | 11.12 (3.40, 43.32) | <0 (<0, 64.40) |
| | 20–40 years | 5 | 7.8[b] | 0.26 | 378 204 | <0 (<0, 0.46) | <0 (<0, 0.05) |
| | >40 years | 5 | 3.8[b] | 0.24 | 201 330 | 1.39 (<0, 8.30) | <0 (<0, 63.69) |
| Time since exposure | 12–15 years | 4 | 2.2[b] | 0.26 | 119 774 | 1.91 (<0, 25.28) | <0 (<0, 81.44) |
| | 15–30 years | 7 | 5.6[b] | 0.25 | 514 582 | 1.42 (0.01, 5.76) | <0 (<0, 55.01) |
| | >30 years | 12 | 6.6[b] | 0.24 | 531 433 | 3.81 (0.99, 10.65) | <0 (<0, 85.38) |
| All | | 23 | 14.4[b] | 0.25 | 1 165 788 | 2.55 (0.87, 5.72) | <0 (<0, 73.21) |
| LSS [L83] | | | | | | | |
| Mucoepidermoid carcinoma | | 11 | n.a. | 0.20[c] | 2 124 057[d] | 8.30 (2.56, 29.6)[c] | 0.21 (0.10, 0.37)[c] |
| Other malignant neoplasm | | 20 | n.a. | 0.20[c] | 2 124 057[d] | 1.36 (–0.01, 4.73)[c] | 0.12 (0.01, 0.28)[c] |
| Warthin's tumour | | 12 | n.a. | 0.20[c] | 2 124 057[d] | 3.05 (0.58, 10.3)[c] | 0.10 (0.01, 0.25)[c] |
| Other benign neoplasm | | 52 | n.a. | 0.20[c] | 2 124 057[d] | 0.30 (–0.10, 1.18)[c] | 0.08 (<0, 0.26)[c] |
| Childhood benign head and neck tumour cohort [S74] | | | | | | | |
| Benign tumours | | 68 | n.a. | 4.2 | n.a. | 19.6 (0.16, ∞)[f] | n.a. |
| Malignant tumours | | 22 | n.a. | 4.2 | n.a. | –0.06 (–∞, 4.0)[f] | n.a. |
| All tumours | | 90 | n.a. | 4.2 | n.a. | 0.82 (0.04, ∞)[f] | n.a. |

[a] 90% CI in parentheses derived from fitting models (4) and (5) for the LSS, and derived from published data for other studies.
[b] All expected numbers calculated by means of fitted relative risk model (4), evaluated at zero dose.
[c] Calculated using shielded kerma dose.
[d] Calculated using all survivors excluding the not-in-city group and those with unknown dose.
[e] Calculated using brain dose.
[f] 95% CI.

**Table 21 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 LSS the exposed group included survivors with doses of 0.005 Sv or more (weighted stomach dose) for incidence or mortality. The studies listed are those for which quantitative estimates of risk could be made

| *Study* | | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|---|
| **EXTERNAL LOW-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| LSS [P48][i] | | | | | | | |
| Sex | Males | 120 | 110.2[j] | 0.22 | 436 180 | 0.48 (0.09, 1.00) | <0 (<0, 1112.5) |
| | Females | 32 | 29.9[j] | 0.21 | 729 608 | 0.70 (<0, 2.28) | 0.02 (<0, 0.45) |
| Age at exposure | <20 years | 40 | 29.3[j] | 0.22 | 586 255 | 1.34 (0.44, 2.82) | <0 (<0, 262.07) |
| | 20–40 years | 44 | 42.3[j] | 0.21 | 378 204 | <0 (<0, 0.76) | <0 (<0, 501.33) |
| | >40 years | 68 | 70.1[j] | 0.20 | 201 330 | 0.33 (<0, 1.06) | 1.90 (0.46, 3.93) |
| Time since exposure | 12–15 years | 9 | 6.4[j] | 0.22 | 119 774 | 0.90 (<0, 5.21) | <0 (<0, 282.42) |
| | 15–30 years | 57 | 56.2[j] | 0.22 | 514 582 | 0.59 (<0, 1.51) | 0.32 (0.04, 0.83) |
| | >30 years | 86 | 77.4[j] | 0.21 | 531 433 | 0.45 (0.03, 1.08) | 4.72 (3.64, 5.98) |
| All | | 152 | 140.2[j] | 0.21 | 1 165 788 | 0.51 (0.14, 0.99) | 0.19 (<0, 0.53) |
| Cervical cancer cohort [B11][c] | | 12 | 11.0 | 0.35 | 178 243 | 0.26 (–1.1, 1.3)[l] | 0.16 (–0.6, 1.3)[l] |
| Springfields uranium workers, United Kingdom [M5] | | 20 | 26.65 | 0.022 8 | 190 795 | –1.96 (<–2.00, 5.95)[n] | n.a. |
| **Mortality** | | | | | | | |
| LSS [P9] | | | | | | | |
| Sex | Males | 128 | 118.8[j] | 0.19 | 666 869 | 0.55 (0.09, 1.17) | 0.25 (0.01, 0.82) |
| | Females | 43 | 33.7[j] | 0.18 | 1 061 687 | 1.40 (0.20, 3.37) | <0 (<0, 151.21) |
| Age at exposure | <20 years | 36 | 24.3[j] | 0.19 | 885 656 | 1.38 (0.18, 3.60) | <0 (<0, 141.53) |
| | 20–40 years | 52 | 41.8[j] | 0.19 | 514 903 | 0.59 (<0, 1.93) | <0 (<0, 353.89) |
| | >40 years | 83 | 86.5[j] | 0.18 | 327 997 | 0.60 (0.05, 1.37) | 1.95 (0.72, 3.60) |
| Time since exposure | 12–15 years | 33 | 27.4[j] | 0.18 | 504 112 | 1.30 (0.16, 3.24) | <0 (<0, <0) |
| | 15–30 years | 57 | 55.5[j] | 0.19 | 592 956 | 0.81 (0.09, 1.92) | <0 (<0, 373.73) |
| | >30 years | 81 | 69.9[j] | 0.19 | 631 488 | 0.40 (<0, 1.23) | <0 (<0, 493.70) |
| All | | 171 | 153.0[j] | 0.19 | 1 728 556 | 0.69 (0.24, 1.28) | <0 (<0, 386.68) |
| Ankylosing spondylitis [W8][d] | | 74 | 38 | 5.55 | 287 095 | 0.17 (0.09, 0.25)[l] | 0.23 (0.1, 0.3)[e, l] |
| Metropathia haemorrhagica [D7] | | 9 | 9.27 | 0.05 | 47 144 | –0.58 (–11.2, 16.8)[b, l] | –1.15 (–22.0, 33.0)[b, l] |
| Nuclear workers in Canada, United Kingdom and United States [C3] | | 104 | n.a. | 0.04 | 2 124 526 | >0[f] | n.a. |
| United Kingdom NRRW [M12] | | 120 | n.a. | 0.040 2 | 2 124 526 | –0.095 (<–1.95, 4.06) | n.a. |
| Los Alamos National Laboratory workers, United States [W6] | | 22 | 27.4 | ~0.016 | 251 651 | >0[h] | n.a. |
| Nuclear workers in Japan [E3] | | 25 | 37.1 | 0.014 | 533 168 | >0[g] | n.a. |
| Nuclear industry workers in Japan [I14] | | 100 | 119.3 | 0.015 | ~1 390 000 | >0[k] | >0[k] |

| *Study* | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk*[a] *at 1 Sv* | *Average excess absolute risk*[a] *($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|
| **INTERNAL LOW-LET EXPOSURES** | | | | | | |
| **Mortality** | | | | | | |
| Semipalatinsk study [B58] | 317 | n.a. | 0.63 | 582 750 | 0.18 (–0.09, 0.66)[l, m] | n.a. |

[a] 90% CI in parentheses derived from fitting models (4) and (5) for the LSS, and derived from published data for the other studies, unless otherwise stated.
[b] Estimates based on method described in the introduction to chapter III of annex I in the UNSCEAR 2000 Report [U2].
[c] The values given are for 10-year survivors.
[d] The values given exclude the period within 5 years of first treatment.
[e] Dose–response analysis based on the number of treatment courses given.
[f] Based on a 10-year lag. Trend not statistically significant.
[g] 90% CI in parentheses derived from published data for the LSS and using exact Poisson methods for the other studies.
[h] Positive dose–response trend ($p < 0.10$).
[i] Calculated using stomach dose.
[j] All expected numbers calculated by means of fitted relative risk model (4), evaluated at zero dose.
[k] Statistically significant increasing trend with dose (2-sided $p < 0.05$, adjusted for multiple comparisons (Bonferroni method)).
[l] 95% CI in parentheses.
[m] Based on a dose–response analysis, restricted to the exposed group only.
[n] Males only.

**Table 22 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 LSS the exposed group included survivors with doses of 0.005 Sv or more (weighted stomach dose) for incidence or mortality. The studies listed are those for which quantitative estimates of risk could be made

| *Study* | | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk*[a] *at 1 Sv* | *Average excess absolute risk*[a] *($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|---|
| **EXTERNAL LOW-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| LSS [P48] | | | | | | | |
| Sex | Males | 1 084 | 1 036.6[v] | 0.22 | 436 180 | 0.26 (0.14, 0.42) | 2.45 (0.92, 4.49) |
| | Females | 1 011 | 913.2[v] | 0.21 | 729 608 | 0.51 (0.33, 0.72) | 4.36 (2.78, 6.15) |
| Age at exposure | <20 years | 435 | 381.2[v] | 0.22 | 586 255 | 0.56 (0.32, 0.85) | 2.74 (1.52, 4.19) |
| | 20–40 years | 809 | 750.6[v] | 0.21 | 378 204 | 0.39 (0.22, 0.59) | 6.18 (3.42, 9.32) |
| | >40 years | 851 | 821.9[v] | 0.20 | 201 330 | 0.23 (0.07, 0.41) | 7.99 (2.25, 14.59) |
| Time since exposure | 12–15 years | 154 | 132.2[v] | 0.22 | 119 774 | 0.37 (<0, 0.92) | 2.40 (0.66, 5.21) |
| | 15–30 years | 796 | 758.5[v] | 0.22 | 514 582 | 0.31 (0.15, 0.50) | 2.71 (1.32, 4.40) |
| | >30 years | 1 145 | 1 059.6[v] | 0.21 | 531 433 | 0.42 (0.27, 0.58) | 6.75 (4.28, 9.48) |
| All | | 2 095 | 1 951.5[v] | 0.21 | 1 165 788 | 0.37 (0.26, 0.49)[b] | 3.61 (2.42, 4.96) |
| Cervical cancer case-control [B8][c] | | 348 | 167.3 | 2 | n.a. | 0.54 (0.05, 1.5) | n.a. |
| Swedish benign breast disease [M3] | | 14 | 15.6 | 0.66 | 26 493 | 1.3 (0, 4.4)[n] | n.a. |
| Stockholm skin haemangioma [L10] | | 5 | ~6 | 0.09 | 406 565 | <0 | <0 |
| Springfields uranium workers, United Kingdom [M5] | | 56 | 73.90 | 0.022 8 | 190 795 | –1.96 (<–2.00, 9.73)[z] | n.a. |

| *Study* | | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|---|
| **Mortality** | | | | | | | |
| LSS [P9] | | | | | | | |
| Sex | Males | 890 | 867.3[v] | 0.19 | 666 869 | 0.11 (<0, 0.30) | 0.32 (<0, 1.33) |
| | Females | 780 | 717.6[v] | 0.18 | 1 061 687 | 0.50 (0.27, 0.75) | 1.46 (0.55, 2.56) |
| Age at exposure | <20 years | 206 | 176.9[v] | 0.19 | 885 656 | 0.72 (0.29, 1.27) | 0.51 (<0, 1.27) |
| | 20–40 years | 530 | 488.1[v] | 0.19 | 514 903 | 0.42 (0.18, 0.71) | 2.78 (1.06, 4.82) |
| | >40 years | 934 | 918.0[v] | 0.18 | 327 997 | 0.12 (<0, 0.31) | 3.46 (<0, 8.03) |
| Time since exposure | 12–15 years | 368 | 356.4[v] | 0.18 | 504 112 | 0.17 (<0, 0.48) | 0.17 (<0, 1.25) |
| | 15–30 years | 623 | 604.9[v] | 0.19 | 592 956 | 0.22 (0.02, 0.46) | 0.62 (<0, 1.76) |
| | >30 years | 679 | 615.7[v] | 0.19 | 631 488 | 0.46 (0.23, 0.73) | 3.89 (2.19, 5.83) |
| All | | 1 670 | 1 585.3[v] | 0.19 | 1 728 556 | 0.28 (0.14, 0.42) | 0.94 (0.31, 1.71) |
| Ankylosing spondylitis [W8][d] | | 127 | 128 | 3.21 | 287 095 | –0.004 (–0.05, 0.05)[e,n] | n.a. |
| Yangjiang background radiation [T14, T16] | | 70 | 77.8 | n.a.[f] | 1 246 340 | –0.27 (–1.37, 2.69)[g,n] | n.a. |
| Peptic ulcer [C4] | | 47 | 14.7 | 14.8 | 41 779 | 0.20 (0.0, 0.73)[h,n] | n.a. |
| Metropathia haemorrhagica [D7][i] | | 33 | 26.8 | 0.23 | 47 144 | 1.01 (–0.65, 3.17)[b,n] | 5.72 (–3.71,18.0)[b,n] |
| Benign gynaecological disorders [I4][j] | | 23 | 21.8 | 0.2 | 71 958 | 0.27 (–4.25, 4.80)[k] | 0.83 (<0, 72.7)[b] |
| Nuclear workers in Canada, United Kingdom and United States [C3] | | 275 | n.a. | 0.040 2 | 2 124 526 | <0[l] | n.a. |
| United Kingdom NRRW [M12] | | 245 | 294.4 | 0.030 5 | 2 063 300 | –0.032 (–0.95, 1.49)[m] | n.a. |
| Canadian National Dose Registry [A8] | | 70 | 121.7 | 0.063 | 2 861 093 | 12.5 (<0, 33)[z] | n.a. |
| Nuclear industry workers in Japan [I14] | | 428 | 481.9 | 0.015 | ~1 390 000 | >0[w] | >0[w] |
| Nuclear power industry workers in the United States [H44] | | 16 | 19.7 | 0.026 | 698 041 | 19.5 (–2.23, 141)[n] | n.a. |
| Japanese radiological technologists [A4] | | 98 | 151.1 | 0.466 | 270 585 | <0 | <0 |
| **INTERNAL LOW-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| Swedish hyperthyroid patients [H6] | | 58[o] | 43.6 | 0.25 Gy | n.a. | 1.32[p] (0.04, 2.84) | n.a. |
| **Mortality** | | | | | | | |
| United States thyrotoxicosis patients [R3] | | 82 | 78 | 0.178 | 385 468 | >0[q] | n.a. |
| Semipalatinsk study [B58] | | 150 | n.a. | 0.63 | 582 750 | 0.95 (0.17, 3.49)[n,y] | n.a. |
| **INTERNAL HIGH-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| $^{224}$Ra ankylosing spondylitis patients [W15] | | 18 | 12.2 | n.a. | 32 800 | 1.56[r,s] | n.a. |
| $^{224}$Ra ankylosing spondylitis patients [N2] | | 13 | ~11 | n.a. | 25 000 | ~1.2[r] | n.a. |
| Danish Thorotrast patients [A5] | | 7 | 6.9 | n.a. | 19 365 | 1.82 (0.61, 5.66)[r,n] | n.a. |
| Danish and Swedish Thorotrast patients [T30] | | 13 | 10.8 | n.a. | 25 480 | 2.7 (1.1, 7.9)[r,x] | n.a. |

| *Study* | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|
| **Mortality** | | | | | | |
| German Thorotrast patients [V3, V4] | 30[t] | n.a. | 20.6 mL[u] | n.a. | 0.6[r] | n.a. |

*a* 90% CI in parentheses derived from fitting models (4) and (5) for the LSS, and derived from published data for the other studies, unless otherwise stated.
*b* Estimates based on method described in the introduction to chapter III of annex I in the UNSCEAR 2000 Report [U2].
*c* Based on 5-year survivors. The observed and expected numbers are for both exposed and unexposed.
*d* The values given exclude the period within 5 years of first treatment.
*e* Dose–response analysis based on the number of treatment courses given.
*f* Mean annual effective dose = 6.4 mSv.
*g* Based on a 10-year latent period.
*h* Trend based on the exposed patients only, with doses of 1–10 Gy.
*i* The values given exclude the period within 5 years of irradiation.
*j* The observed and expected numbers of cases are for 10-year survivors. The estimated number of expected cases incorporated an adjustment based on the Poisson regression model given in reference [I4].
*k* Wald-type CI.
*l* Based on a 10-year lag. Trend not statistically significant.
*m* Tabulation and analysis with a 10-year lag. Risk estimate based on a dose–response analysis.
*n* 95% CI in parentheses.
*o* Restricted to the period 10 or more years after treatment.
*p* Relative risk at 1 Gy.
*q* No apparent trend with administered activity of $^{131}$I, although a significance test was not performed.
*r* Risk relative to unexposed controls.
*s* In the control group, 16 stomach cancers were diagnosed, compared with 16.9 expected.
*t* Number quoted in an earlier follow-up [V3].
*u* Amount of Thorotrast administered.
*v* All expected numbers calculated by means of fitted relative risk model (4), evaluated at zero dose.
*w* Statistically significant increasing trend with dose (2-sided $p < 0.05$ (unadjusted for multiple comparisons), 2-sided $p > 0.2$ (adjusted for multiple comparisons using Bonferroni method)).
*x* Relative risk and 95% CI (compared with Thorotrast unexposed group), but there is no statistically significant trend with administered Thorotrast ($p = 0.997$).
*y* Based on a dose–response analysis, restricted to the exposed group only.
*z* Males only.

**Table 23 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 LSS the exposed group included survivors with doses of 0.005 Sv or more (weighted colon dose) for incidence or mortality. The studies listed are those for which quantitative estimates of risk could be made

| *Study* | | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|---|
| **EXTERNAL LOW-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| LSS [P48] | | | | | | | |
| Sex | Males | 323 | 274.0[o] | 0.21 | 436 180 | 0.85 (0.52, 1.26) | 1.41 (0.10, 3.07) |
| | Females | 348 | 330.3[o] | 0.20 | 729 607 | 0.42 (0.14, 0.76) | 1.46 (0.69, 2.45) |
| Age at exposure | <20 years | 229 | 205.2[o] | 0.21 | 586 255 | 0.81 (0.46, 1.24) | 0.99 (0.31, 1.92) |
| | 20–40 years | 301 | 274.0[o] | 0.21 | 378 204 | 0.44 (0.14, 0.82) | 1.78 (0.56, 3.46) |
| | >40 years | 141 | 129.6[o] | 0.19 | 201 329 | 0.45 (<0, 1.13) | 3.11 (0.22, 6.54) |
| Time since exposure | 12–15 years | 12 | 7.5[o] | 0.21 | 119 774 | 2.02 (<0, 9.30) | <0 (<0, 349.91) |
| | 15–30 years | 97 | 77.1[o] | 0.21 | 514 582 | 1.24 (0.51, 2.25) | 1.14 (0.44, 2.09) |
| | >30 years | 562 | 520.5[o] | 0.20 | 531 432 | 0.52 (0.30, 0.78) | 2.95 (1.32, 4.89) |
| All | | 671 | 603.7[o] | 0.21 | 1 165 787 | 0.64 (0.42, 0.90) | 1.44 (0.76, 2.27) |
| Cervical cancer case-control [B8][c] | | 409 | 409 | 24 | n.a. | 0.00 (–0.01, 0.02) | 0.01 (–0.09, 0.18) |
| Swedish metropathia cohort [R26] | | 12 | 8.2 | 0.093 | 9 289 | 5.0 (–2.2, 16)[k] | n.a. |
| Stockholm skin haemangioma [L10] | | 12 | ~11 | 0.07 | 406 565 | 0.37[d] | 0.11 |
| Canadian National Dose Registry [S8] | | 315 | 349.4 | 0.066 2 | 2 667 903 | 2.6 (<0, 7.5)[m] | n.a. |

| *Study* | | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|---|
| Capenhurst uranium facility, United Kingdom [M4][b] | | 14 | 13.60 | 0.098 5 | 40 933 | –1.30 (<–1.30, 23.97)[n] | n.a. |
| Springfields uranium workers, United Kingdom [M5] | | 52 | 71.37 | 0.022 8 | 190 795 | 11.41 (<–6.27, 36.45)[n] | n.a. |
| United Kingdom Chapelcross workers [M6] | | 8 | 9.37 | 0.083 6 | 39 210 | 2.10 (<–2.65, 13.92)[n] | n.a. |
| **Mortality** | | | | | | | |
| LSS [P9] | | | | | | | |
| Sex | Males | 118 | 108.4[o] | 0.18 | 666 689 | 0.53 (0.04, 1.20) | <0 (<0, 707.28) |
| | Females | 147 | 145.3[o] | 0.18 | 1 061 687 | 0.50 (0.06, 1.09) | <0 (<0, 623.23) |
| Age at exposure | <20 years | 51 | 43.0[o] | 0.18 | 885 656 | 1.13 (0.32, 2.34) | <0 (<0, 210.88) |
| | 20–40 years | 115 | 112.3[o] | 0.18 | 514 903 | 0.23 (<0, 0.84) | <0 (<0, 966.47) |
| | >40 years | 99 | 100.4[o] | 0.17 | 327 997 | 0.38 (<0, 1.12) | <0 (<0, 1440.1) |
| Time since exposure | 12–15 years | 11 | 10.9[o] | 0.18 | 504 112 | <0 (<0, 2.85) | <0 (<0, 74.98) |
| | 15–30 years | 64 | 55.0[o] | 0.18 | 592 956 | 1.12 (0.27, 2.41) | <0 (<0, 457.15) |
| | >30 years | 190 | 190.1[o] | 0.18 | 631 488 | 0.30 (<0, 0.73) | <0 (<0, 1309.2) |
| All | | 265 | 253.7[o] | 0.18 | 1 728 556 | 0.51 (0.17, 0.94) | <0 (<0, 656.32) |
| Benign gynaecological disorders [I4][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 | 33.0 | 3.2 | 47 144 | 0.13 (0.01, 0.26)[g,q] | 0.93 (0.11, 1.95)[b,g] |
| Peptic ulcer [C4] | | 36 | 26.9 | 10 | 41 779 | –0.01 (<–0.01, 0.07)[g,k,p] | n.a. |
| United Kingdom NRRW [M12] | | 228 | 243.4 | 0.031 | 2 063 300 | –0.71 (–1.36, 0.49)[m] | n.a. |
| Nuclear power industry workers in the United States [H44] | | 36 | 47.8 | 0.026 | 698 041 | –2.28 (<–2.51, 10.5)[g] | n.a. |
| 5 rem study in the United States [F3] | | 14 | 9.86 | 0.228 | 69 000 | 1.8 (–1.0, 6.1)[l] | 2.6 (–1.4, 8.6) |
| Japanese radiological technologists [A4] | | 35 | 27.1 | 0.466 | 270 585 | 0.62 (–0.2, 1.7)[k] | 0.6 (–0.2, 1.7) |
| **INTERNAL HIGH-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| Danish and Swedish Thorotrast patients [T30] | | 16 | 10.7 | n.a. | 25 480 | 1.5 (0.7, 3.0)[g,h] | n.a. |
| **Mortality** | | | | | | | |
| German Thorotrast patients [V3, V4] | | 10[i] | n.a. | 20.6 mL[j] | n.a. | ~0.5[h] | n.a. |
| United States Thorotrast patients [T30] | | 5 | 3.3 | n.a. | 8 740 | ∞ (0.5, ∞)[g,h] | n.a. |

*a* 90% CI in parentheses derived from fitting models (4) and (5) for the LSS, and derived from published data for the other studies.
*b* Estimates based on method described in the introduction to chapter III of annex I in the UNSCEAR 2000 Report [U2].
*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 underlying cancer incidence, estimated using the cervical cancer cohort study [B11].
*d* Not statistically significantly different from zero.
*e* The observed and expected numbers of cases are for 10-year survivors. The estimated number of expected cases incorporated an adjustment based on the Poisson regression model given in reference [I4].
*f* The values given exclude the period within 5 years of irradiation.
*g* 95% CI in parentheses.
*h* Risk relative to unexposed controls.
*i* Number quoted in earlier follow-up [V3].
*j* Amount of Thorotrast administered.
*k* Excess relative risk and excess absolute risk values were calculated from the mean dose and the observed and expected cancers (or the relative risk and confidence interval) reported in the paper.
*l* Includes both small and large intestine.
*m* Tabulation and analysis with a 10-year lag. Risk estimate based on a dose–response analysis.
*n* Males only.
*o* All expected numbers calculated by means of fitted relative risk model (4), evaluated at zero dose.
*p* Based on follow-up of 11 or more years after radiotherapy.
*q* Based on a dose–response analysis.

**Table 24 Risk estimates for cancer incidence and mortality from studies of radiation exposure: rectal 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 LSS the exposed group included survivors with doses of 0.005 Sv or more (weighted colon dose) for incidence or mortality. The studies listed are those for which quantitative estimates of risk could be made

| *Study* | | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|---|
| **EXTERNAL LOW-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| LSS [P48] | | | | | | | |
| Sex | Males | 177 | 185.2[b] | 0.21 | 436 180 | <0 (<0, 0.28) | <0 (<0, 0.35) |
| | Females | 199 | 169.7[b] | 0.20 | 729 607 | 0.46 (0.08, 0.97) | 0.40 (0.03, 1.11) |
| Age at exposure | <20 years | 114 | 117.3[b] | 0.21 | 586 255 | 0.16 (<0, 0.60) | 0.10 (<0, 0.58) |
| | 20–40 years | 153 | 141.3[b] | 0.21 | 378 204 | 0.12 (<0, 0.58) | <0 (<0, 1.70) |
| | >40 years | 109 | 97.1[b] | 0.19 | 201 329 | 0.24 (<0, 0.97) | 0.64 (<0, 3.44) |
| Time since exposure | 12–15 years | 11 | 10.7[b] | 0.21 | 119 774 | <0 (<0, 2.47) | 2.44 (1.15, 4.47) |
| | 15–30 years | 88 | 84.7[b] | 0.21 | 514 582 | <0 (<0, <0) | <0 (<0, 0.12) |
| | >30 years | 277 | 262.6[b] | 0.20 | 531 432 | 0.32 (0.05, 0.66) | 0.59 (<0, 2.02) |
| All | | 376 | 354.6[b] | 0.21 | 1 165 787 | 0.18 (<0, 0.46) | 0.19 (<0, 0.64) |
| Canadian National Dose Registry [S8] | | 145 | 199.0 | 0.0662 | 2 667 903 | 13.8 (3.7, 33.6)[c] | n.a. |
| Springfields uranium workers, United Kingdom [M5] | | 49 | 57.62 | 0.0228 | 190 795 | –0.17 (<–3.42, 11.95)[f] | n.a. |
| **Mortality** | | | | | | | |
| LSS [P9] | | | | | | | |
| Sex | Males | 96 | 98.5[b] | 0.18 | 666 869 | <0 (<0, 0.33) | <0 (<0, 601.18) |
| | Females | 127 | 104.7[b] | 0.18 | 1 061 687 | 0.95 (0.28, 1.86) | <0 (<0, 488.26) |
| Age at exposure | <20 years | 38 | 35.9[b] | 0.18 | 885 656 | 0.48 (<0, 1.82) | <0 (<0, 167.70) |
| | 20–40 years | 77 | 68.9[b] | 0.18 | 514 903 | 0.20 (<0, 1.08) | <0 (<0, 590.50) |
| | >40 years | 108 | 97.3[b] | 0.17 | 327 997 | 0.49 (<0, 1.37) | 1.11 (<0, 3.23) |
| Time since exposure | 12–15 years | 31 | 30.5[b] | 0.18 | 504 112 | 0.38 (<0, 2.00) | <0 (<0, 262.78) |
| | 15–30 years | 63 | 62.1[b] | 0.18 | 592 956 | <0 (<0, 0.40) | <0 (<0, 426.25) |
| | >30 years | 129 | 111.0[b] | 0.18 | 631 488 | 0.68 (0.11, 1.47) | <0 (<0, 848.25) |
| All | | 223 | 202.7[b] | 0.18 | 1 728 556 | 0.36 (<0, 0.88) | <0 (<0, 532.76) |
| United Kingdom NRRW [M12] | | 123 | 155.6 | 0.031 | 2 063 300 | 1.69 (–0.12, 5.01)[c] | n.a. |
| Metropathia haemorrhagica [D7] | | 14 | 12.36 | 4.9 | 47 144 | 0.04 (–0.09, 0.16)[d] | 0.07 (–0.20, 0.48)[g] |
| Benign gynaecological disorders [I4] | | 15 | 15 | 3.0 | 71 958 | 0.03 (–0.14, 0.19) | n.a. |
| **INTERNAL HIGH-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| Danish and Swedish Thorotrast patients [T30] | | 8 | 8.0 | n.a. | 25 480 | 1.8 (0.6, 5.3)[e] | n.a. |

[a] 90% CI in parentheses derived from fitting models (4) and (5) for the LSS, and derived from published data for the other studies.

[b] All expected numbers calculated by means of fitted relative risk model (4), evaluated at zero dose.

[c] Tabulation and analysis with a 10-year lag. Risk estimate based on a dose–response analysis.

[d] Risk estimate based on a dose–response analysis, with 95% CI.

[e] Risk relative to unexposed controls, with 95% CI.

[f] Males only.

[g] Estimates (with 95% confidence intervals) are based on method described in the introduction to chapter III of annex I in the UNSCEAR 2000 Report [U2].

**Table 25 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 LSS the exposed group included survivors with doses of 0.005 Sv or more (weighted liver dose) for incidence or mortality. The studies listed are those for which quantitative estimates of risk could be made

| *Study* | | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|---|
| **EXTERNAL LOW-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| LSS [P48] | | | | | | | |
| Sex | Males | 393 | 354.5[o] | 0.23 | 436 180 | 0.42 (0.18, 0.70) | 0.29 (<0, 1.96) |
| | Females | 252 | 253.0[o] | 0.21 | 729 608 | 0.39 (0.09, 0.76) | 0.52 (0.12, 1.14) |
| Age at exposure | <20 years | 260 | 226.3[o] | 0.22 | 586 255 | 0.50 (0.21, 0.85) | 0.48 (0.09, 1.08) |
| | 20–40 years | 221 | 236.8[o] | 0.22 | 378 204 | 0.21 (<0, 0.54) | 0.72 (<0, 2.02) |
| | >40 years | 164 | 144.7[o] | 0.21 | 201 330 | 0.61 (0.14, 1.23) | 3.03 (0.02, 6.75) |
| Time since exposure | 12–15 years | 23 | 21.9[o] | 0.22 | 119 774 | 0.54 (<0, 2.18) | <0 (<0, 0.92) |
| | 15–30 years | 129 | 108.9[o] | 0.22 | 514 582 | 0.57 (0.13, 1.19) | 0.39 (0.02, 1.08) |
| | >30 years | 493 | 477.5[o] | 0.21 | 531 433 | 0.37 (0.16, 0.61) | 1.23 (0.24, 2.69) |
| All | | 645 | 607.4[o] | 0.22 | 1 165 788 | 0.41 (0.22, 0.63) | 0.50 (0.12, 1.06) |
| 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 [M3] | | 12 | 11.3 | 0.66 | 26 493 | 0.09 (<0, 1.4)[m] | n.a. |
| Springfields uranium workers, United Kingdom [M5] | | 12[i] | 22.72[i] | 0.022 8 | 190 795 | –1.96 (<–2.08, 21.58)[i,q] | n.a. |
| **Mortality** | | | | | | | |
| LSS [P9][e] | | | | | | | |
| Sex | Males | 408 | 374.7[o] | 0.19 | 666 869 | 0.61 (0.33, 0.94) | <0 (<0, 0.89) |
| | Females | 289 | 283.1[o] | 0.19 | 1 061 688 | 0.36 (0.05, 0.74) | <0 (<0, 1091.7) |
| Age at exposure | <20 years | 219 | 195.7[o] | 0.19 | 885 656 | 0.46 (0.13, 0.89) | <0 (<0, 0.34) |
| | 20–40 years | 233 | 230.5[o] | 0.20 | 514 903 | 0.58 (0.23, 1.01) | 0.30 (<0, 1.58) |
| | >40 years | 245 | 232.2[o] | 0.18 | 327 998 | 0.45 (0.09, 0.92) | 2.00 (<0, 4.59) |
| Time since exposure | 12–15 years | 97 | 100.1[o] | 0.19 | 504 112 | 0.24 (<0, 0.84) | <0 (<0, 0.25) |
| | 15–30 years | 138 | 125.0[o] | 0.19 | 592 957 | 0.68 (0.19, 1.33) | 0.08 (<0, 0.91) |
| | >30 years | 462 | 434.1[o] | 0.19 | 631 488 | 0.51 (0.25, 0.81) | 0.90 (0.01, 2.21) |
| All | | 697 | 657.4[o] | 0.19 | 1 728 557 | 0.51 (0.30, 0.75) | <0 (<0, 0.41) |
| Ankylosing spondylitis [W8][f] | | 11 | 13.6 | 2.13 | 287 095 | –0.09 (–0.24, 0.2)[c] | n.a. |
| Metropathia haemorrhagica [D7][i] | | 2 | 5.99 | 0.27 | 47 144 | –2.47 (–3.56, 0.78)[c,m] | –3.13 (–4.52, 0.99)[c,m] |
| Peptic ulcer [C4] | | 11 | 6.1 | 4.8 | 41 779 | –0.03 (<–0.03, 0.31)[b,g,m] | n.a. |
| Benign gynaecological disorders [I4][h] | | 9[i] | 16.6 | 0.21 | 71 958 | –2.18(–3.26, 0.3)[c] | n.a. |
| Yangjiang background radiation [T14, T16] | | 171 | 213.8 | n.a.[j] | 1 246 340 | –0.99 (–1.60, 0.10)[k,m] | n.a. |
| Nuclear workers in Canada, United Kingdom and United States [C3] | | 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. |
| **INTERNAL LOW-LET EXPOSURES** | | | | | | | |
| **Mortality** | | | | | | | |
| Semipalatinsk study [B58] | | 60 | n.a. | 0.63 | 582 750 | –0.08 (–0.41, 1.00)[m,p] | n.a. |

| *Study* | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average relative risk* |
|---|---|---|---|---|---|
| **INTERNAL HIGH-LET EXPOSURES** | | | | | |
| **Incidence** | | | | | |
| Danish Thorotrast patients [A5] | 84 | 0.7 | 3.9–6.1 Gy | n.a. | 194.2 (31.0, 1216)[m,n] |
| Danish and Swedish Thorotrast patients [T30] | 136 | 1.3 | n.a. | 25 480 | ∞ (44.2, ∞)[m] |
| **Mortality** | | | | | |
| German Thorotrast patients [V1, V4] | 454 | 3.6 | 4.9 Gy | n.a. | 25 $Gy^{-1}$ |
| Portuguese Thorotrast patients [D21] | 104 | 6.6 | 26 mL | 16 963 | 5.7[n] |
| Combined Japanese Thorotrast patients [M14] | 143 | 4 | n.a. | 10 685 | n.a. |
| United States Thorotrast patients [T30] | 22 | 0.9 | n.a. | 8 740 | 22.5 (1.8, 464.3)[m] |

[a] 90% CI in parentheses derived from fitting models (4) and (5) for the LSS, and derived from published data for the other studies, unless otherwise stated.
[b] Based on follow-up of 11 or more years after radiotherapy.
[c] Estimates based on method described in the introduction to chapter III of annex I in the UNSCEAR 2000 Report [U2].
[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 5 years of first treatment.
[g] Excess relative risk value was calculated from the mean dose and the relative risk and confidence interval reported in the paper.
[h] The estimated number of expected cases incorporated an adjustment based on the Poisson regression model given in reference [I4].
[i] Including gall bladder.
[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.
[o] All expected numbers calculated by means of fitted relative risk model (4), evaluated at zero dose.
[p] Based on a dose–response analysis, restricted to the exposed group only.
[q] Males only.

**Table 26 Risk estimates for cancer incidence and mortality from studies of radiation exposure: pancreatic 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 LSS of cancer incidence and mortality the exposed group included survivors with pancreatic doses of 0.005 Sv or more. The studies listed are those for which quantitative estimates of risk could be made

| *Study* | | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|---|
| **EXTERNAL LOW-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| LSS [P48] | | | | | | | |
| Sex | Males | 99 | 91.8[c] | 0.21 | 436 180 | 0.09 (<0, 0.63) | <0 (<0, 0.36) |
| | Females | 130 | 119.9[c] | 0.19 | 729 607 | 0.54 (0.00, 1.26) | 0.44 (0.05, 1.04) |
| Age at exposure | <20 years | 38 | 27.6[c] | 0.20 | 586 255 | 1.00 (0.01, 2.71) | <0 (<0, 264.97) |
| | 20–40 years | 94 | 92.0[c] | 0.20 | 378 204 | 0.24 (<0, 0.94) | 0.13 (<0, 1.13) |
| | >40 years | 97 | 93.6[c] | 0.19 | 201 329 | 0.07 (<0, 0.67) | <0 (<0, 1.43) |
| Time since exposure | 12–15 years | 10 | 12.4[c] | 0.20 | 119 774 | <0 (<0, <0) | <0 (<0, <0) |
| | 15–30 years | 72 | 70.0[c] | 0.20 | 514 582 | <0 (<0, 0.59) | <0 (<0, 0.27) |
| | >30 years | 147 | 130.8[c] | 0.20 | 531 432 | 0.62 (0.12, 1.28) | 1.22 (0.46, 2.27) |
| All | | 229 | 212.6[c] | 0.20 | 1 165 787 | 0.29 (<0, 0.72) | 0.22 (<0, 0.63) |
| Canadian National Dose Registry [S8] | | 76 | 101.1 | 0.006 6 | 2 667 903 | 6.9 (<0, 27.1)[d] | n.a. |
| Cervical cancer case-control study [B8] | | 221 | n.a. | 1.9 | n.a. | 0.21 (–0.16, 0.89) | n.a. |

| *Study* | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|
| Stockholm skin haemangioma [L10] | 9 | 2.7 | 0.09[f] | 406 565 | 25.1 (5.5, 57.7)[e] | 1.7 |
| Swedish benign breast disease [M3] | 14 | 11.0 | 0.37 | 26 493 | –0.37 (<0, 0.8)[e] | n.a. |
| Springfields uranium workers, United Kingdom [M5] | 23 | 31.73 | 0.022 8 | 190 795 | 3.60 (<–12.05, 34.01)[h] | n.a. |
| **Mortality** | | | | | | |
| LSS [P9] | | | | | | |
| Sex Males | 103 | 94.5[c] | 0.18 | 666 869 | 0.02 (<0, 0.65) | <0 (<0, 621.53) |
| Females | 134 | 139.4[c] | 0.17 | 1 061 681 | <0 (<0, 0.41) | <0 (<0, 535.39) |
| Age at exposure <20 years | 44 | 38.5[c] | 0.18 | 885 656 | 0.56 (<0, 1.82) | <0 (<0, 218.32) |
| 20–40 years | 96 | 100.8[c] | 0.18 | 514 903 | <0 (<0, 0.41) | <0 (<0, 745.72) |
| >40 years | 97 | 95.3[c] | 0.16 | 327 991 | <0 (<0, 0.28) | <0 (<0, 1307.5) |
| Time since exposure 12–15 years | 20 | 23.3[c] | 0.17 | 504 112 | <0 (<0, <0) | <0 (<0, 153.39) |
| 15–30 years | 58 | 57.5[c] | 0.18 | 592 956 | <0 (<0, 0.78) | <0 (<0, 410.14) |
| >30 years | 159 | 156.5[c] | 0.18 | 631 482 | <0 (<0, 0.51) | <0 (<0, 1051.6) |
| All | 237 | 233.8[c] | 0.18 | 1 728 550 | <0 (<0, 0.33) | 0.14 (0.02, 0.35) |
| Canadian National Dose Registry [A8] | | | | | | |
| Sex Males | 72 | 89.7 | 0.063 | 2 861 093[b] | 7.3 (<0, 19.0) | n.a. |
| Females | 15 | 25.0 | 0.063 | 2 861 093[b] | <0 (<0, 18.3) | n.a. |
| United Kingdom NRRW [M12] | 126 | 153.86 | 0.031 | 2 063 300 | <0 (<0, 2.31) | n.a. |
| Nuclear power industry workers in the United States [H44] | 18 | 29.0 | 0.026 | 698 041 | –9.38 (<–2.5, 89.7)[e] | n.a. |
| Metropathia haemorrhagica [D7] | 9 | 13.57 | 0.29 | 47 144 | –1.16 (–2.41, 0.90)[j] | –3.34 (–6.95, 2.58)[j] |
| Peptic ulcer [C4] | 37 | 13.4 | 13.5 | 41 779 | 0.04 (0.00, 0.08)[e,i] | n.a. |
| Benign gynaecological disorders [I4] | 37 | 24.7 | 0.16 | 71 958 | 0.14 (–2.76, 28.84) | n.a. |
| **INTERNAL HIGH-LET EXPOSURES** | | | | | | |
| **Incidence** | | | | | | |
| Danish and Swedish Thorotrast patients [T30] | 11 | 4.6 | n.a. | 25 480 | 3.8 (1.3, 12.3)[e,g] | n.a. |
| **Mortality** | | | | | | |
| United States Thorotrast patients [T30] | 3 | 1.6 | n.a. | 8 740 | 0.9 (0.1, 4.4)[e,g] | n.a. |

[a] 90% CI in parentheses derived from fitting models (4) and (5) for the LSS, and derived from published data for the other studies.
[b] Person-years of follow-up for males and females.
[c] All expected numbers calculated by means of fitted relative risk model (4), evaluated at zero dose.
[d] Tabulation and analysis with a 10-year lag. Risk estimate based on a dose–response analysis.
[e] 95% CI in parentheses.
[f] Stomach dose.
[g] Relative risk in Thorotrast-exposed group compared with control group.
[h] Males only.
[i] Trend based on the exposed patients only.
[j] Estimates (with 95% CI) based on method described in the introduction to chapter III of annex I in the UNSCEAR 2000 Report [U2].

**Table 27 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 LSS the exposed group included survivors with doses of 0.005 Sv or more (weighted lung dose) for incidence or mortality. The studies listed are those for which quantitative estimates of risk could be made

| *Study* | | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk*[a] *at 1 Sv* | *Average excess absolute risk*[a] *($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|---|
| **EXTERNAL LOW-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| LSS [P48] | | | | | | | |
| Sex | Males | 428 | 408.7[v] | 0.24 | 436 180 | 0.32 (0.13, 0.55) | 0.57 (0.04, 1.54) |
| | Females | 361 | 269.1[v] | 0.23 | 729 608 | 1.48 (1.04, 1.99) | 2.38 (1.37, 3.53) |
| Age at exposure | <20 years | 140 | 118.1[v] | 0.23 | 586 255 | 0.68 (0.28, 1.20) | 0.64 (0.10, 1.38) |
| | 20–40 years | 316 | 280.2[v] | 0.24 | 378 204 | 0.65 (0.35, 1.00) | 2.65 (1.04, 4.60) |
| | >40 years | 333 | 284.5[v] | 0.22 | 201 330 | 0.71 (0.40, 1.09) | 9.47 (5.75, 13.78) |
| Time since exposure | 12–15 years | 18 | 13.5[v] | 0.24 | 119 774 | 1.41 (0.07, 4.09) | 5.49 (0.00, 32.06) |
| | 15–30 years | 256 | 207.4[v] | 0.24 | 514 582 | 0.96 (0.57, 1.44) | 0.89 (0.21, 1.86) |
| | >30 years | 515 | 461.8[v] | 0.23 | 531 433 | 0.53 (0.31, 0.78) | 3.35 (1.93, 5.02) |
| All | | 789 | 681.7[v] | 0.23 | 1 165 788 | 0.69 (0.49, 0.92) | 1.55 (0.84, 2.37) |
| Hodgkin's disease (international) [K9] | | 79 | n.a. | 2.2 | n.a. | n.a.[c] | n.a. |
| Hodgkin's disease (international) [G23, T3, V2] (5-year lagged dose > 0)[a,o] | | 146 | n.a. | 25 Gy | 271 exposed controls | 0.15 (0.06, 0.39) | n.a. |
| Breast cancer [I7] | | 17 | n.a. | 15.2[d] dose to ipsilateral lung | n.a. | 0.20 (–0.62, 1.03)[e,x] | n.a. |
| Swedish benign breast disease [M3] | | 10 | 11.2 | 0.75 | 26 493 | 0.38 (<0, 0.6)[x] | n.a. |
| Stockholm skin haemangioma [L10] | | 11 | ~9 | 0.12 | 406 565 | 1.4 (n.s.) | 0.33 |
| Canadian National Dose Registry [S8] | | 476 | 717.1 | 0.066 2 | 2 667 903 | 3.0 (0.5, 6.8)[w] | n.a. |
| Capenhurst uranium facility, United Kingdom [M4][b] | | 49 | 58.13 | 0.098 5 | 40 933 | –1.30 (<–1.30, 9.66)[z] | n.a. |
| Springfields uranium workers, United Kingdom [M5] | | 225 | 301.37 | 0.022 8 | 190 795 | 1.48 (<–2.43, 6.06)[z] | n.a. |
| United Kingdom Chapelcross workers [M6] | | 25 | 39.32 | 0.083 6 | 39 210 | 0.63 (–1.61, 5.95)[z] | n.a. |
| **Mortality** | | | | | | | |
| LSS [P9] | | | | | | | |
| Sex | Males | 403 | 367.7[v] | 0.20 | 666 870 | 0.57 (0.30, 0.89) | 0.19 (<0, 0.85) |
| | Females | 347 | 272.0[v] | 0.20 | 1 061 688 | 1.28 (0.84, 1.80) | <0 (<0, 1269.1) |
| Age at exposure | <20 years | 117 | 99.1[v] | 0.20 | 885 656 | 0.94 (0.42, 1.63) | 0.11 (<0, 0.56) |
| | 20–40 years | 314 | 271.4[v] | 0.21 | 514 903 | 0.78 (0.43, 1.19) | 0.51 (<0, 1.83) |
| | >40 years | 319 | 272.3[v] | 0.19 | 327 999 | 0.76 (0.38, 1.23) | <0 (<0, 4062.9) |
| Time since exposure | 12–15 years | 40 | 35.3[v] | 0.20 | 504 112 | 0.72 (<0, 2.16) | <0 (<0, 294.01) |
| | 15–30 years | 221 | 180.8[v] | 0.20 | 592 958 | 0.90 (0.43, 1.49) | 0.24 (<0, 0.97) |
| | >30 years | 489 | 429.8[v] | 0.20 | 631 488 | 0.71 (0.44, 1.02) | 2.56 (1.32, 4.03) |
| All | | 750 | 640.7[v] | 0.20 | 1 728 558 | 0.84 (0.59, 1.11) | 0.37 (0.02, 0.87) |

| *Study* | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|
| LSS [P17] (adjusted for smoking, and based on additive model for smoking and radiation) | 357 | n.a. | n.a. (similar to LSS [P9]) | n.a. | 0.9 (S.E. = 0.64) sex-averaged | n.a. |
| Ankylosing spondylitis [W8][f] | 563 | 469 | 8.9[bb] | 287 095 | 0.05 (0.002, 0.09)[g,x] | n.a. |
| Canadian TB fluoroscopy [H7][h] | 455 | 473.7 | 1.02 | 672 071 | 0.00 (–0.06, 0.07)[x] | 0.00 (–0.4, 0.4)[x] |
| 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] |
| Peptic ulcer [C4] | 125 | 62.8 | 1.8 | 41 779 | 0.24 (0.07, 0.44)[i,x] | n.a. |
| Yangjiang background radiation [T14, T16] | 62 | 76.5 | n.a.[j] | 1 246 340 | –0.68 (–1.58, 1.67)[k,x] | n.a. |
| Male Mayak nuclear workers [K34] (external dose; adjusted for plutonium exposure) | 219 | n.a. | 1.23 Gy | 109 290 | 0.06 (–0.07, 0.20)[x] | |
| Mayak nuclear workers [G12] (external dose; adjusted for plutonium exposure) | | | | | | |
| Males | 594 | n.a. | 0.80 | 485 862 | 0.17 (0.052, 0.32)[x,aa] | 2.4 (0.56, 4.4)[x,aa] |
| Females | 61 | n.a. | 0.82 | 184 616 | 0.32 (<0, 1.3)[x,aa] | 0.43 (<0, 1.6)[x,aa] |
| Nuclear workers in Canada, United Kingdom and United States [C3] | 1 238 | n.a. | 0.04 | 2 124 526 | <0[l] | n.a. |
| United Kingdom NRRW [M12] | 921 | 1 300 | 0.031 | 2 063 300 | –0.11 (–0.72, 0.72) | n.a. |
| Canadian National Dose Registry [A8] | 386 | 631.3 | 0.063 | 2 861 093 | 3.6 (0.4, 6.9)[z] | n.a. |
| Nuclear industry workers in Japan [I14] | 397 | 410.9 | 0.015 | ~1 390 000 | <0[l] | <0 |
| Nuclear power industry workers in the United States [H44] | 125 | 210.4 | 0.026 | 698 041 | 0.25 (<–2.51, 8.44)[x] | n.a. |
| Nuclear power station workers in France [R54] | 23 | 47.5 | 0.018 | 261 418 | 0.1 (–7.5, 17.4)[t] | n.a. |
| **INTERNAL LOW-LET EXPOSURES** | | | | | | |
| **Mortality** | | | | | | |
| Semipalatinsk study [B58] | 130 | n.a. | 0.63 | 582 750 | 1.76 (0.48, 8.83)[x,y] | n.a. |
| **INTERNAL HIGH-LET EXPOSURES (plutonium)** | | | | | | |
| **Mortality** | | | | | | |
| Male Mayak nuclear workers [K34] (dose from plutonium; adjusted for external dose) | 127 | n.a. | 0.24 Gy (4.8 Sv) | 30 477 | 4.50 (3.15, 6.10)[x] | n.a. |
| Mayak nuclear workers [G12] (dose from plutonium; adjusted for external dose) | | | | | | |
| Males | 167 | n.a. | 0.21 Gy | 52 546 | 4.7 (3.3, 6.7)[x,aa] | 115 (81, 156)[x,aa] |
| Females | 25 | n.a. | 0.38 Gy | 17 476 | 19 (9.5, 39)[x,aa] | 49 (29, 78)[x,aa] |
| Sellafield plutonium workers [O1] | 133 | 145.8 | 0.01 Gy (0.19 Sv) | 134 817 | 1.12[m,cc] | n.a. |

| *Study* | *Observed cases* | *Expected cases* | *Mean dose* | *Person-years* | *Average relative risk*[n] |
|---|---|---|---|---|---|
| **INTERNAL HIGH-LET EXPOSURES (other than radon and plutonium)** | | | | | |
| **Incidence** | | | | | |
| $^{224}$Ra ankylosing spondylitis patients [W15] | 25 | 35.7 | n.a. | 32 800 | 1.20[u] |
| $^{224}$Ra ankylosing spondylitis patients [N2] | 20 | 30 | n.a. | 25 500 | 0.67 |
| Danish Thorotrast patients [A5] | 21 | 10.9[o] | 0.18 Gy[p] | 19 365 | 0.7 (0.3, 1.7)[q,x] |
| Danish and Swedish Thorotrast patients [T30] | 28 | 13.3 | n.a. | 25 480 | 1.3 (0.7, 2.2)[x] |
| **Mortality** | | | | | |
| Japanese Thorotrast patients, combined data [M14] | 11 | n.a. | 17 mL[r] | 10 685 | 2.0 (1.0, 3.9)[x] |
| German Thorotrast patients [V1] | 53 | n.a. | 20.6 mL[s] | n.a. | 0.75 |
| United States Thorotrast patients [T30] | 11 | 5.5 | n.a. | 8 740 | 3.3 (0.7, 14)[x] |

*a* 90% CI in parentheses derived from fitting models (4) and (5) for the LSS, and derived from published data for the other studies, unless otherwise stated.
*b* Estimates based on method described in the introduction to chapter III of annex I in the UNSCEAR 2000 Report [U2].
*c* Relative risks quoted in Section III.E of Annex I in reference [U2].
*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 5 years of first treatment.
*g* Dose–response analysis based on the number of treatment courses given.
*h* The values given exclude the period within 10 years of exposure and ages at risk less than 20 years old.
*i* Trend based on the exposed patients only.
*j* Mean annual effective dose = 6.4 mSv.
*k* Based on a 10-year latent period.
*l* Trend not statistically significant.
*m* Relative to other radiation workers at Sellafield; difference is not statistically significant [O1].
*n* Risk relative to unexposed controls.
*o* Based on national rates [A5].
*p* As given in reference [A12].
*q* Risk relative to unexposed controls, with adjustment for sex, age at angiography and calendar period.
*r* Mean amount of Thorotrast administered in the first series of Japanese patients [M19].
*s* Amount of Thorotrast administered.
*t* Trend for all respiratory cancers, based on a 10-year latent period.
*u* Risk relative to unexposed controls, among whom 29 cases were observed, compared with 49.6 expected [W15].
*v* All expected numbers calculated by means of fitted relative risk model (4), evaluated at zero dose.
*w* Tabulation and analysis with a 10-year lag. Risk estimate based on a dose–response analysis.
*x* 95% CI in parentheses.
*y* Based on a dose–response analysis, restricted to the exposed group only.
*z* Males only.
*aa* At attained age 60.
*bb* Dose to main bronchi used in dose–response analyses.
*cc* Plutonium workers compared with other radiation workers.

**Table 28 Risk estimates for lung cancer mortality from studies of radon daughter exposure of underground miners**
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

| *Study* | *Observed case* | *Expected cases* | *Mean exposure (WLM)* | *Person-years* | *Average excess relative risk[a] at 100 WLM* |
|---|---|---|---|---|---|
| **INTERNAL HIGH-LET EXPOSURES (occupational exposure to radon)** | | | | | |
| Chinese tin miners [L8, X2][b] | 936 | 649 | 277.4 | 135 357 | 0.16 (0.1, 0.2) |
| West Bohemia uranium miners [T48][c] | 915 | 240.8 | 70.0 | 261 428 | 1.6 (1.2, 2.2) |
| Colorado Plateau uranium miners [H17, L8][a] | 327 | 74 | 807.2 | 75 032 | 0.42 (0.3, 0.7) |
| Ontario uranium miners [K12, L8][a] | 282 | 221 | 30.8 | 319 701 | 0.89 (0.5, 1.5) |
| Newfoundland fluorspar miners [L8, M15][d] | 138 | 32.1 | 382.8 | 48 189 | 0.70 (0.44, 1.14) |
| Swedish iron miners [L8, R8][a] | 79 | 44.7 | 80.6 | 32 452 | 0.95 (0.1, 4.1) |
| New Mexico uranium miners [L8, S19][a] | 68 | 23.5 | 110.3 | 46 797 | 1.72 (0.6, 6.7) |
| Beaverlodge uranium miners [H15, H18, L8][a] | 56 | 15.4 | 81.3[e] | 68 040 | 3.25 (1.0, 9.6)[f] |
| Port Radium uranium miners [H16, L8][a] | 39 | 26.7 | 242.8 | 31 454 | 0.19 (0.1, 0.6) |
| Radium Hill uranium miners [L8, W10][a] | 32 | 23.1 | 7.6 | 25 549 | 5.06 (1.0, 12.2) |
| French uranium miners [L8, L92, R39, T8][a] | 125 | 83.1 | 36.5 | 133 521 | 0.8 (0.3, 1.4)[g] |
| Cornish tin miners [H23] | 82 | n.a. | 65 | 66 900 | 0.045[h] |

[a] 95% CI in parentheses.
[b] The values cited are from reference [L8] unless otherwise noted, and except for the expected number of cases, which has been calculated as $O/(1 + 100\alpha D)$, where $O$ is the number of observed cases, $\alpha$ is the excess relative risk at 100 WLM and $D$ is the mean exposure in WLM.
[c] Values cited are based on data from references [T11, T48].
[d] Values cited are from reference [M15] and include unexposed miners.
[e] Revised value for persons in nested case-control study [H18].
[f] Values based on case-control analysis with revised exposure estimates [H18].
[g] Coefficient based on internal regression, taken from reference [R39].
[h] Coefficient based on time-weighted cumulative exposure.

**Table 29 Results from analyses of pooled data from case-control studies in China** [L61]**, Europe** [D24] **and North America** [K38]

Summary information is based on pooled analyses and may differ slightly from original publications

| *Study* | *Number of subjects* | | *Mean radon concentration (Bq/m³)* | | *EOR[a] for 100 Bq/m³ (95% CI)* |
|---|---|---|---|---|---|
| | *Cases* | *Controls* | *Cases* | *Controls* | |
| **Studies in China[b]** | | | | | |
| Shenyang [B37] | 285 | 338 | 122 | 123 | –0.02 (–0.13, 0.43) |
| Gansu [W27] | 768 | 1 659 | 232 | 226 | 0.18 (0.02, 0.49) |
| **Studies in Europe[c]** | | | | | |
| Austria [O10] | 183 | 188 | 267 | 130 | 0.46 (n.a.[d], >5.00) |
| Czech Republic [T35] | 171 | 713 | 528 | 493 | 0.19 (–0.00, 2.07) |
| Finland (nationwide) [A26] | 881 | 1 435 | 104 | 103 | 0.03 (n.a., 0.17) |
| Finland (south) [R40] | 160 | 328 | 221 | 212 | 0.06 (–0.08, 1.58) |
| France [B41] | 571 | 1 209 | 138 | 131 | 0.11 (–0.01, 0.41) |
| Germany (eastern) [W28] | 945 | 1 516 | 78 | 74 | 0.18 (–0.00, 0.56) |
| Germany (western) [W28] | 1 323 | 2 146 | 49 | 51 | –0.02 (n.a., 0.36) |
| Italy [B38] | 384 | 405 | 113 | 102 | 0.10 (–0.18, 1.40) |
| Spain [B39] | 156 | 235 | 123 | 137 | –0.11 (n.a., 0.59) |
| Sweden (nationwide) [P18] | 960 | 2 045 | 99 | 94 | 0.11 (–0.04, 0.46) |
| Sweden (never-smokers) [L65] | 258 | 487 | 79 | 72 | 0.24 (–0.08, 0.95) |
| Sweden (Stockholm) [P30] | 196 | 375 | 131 | 136 | 0.12 (–0.14, 1.41) |
| United Kingdom [D13] | 960 | 3 126 | 57 | 54 | 0.04 (–0.05, 0.22) |
| **Studies in North America[b,e]** | | | | | |
| New Jersey [S62] | 429 | 396 | 27 | 25 | 0.56 (–0.22, 2.97) |
| Winnipeg [L64] | 647 | 693 | 137 | 147 | 0.02 (–0.05, 0.25) |
| Missouri-I [A27] | 530 | 1 177 | 62 | 63 | 0.01 (n.a., 0.42) |
| Missouri-II [A9] | 477 | 516 | 55 | 56 | 0.27 (–0.12, 1.53) |
| Iowa [F12] | 412 | 613 | 136 | 121 | 0.44 (0.05, 1.59) |
| Connecticut [S66] | 726 | 779 | 32 | 33 | 0.02 (–0.21, 0.51) |
| Utah, southern Idaho [S66] | 441 | 792 | 55 | 58 | 0.03 (–0.20, 0.55) |
| **Combined studies** | | | | | |
| China [L61] | 1 053 | 1 997 | 202 | 209 | 0.13 (0.01, 0.36) |
| Europe [D24, D30] | 7 148 | 14 208 | 104 | 97 | 0.08 (0.030, 0.16) |
| North America [K38, K39] | 4 081 | 5 281 | 74 | 74 | 0.11 (0.00, 0.28) |

[a] Estimates of excess odds ratio (EOR) for 100 Bq/m$^3$ based on fitted linear model for time-weighted radon concentration ($x$): $OR(x) = 1 + \beta x$.

[b] Study mean concentrations based on residential occupancy 5–30 years prior to index date.

[c] Study mean concentrations based on residential occupancy 5–35 years prior to index date.

[d] "n.a." denotes estimate could not be calculated.

[e] Includes subjects with radon concentration measurements made using alpha track air monitoring detectors.

**Table 30 Risk estimates for cancer incidence and mortality from studies of radiation exposure: malignant tumours 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 LSS the exposed group included survivors with organ doses of 0.005 Sv or more (weighted skeletal dose) for incidence or mortality. The studies listed are those for which quantitative estimates of risk could be made

| *Study* | | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|---|
| **EXTERNAL LOW-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| LSS [P48] | | | | | | | |
| Sex | Males | 4 | 4.1[p] | 0.24 | 436 180 | 3.34 (0.90, 9.69) | <0 (<0, <0) |
| | Females | 3 | 7.6[p] | 0.23 | 729 608 | <0 (<0, <0) | <0 (<0, 9.75) |
| Age at exposure | <20 years | 3 | 2.3[p] | 0.23 | 586 255 | 4.33 (0.90, 16.11) | <0 (<0, <0) |
| | 20–40 years | 2 | 1.2[p] | 0.23 | 378 204 | 3.16 (<0, 24.05) | <0 (<0, 12.66) |
| | >40 years | 2 | 8.8[p] | 0.22 | 201 330 | <0 (<0, <0) | <0 (<0, <0) |
| Time since exposure | 12–15 years | 3 | 5.8[p] | 0.24 | 634 356 | 1.27 (0.07, 4.55) | <0 (<0, 10.87) |
| | 15–30 years | 4 | 2.9[p] | 0.23 | 531 433 | 2.28 (0.23, 9.32) | <0 (<0, 18.77) |
| | >30 years | 7 | 8.7[p] | 0.23 | 1 165 788 | 1.64 (0.40, 4.31) | <0 (<0, 14.36) |
| Retinoblastoma patients [W11] (bone and soft-tissue sarcoma)[c] | | 81 | 16.9 | 0.0[d] | n.a. | 0.19 (0.14, 0.32)[j] | n.a. |
| Childhood radiotherapy (international) [T10] | | 54 | 20 | 27 | n.a. | 0.06 (0.01, 0.2)[b] | n.a. |
| United Kingdom childhood cancer [H27] (bone)[e] | | 49 | 18.8 | 10[d] | n.a. | 0.16 (0.07, 0.37)[j] | n.a. |
| French breast cancer [R52] | | 12 | 1.7 | >11.8[q] | 48 993 | 0.05 (n.a., 1.18)[r] | n.a. |
| Cervical cancer case-control [B8] (connective tissue)[f] | | 46 | 70.8 | 7 | n.a. | –0.05 (–0.11, 0.13) | –0.01 (–0.03, 0.03) |
| Cervical cancer case-control [B8] (bone)[f] | | 15 | 10.4 | 22 | n.a. | 0.02 (–0.03, 0.21)[b] | n.a. |
| Canadian National Dose Registry [S8] | | | | | | | |
| | Bone | 16 | 23 | 0.066 2 | 2 667 903 | <0 | <0 |
| | Connective tissue | 42 | 46.4 | | | <0 | <0 |
| **Mortality** | | | | | | | |
| LSS [P9] | | | | | | | |
| Sex | Males | 6 | 7.5[p] | 0.20 | 666 869 | 1.24 (0.03, 4.47) | <0 (<0, 24.40) |
| | Females | 8 | 7.0[p] | 0.20 | 1 061 688 | <0 (<0, 3.15) | <0 (<0, 25.43) |
| Age at exposure | <20 years | 2 | 2.3[p] | 0.20 | 885 656 | 2.11 (<0, 11.62) | <0 (<0, 7.21) |
| | 20–40 years | 5 | 1.9[p] | 0.21 | 514 903 | 8.26 (0.70, 50.09) | <0 (<0, <0) |
| | >40 years | 7 | 10.3[p] | 0.19 | 327 998 | <0 (<0, 0.01) | <0 (<0, 35.48) |
| Time since exposure | 12–15 years | 8 | 9.2[p] | 0.20 | 1 097 069 | 1.33 (0.05, 4.70) | 0.08 (0.01, 0.26) |
| | 15–30 years | 6 | 5.2[p] | 0.20 | 631 488 | <0 (<0, 4.20) | <0 (<0, 31.08) |
| | >30 years | 14 | 14.2[p] | 0.20 | 1 728 557 | 0.88 (<0, 3.03) | <0 (<0, 21.23) |
| Ankylosing spondylitis [W8] (bone and connective and soft tissue)[g] | | 19 | 6.3 | 4.54 | 287 095 | 0.44[b] | 0.097[b] |
| Nuclear workers in Canada, United Kingdom and United States [C3] (bone) | | 11 | n.a. | 0.04 | 2 124 526 | <0[i] | n.a. |

| *Study* | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|
| Nuclear workers in Canada, United Kingdom and United States [C3] (connective tissue) | 19 | n.a. | 0.04 | 2 124 526 | >0[i] | n.a. |
| Oak Ridge National Laboratory workers, United States, 1943–1947 [F2] (bone) | 11 | 10.4 | n.a. | n.a. | n.a. | n.a. |
| United States radiologic technologists [M10] | 5 | 13.3 | n.a. | ~3 900 000 | <0 | <0 |
| Canadian National Dose Registry [A8] | 3[s] | 8.3[s] | 0.063 | 2 861 093 | –0.9 (–57.5, 55.7)[s] | n.a. |
| **INTERNAL HIGH-LET EXPOSURES** | | | | | | |
| **Incidence** | | | | | | |
| $^{224}$Ra TB and ankylosing spondylitis patients [N3] (bone) | 55 | 0.2 | 30.6 Gy | 25 500 | n.a. | n.a. |
| $^{224}$Ra ankylosing spondylitis patients [W15] (bone and connective tissue) | 4 | 1.3 | ~6 Gy | 32 800 | 4.3[k] | n.a. |
| German Thorotrast patients [V4] (bone sarcoma) | 4 | n.a. | 20.6 mL[l] | n.a. | ~3.3[m] | n.a. |
| **Mortality** | | | | | | |
| United States radium luminizers [C11, R18, S12, S13, S16, S25] (bone)[n] | 46 | <1 | 8.6 Gy | 35 819 | n.a. | ~13 |
| Portuguese Thorotrast patients [D15] (bone) | 16 | n.a. | 26.3 mL[l] | 16 963 | 7.08 (1.65, 30.3)[h,j,o] | n.a. |
| United States Thorotrast patients [T30] | 2 | 0.1 | n.a. | 8 740 | ∞ (0.1, ∞)[h,j] | n.a. |

[a] 90% CI in parentheses derived from fitting models (4) and (5) for the LSS, and derived from published data for the other studies, unless otherwise stated.
[b] Estimates based on method described in the introduction to chapter III of annex I in the UNSCEAR 2000 Report [U2].
[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 1-year survivors. The observed and expected numbers cover both exposed and unexposed persons. The excess absolute risk for connective tissue is computed using underlying cancer incidence data derived from the cohort study [B11].
[g] The values given exclude the period within 5 years of first treatment.
[h] Risk relative to unexposed controls.
[i] Based on a 10-year lag. Trend not statistically significantly different from zero.
[j] 95% CI in parentheses.
[k] Risk relative to unexposed controls, among whom 1 case was observed compared with 1.4 expected [W15].
[l] Amount of Thorotrast administered.
[m] Crude relative risk, based on one case in the control group. This relative risk is not significantly different from 1 ($p > 0.05$) [V4].
[n] Based on pre-1930 workers with an average skeletal dose greater than zero [C11].
[o] Based on 5 deaths in the control group, and excluding the first 5 years after administration of Thorotrast [D15].
[p] All expected numbers calculated by means of fitted relative risk model (4) (with purely quadratic dose response), evaluated at zero dose.
[q] All cases have at least 11.8 Gy.
[r] Lower bound did not converge.
[s] Males only.

**Table 31 Risk estimates for cancer incidence and mortality from studies of radiation exposure: cutaneous malignant melanoma**

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 LSS the exposed group included survivors with doses of 0.005 Sv or more (weighted skin dose) for incidence or mortality. The studies listed are those for which quantitative estimates of risk could be made

| *Study* | | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|---|
| **EXTERNAL LOW-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| LSS [P48] | | | | | | | |
| Sex | Males | 3 | 3.3[b] | 0.33 | 436 183 | 0.01 (<0, 2.66) | <0 (<0, 6.99) |
| | Females | 4 | 4.3[b] | 0.32 | 729 610 | <0 (<0, 0.57) | <0 (<0, 1.56) |
| Age at exposure | <40 years | 3 | 3.7[b] | 0.32 | 964 458 | <0 (<0, 0.68) | <0 (<0, 1.09) |
| | >40 years | 4 | 3.8[b] | 0.31 | 201 334 | 0.07 (<0, 2.73) | <0 (<0, <0) |
| Time since exposure | 12–30 years | 4 | 4.5[b] | 0.33 | 634 360 | <0 (<0, 2.10) | <0 (<0, 5.05) |
| | >30 years | 3 | 3.0[b] | 0.31 | 531 433 | <0 (<0, 0.96) | <0 (<0, 2.18) |
| All | | 7 | 7.4[b] | 0.32 | 1 165 793 | <0 (<0, 0.74) | <0 (<0, 0.03) |
| Canadian National Dose Registry [S8] | | 222 | 191.3 | 0.006 6 | 2 667 903 | 4.3 (<0, 19.6)[c] | n.a. |
| Capenhurst uranium facility, United Kingdom [M4][b] | | 35 | 30.22 | 0.098 5 | 40 933 | –1.30 (<–1.30, 10.51)[e] | n.a. |
| Springfields uranium workers, United Kingdom [M5] | | 161 | 153.01 | 0.022 8 | 190 795 | 4.38 (–0.21, 11.78)[e] | n.a. |
| United Kingdom Chapelcross workers [M6] | | 29[d] | 21.56[d] | 0.083 6 | 39 210 | 0.15 (<–2.23, 6.43)[e] | n.a. |
| **Mortality** | | | | | | | |
| LSS [P9] | | | | | | | |
| Sex | Males | 3 | 1.2[b] | 0.28 | 666 872 | 1.91 (<0, 15.25) | 0.03 (<0, 0.13) |
| | Females | 4 | 6.0[b] | 0.28 | 1 061 688 | <0 (<0, <0) | <0 (<0, 5.84) |
| Age at exposure | <40 years | 3 | 3.0[b] | 0.28 | 1 400 559 | 0.66 (<0, 4.11) | <0 (<0, 1.13) |
| | >40 years | 4 | 3.1[b] | 0.27 | 328 000 | <0 (<0, 0.58) | 0.36 (0.14, 2.32) |
| Time since exposure | 12–30 years | 3 | 3.2[b] | 0.28 | 1 097 072 | <0 (<0, 0.40) | <0 (<0, <0) |
| | >30 years | 4 | 3.0[b] | 0.28 | 631 488 | 0.66 (<0, 4.11) | <0 (<0, 11.93) |
| All | | 7 | 5.4[b] | 0.28 | 1 728 560 | 0.30 (<0, 2.10) | <0 (<0, 6.25) |
| Canadian National Dose Registry [A8] | | | | | | | |
| Sex | Males | 21 | n.a. | 0.006 6 | 2 861 093 | 44.9 (–67.1, 156.8) | n.a. |
| | Females | | | | | –0.1 (–1340.0, 1339.0) | n.a. |
| **INTERNAL HIGH-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| Danish and Swedish Thorotrast patients [T30] | | 2 | 2.0 | n.a. | 25 480 | 0.4 (0.1, 2.1)[f,g] | n.a. |

[a] 90% CI in parentheses derived from fitting models (4) and (5) for the LSS, and derived from published data for the other studies.
[b] All expected numbers calculated by means of fitted relative risk model (4), evaluated at zero dose.
[c] Tabulation and analysis with a 10-year lag. Risk estimate based on a dose–response analysis.
[d] Melanoma and other skin cancers.
[e] Males only.
[f] Risk relative to unexposed controls.
[g] 95% CI in parentheses.

**Table 32 Risk estimates for cancer incidence and mortality from studies of radiation exposure: non-melanoma 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 LSS the exposed group included survivors with doses of 0.005 Sv or more (weighted skin dose) for incidence. For case-control studies, the observed number of cases covers both exposed and unexposed persons. The studies listed are those for which quantitative estimates of risk could be made

| *Study* | | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk*[a] *at 1 Sv* | *Average excess absolute risk*[a] *($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|---|
| **EXTERNAL LOW-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| LSS [P48] | | | | | | | |
| Sex | Males | 66 | 45.6[b] | 0.33 | 436 183 | 1.27 (0.65, 2.17) | 1.23 (0.65, 1.96) |
| | Females | 101 | 78.1[b] | 0.32 | 729 610 | 1.37 (0.81, 2.12) | 1.07 (0.68, 1.56) |
| Age at exposure | <20 years | 41 | 14.0[b] | 0.32 | 586 255 | 5.69 (3.16, 10.27) | <0 (<0, 150.01) |
| | 20–40 years | 67 | 52.6[b] | 0.33 | 378 204 | 0.90 (0.38, 1.66) | 0.98 (0.43, 1.72) |
| | >40 years | 10 | 8.7[b] | 0.33 | 119 776 | <0 (<0, 1.73) | 0.38 (0.04, 1.42) |
| Time since exposure | 12–15 years | 36 | 29.1[b] | 0.33 | 514 584 | 0.90 (0.20, 2.08) | 0.42 (0.16, 0.84) |
| | 15–30 years | 121 | 86.9[b] | 0.31 | 531 433 | 1.53 (1.00, 2.24) | 2.31 (1.62, 3.14) |
| | >30 years | 167 | 123.7[b] | 0.32 | 1 165 793 | 1.33 (0.89, 1.88) | 1.12 (0.79, 1.52) |
| **Childhood exposures** | | | | | | | |
| Israel tinea capitis [L42, R16][c] | | 41 | 21.7 | 6.8 | 662 950 | 0.70 (0.35, 1.32) | 1.31 (0.94, 1.77)[d] |
| New York tinea capitis (whites) [S7][c] | | 124 | 37.7 | 4.3[e] | 125 357 | 0.6 (0.3, 1.1)[f] | 1.9 (0.5, 3.3)[f] |
| Rochester thymic irradiation [H26, L42] | | 14 | 4.2 | 2.3 | 87 000[g] | 1.05 (0.50, 1.84) | 15.9 (7.5, 27.9)[d] |
| Tonsil irradiation [L42, S17] | | 63 | 45.0 | 3.8 | 96 000[g] | 0.11 (0.04, 0.19) | 10.2 (3.3, 18.3)[d] |
| **Adult exposures** | | | | | | | |
| Cervical cancer cohort [B11, L42] | | 88 | 100 | 10 | 342 786[j] | <0 (<0, 0.01) | <0 (<0, 0.6)[h] |
| Massachusetts TB fluoroscopy [D6, L42] | | 80 | 75.3 | 9.6 | 122 000[g] | 0.007 (0, 0.03) | 0.9 (<0, 4.5)[h] |
| New York mastitis [L42] | | 14 | 10.7 | 2.6 | 14 000[g] | 0.12 (<0, 0.38) | 60 (<0, 193.5)[h] |
| **INTERNAL HIGH-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| Danish and Swedish Thorotrast patients [T30] | | 14 | 9.5 | n.a. | 25 480 | 1.3 (0.6, 2.8)[f,i] | n.a. |

[a] 90% CI in parentheses derived from fitting models (4) and (5) for the LSS, and derived from published data for the other studies.
[b] All expected numbers calculated by means of fitted relative risk model (4), evaluated at zero dose.
[c] All estimates are for basal cell carcinoma.
[d] Risks normalized to 3 000 cm$^2$ of UVR-exposed skin (as in reference [L42]).
[e] Average dose to the scalp and the margin around the scalp in exposed group.
[f] 95% CI in parentheses.
[g] Person-years estimated from data presented by Shore [S22].
[h] Risks normalized to 15 000 cm$^2$ of UVR-unexposed skin (as in reference [L42]).
[i] Risk relative to unexposed controls.
[j] Five or more years of follow-up.

**Table 33 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 LSS the exposed group included survivors with doses of 0.005 Sv or more (weighted breast dose) for incidence or mortality. For case-control studies, the observed number of cases covers both exposed and unexposed persons. The studies listed are those for which quantitative estimates of risk could be made

| *Study* | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|
| **EXTERNAL LOW-LET EXPOSURES** | | | | | | |
| **Incidence** | | | | | | |
| LSS [P48] | | | | | | |
| Age at exposure <20 years | 246 | 166.7[q] | 0.26 | 315 537 | 1.89 (1.38, 2.50) | 8.78 (6.54, 11.28) |
| 20–40 years | 222 | 170.8[q] | 0.26 | 287 982 | 1.31 (0.86, 1.87) | 6.97 (4.71, 9.54) |
| >40 years | 59 | 56.6[q] | 0.23 | 126 090 | 0.62 (0.04, 1.51) | 2.49 (0.02, 5.82) |
| Time since exposure 12–15 years | 15 | 12.7[q] | 0.26 | 72 566 | 1.45 (0.09, 4.18) | <0 (<0, 3.01) |
| 15–30 years | 153 | 99.0[q] | 0.26 | 318 513 | 1.94 (1.30, 2.77) | 6.07 (4.29, 8.09) |
| >30 years | 359 | 282.3[q] | 0.25 | 338 529 | 1.30 (0.94, 1.73) | 11.08 (8.36, 14.05) |
| All | 527 | 393.0[q] | 0.26 | 729 608 | 1.49 (1.17, 1.85) | 7.55 (6.08, 9.14) |
| Pooled analysis: eight cohorts [P3][m] | 829 | 509 | 0.17–5.8 for various studies | 839 907 | 0.86 (0.7, 1.04)[n] | 13.4 (9.5, 17)[n] |
| 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 [S5] | 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, M17] | 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 [B7][c] | 953[d] | 1 083.0 | 0.31 | n.a. | –0.2 (<–0.2, 0.3) | <–0.3 (<–0.3, 0.2)[b] |
| 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 H10][f] | 22 | 7.8 | 0.76 | 38 200 | 2.39 (1.2, 4.0)[b] | 4.89 (2.4, 8.1)[b] |
| Childhood skin haemangioma [L12][f] | 245 | 204 | 0.33 | 600 000 | 0.35 (0.18, 0.59)[r] | 1.44 (0.78, 2.28)[r] |
| French–United Kingdom childhood cancer [G29] | 16 | n.a. | 5.06 | ~29 000 | 0.13 (<0, 0.75) | n.a. |
| Hodgkin's disease (Stanford) [H20] | 25 | 6.1 | 44.0 | 100 057 | 0.07 (0.04, 0.11)[b] | 0.04 (0.03, 0.07)[b] |
| Hodgkin's disease (Netherlands) [V8] | 48 | n.a. | 25.2 | Mean follow-up 18.7 years | 0.06 (0.01, 0.13) | n.a. |
| Hodgkin's disease (international) [T25] | 105 | n.a. | 25.1 | Mean follow-up 18.0 years | 0.15 (0.04, 0.73) (radiotherapy alone) | n.a. |
| Canadian National Dose Registry [S8] | 544 | 584 | 0.017 5 | n.a. | <0 | <0 |
| Chinese medical X-ray workers [W3] | | | | | | |
| Employed before 1970 | 29 | 21.64 | 0.551 | 357 753 | 0.62 (–0.16, 1.6) | 0.37 (–0.09, 1.0) |
| Employed only 1970–1980 | 17 | 12.79 | 0.082 | 337 133 | 4.0 (–2.4, 13)[o] | 1.5 (–0.9, 5.0) |

| *Study* | | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|---|
| **Mortality** | | | | | | | |
| LSS [P9] | | | | | | | |
| Age at exposure | <20 years | 66 | 38.7[q] | 0.23 | 469 884 | 2.94 (1.63, 4.86) | <0 (<0, 437.60) |
| | 20–40 years | 70 | 54.5[q] | 0.23 | 391 356 | 1.01 (0.31, 2.06) | <0 (<0, 556.08) |
| | >40 years | 34 | 39.6[q] | 0.21 | 200 448 | <0 (<0, 0.99) | <0 (<0, 622.72) |
| Time since exposure | 12–15 years | 28 | 25.2[q] | 0.22 | 301 146 | 0.04 (<0, 1.61) | <0 (<0, 279.27) |
| | 15–30 years | 50 | 38.2[q] | 0.23 | 365 465 | 1.33 (0.46, 2.68) | 1.13 (0.30, 2.23) |
| | >30 years | 92 | 68.7[q] | 0.23 | 395 077 | 1.82 (0.98, 2.98) | 3.28 (1.97, 4.83) |
| All | | 170 | 131.5[q] | 0.23 | 1 061 688 | 1.39 (0.83, 2.10) | <0 (<0, 513.45) |
| Scoliosis patients [D17][f] | | 70 | 35.7 | 0.11 | 184 508 | 5.4 (1.2, 14.1)[r] | 12.9 (4.0, 21.0)[r] |
| Ankylosing spondylitis [W8][g] | | 42 | 39.3 | 0.59 | n.a. | 0.08 (–0.30, 0.65)[h,r] | n.a. |
| Canadian TB fluoroscopy [H9] | | 349 | 237 | 0.89 | 411 706 | 0.90 (0.55, 1.39)[i,r] | 3.16 (1.97, 4.78)[j,r] |
| Peptic ulcer [C4] | | 14 | 7.7 | 0.2 | 41 779 | 0.10 (<0, 10.40)[o,r,u] | n.a. |
| Nuclear workers in Canada, United Kingdom and United States [C3] | | 84 | n.a. | 0.04 | n.a. | >0[k] | n.a. |
| United Kingdom NRRW [M12] | | 25 | 39.1 | 0.006 | ~192 000 | 0.12 (<–1.95, 40.5)[p] | n.a. |
| **INTERNAL LOW-LET EXPOSURES** | | | | | | | |
| **Mortality** | | | | | | | |
| Semipalatinsk study [B58] | | 61 | n.a. | 0.63 | 582 750 | 1.09 (–0.05, 15.8)[r,s] | n.a. |
| **INTERNAL HIGH-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| $^{224}$Ra TB and ankylosing spondylitis patients [N2] | | 28 | 8 | ~0.1 Gy[l] | n.a. | 0.9 | n.a. |
| Danish and Swedish Thorotrast patients [T30] | | 27 | 10.0 | n.a. | 12 247 | 1.6 (0.9, 2.8)[r,t] | n.a. |
| **Mortality** | | | | | | | |
| United States Thorotrast patients [T30] | | 6 | 2.9 | n.a. | 4 613 | 0.9 (0.3, 7.2)[r,t] | n.a. |

*a* 90% CI in parentheses derived from fitting models (4) and (5) for the LSS, and derived from published data for the other studies, unless otherwise stated.
*b* Estimates based on method described in the introduction to chapter III of annex I in the UNSCEAR 2000 Report [U2].
*c* Excess absolute risk among cervical cancer patients is computed using underlying cancer 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* The values given exclude the period within 5 years of first treatment.
*h* Dose–response analysis based on the number of treatment courses given.
*i* Including a factor to allow for differences between Nova Scotia and other Canadian provinces. Values apply to exposure at age 15 years.
*j* Including a factor to allow for differences between Nova Scotia and other Canadian provinces. Values apply for 20 years following exposure at age 15 years.
*k* Based on a 10-year lag. Trend not statistically significant.
*l* High-LET breast dose from $^{224}$Ra.
*m* Cohorts are: LSS of the survivors of the atomic bombings in Japan, two Massachusetts multiple fluoroscopy cohorts, and New York mastitis, Rochester thymus, Swedish benign breast disease, Gothenburg haemangioma and Stockholm haemangioma studies.
*n* Risk estimate for exposure at age 25 years, except for the infant exposure cohorts where risk was modelled for 0.5 years of age at exposure.
*o* Excess relative risk and excess absolute risk values were calculated from the mean dose and the observed and expected cancers (or the relative risk and confidence interval) reported in the paper.
*p* Tabulation and analysis with a 10-year lag. Risk estimate based on a dose–response analysis.
*q* All expected numbers calculated by means of fitted relative risk model (4), evaluated at zero dose.
*r* 95% CI in parentheses.
*s* Based on a dose–response analysis, restricted to the exposed group only.
*t* Risk relative to unexposed controls.
*u* Based on follow-up of 11 or more years after radiotherapy.

**Table 34 Risk estimates for cancer incidence and mortality from studies of radiation exposure: uterine 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 LSS the exposed group included survivors with doses of 0.005 Sv or more (weighted uterine dose) for incidence or mortality. The studies listed are those for which quantitative estimates of risk could be made

| *Study* | | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|---|
| **EXTERNAL LOW-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| LSS [P48] | | | | | | | |
| Age at exposure | <20 years | 130 | 120.8[b] | 0.20 | 315 537 | 0.38 (<0, 0.90) | 0.75 (<0, 2.59) |
| | 20–40 years | 230 | 227.4[b] | 0.19 | 287 982 | <0 (<0, 0.33) | 0.20 (<0, 2.85) |
| | >40 years | 144 | 142.7[b] | 0.17 | 126 089 | <0 (<0, 0.41) | 0.09 (<0, 4.88) |
| Time since exposure | 12–15 years | 45 | 52.8[b] | 0.20 | 72 566 | <0 (<0, 0.28) | <0 (<0, 1.61) |
| | 15–30 years | 243 | 231.5[b] | 0.20 | 318 513 | <0 (<0, 0.09) | <0 (<0, 0.67) |
| | >30 years | 216 | 205.8[b] | 0.19 | 338 528 | 0.53 (0.17, 0.99) | 2.86 (0.83, 5.31) |
| All | | 504 | 490.2[b] | 0.19 | 729 607 | 0.10 (<0, 0.32) | 0.09 (<0, 1.48) |
| Cervical cancer [B8] | | | | | | | |
| Age at treatment[c] | <45 years | 130 | n.a. | 166[d] | n.a. | 0.002 3[e,f] | n.a. |
| | 45–54 years | 100 | | 166 | | 0.004 8 | |
| | 55–64 years | 60 | | 158 | | 0.000 8 | |
| | ≥65 years | 23 | | 170 | | 0.000 0 | |
| Time since treatment | 1–<5 years | 19 | n.a. | 168 | n.a. | –0.004 5 | n.a. |
| | 5–<10 years | 66 | | 169 | | 0.002 4 | |
| | 10–<15 years | 85 | | 165 | | –0.002 0 | |
| | ≥15 years | 143 | | 163 | | 0.030 7 | |
| **Mortality** | | | | | | | |
| LSS [P9] | | | | | | | |
| Age at exposure | <20 years | 40 | 34.2[b] | 0.18 | 469 884 | 0.42 (<0, 1.68) | <0 (<0, 333.82) |
| | 20–40 years | 133 | 122.6[b] | 0.18 | 391 356 | 0.17 (<0, 0.77) | <0 (<0, 1.61) |
| | >40 years | 148 | 138.9[b] | 0.16 | 200 441 | <0 (<0, 0.51) | <0 (<0, 3.53) |
| Time since exposure | 5–15 years | 96 | 82.6[b] | 0.17 | 301 146 | 0.31 (<0, 1.23) | <0 (<0, 0.26) |
| | 15–30 years | 115 | 109.3[b] | 0.18 | 365 464 | <0 (<0, <0) | <0 (<0, 0.07) |
| | >30 years | 110 | 103.7[b] | 0.18 | 395 071 | 0.52 (0.01, 1.24) | <0 (<0, 1229.1) |
| All | | 321 | 295.5[b] | 0.17 | 1 061 681 | 0.09 (<0, 0.44) | <0 (<0, 0.33) |
| Benign gynaecological disorders [I4] | | | | | | | |
| All uterus | | 105 | 57.2 | 32.0[d] | 109 911 | 0.006[g] | 0.14[h] |
| Cervix | | 10 | 16.4 | 32.0 | 109 911 | –0.01[e] | –0.02 |
| Metropathia [D7] | | | | | | | |
| All uterus | | 25 | 17.73 | 5.2[d] | 47 144 | 0.09 (–0.02, 0.19)[g,j] | 0.30 (–0.07, 0.78)[h,j] |
| Cervix | | 12 | 9.20 | 5.2 | 47 144 | 0.06 (–0.06, 0.25)[e,j] | 0.11 (–0.12, 0.48)[h,j] |

| *Study* | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|
| Spondylitis [W8] | | | | | | |
| All uterus | 13 | 13.57 | 4.94[d] | 61 619 | –0.01[e] | –0.02[h] |
| Cervix | 3 | 8.33 | 4.94 | 61 619 | –0.13 | –0.18 |
| Other uterus | 10 | 5.24 | 4.94 | 61 119 | 0.18 | 0.16 |
| **INTERNAL HIGH-LET EXPOSURES** | | | | | | |
| **Incidence** | | | | | | |
| Danish and Swedish Thorotrast patients [T30] | | | | | | |
| Uterine cervix | 6 | 6.0 | n.a. | 12 247 | 0.6 (0.2, 1.8)[i] | n.a. |
| Uterine corpus | 5 | 4.5 | n.a. | 12 247 | 0.6 (0.2, 1.8)[i] | n.a. |

[a] 90% CI derived from fitting models (4) and (5) for the LSS, and derived from published data for the other studies.
[b] All expected numbers calculated by means of fitted relative risk model (4), evaluated at zero dose.
[c] Data are for uterine corpus cancer.
[d] Dose in grays.
[e] Calculated as [RR – 1] divided by the mean dose.
[f] Reference group includes women with uterine dose of <100 Gy.
[g] Slope of linear dose response.
[h] Calculated as [observed – expected] × $10^4$ divided by [PY × mean dose].
[i] Risk relative to unexposed controls, with 95% CI in parentheses.
[j] 95% CI in parentheses.

**Table 35 Risk estimates for cancer incidence and mortality from studies of radiation exposure: ovarian 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 LSS the exposed group included survivors with doses of 0.005 Sv or more (weighted ovarian dose) for incidence or mortality. For case-control studies, the observed number of cases covers both exposed and unexposed persons. The studies listed are those for which quantitative estimates of risk could be made

| *Study* | | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|---|
| **EXTERNAL LOW-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| LSS [P48] | | | | | | | |
| Age at exposure | <20 years | 29 | 27.1[d] | 0.20 | 315 537 | 1.16 (0.15, 2.86) | 0.71 (0.09, 1.72) |
| | 20–40 years | 45 | 46.1[d] | 0.19 | 287 982 | <0 (<0, 0.71) | <0 (<0, 0.71) |
| | >40 years | 29 | 24.6[d] | 0.17 | 126 089 | 1.73 (0.20, 4.45) | 3.24 (0.45, 7.21) |
| Time since exposure | 12–15 years | 4 | 5.1[d] | 0.19 | 72 566 | <0 (<0, 0.04) | <0 (<0, 0.71) |
| | 15–30 years | 35 | 32.1[d] | 0.19 | 318 513 | 1.47 (0.37, 3.26) | 1.04 (0.21, 2.30) |
| | >30 years | 64 | 63.0[d] | 0.19 | 338 528 | 0.23 (<0, 1.11) | 0.54 (<0, 1.92) |
| All | | 103 | 98.6[d] | 0.19 | 729 607 | 0.61 (0.08, 1.35) | 0.59 (0.07, 1.34) |
| Cervical cancer case-control [B8] | | 309 | n.a. | 32.1 | n.a. | 0.01 (–0.02, 0.14) | 0.05 (–0.08, 0.60) |
| Stockholm skin haemangioma [L10] | | 15 | n.a. | 0.05 | 406 565 | 0.62 | 0.33 |

| *Study* | | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk*[a] *at 1 Sv* | *Average excess absolute risk*[a] *($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|---|
| **Mortality** | | | | | | | |
| LSS [P9] | | | | | | | |
| Age at exposure | <20 years | 20 | 17.7[d] | 0.18 | 469 884 | 1.53 (0.19, 4.06) | <0 (<0, 185.15) |
| | 20–40 years | 34 | 29.7[d] | 0.18 | 391 356 | 0.92 (<0, 2.65) | <0 (<0, 386.99) |
| | >40 years | 31 | 22.6[d] | 0.16 | 200 447 | 1.33 (<0, 4.25) | <0 (<0, 717.59) |
| Time since exposure | 5–15 years | 13 | 14.8[d] | 0.17 | 301 146 | <0 (<0, 9171.6) | <0 (<0, 187.74) |
| | 15–30 years | 26 | 19.5[d] | 0.18 | 365 464 | 2.65 (0.78, 6.00) | <0 (<0, 298.86) |
| | >30 years | 46 | 38.6[d] | 0.18 | 395 077 | 0.88 (<0, 2.41) | <0 (<0, 513.47) |
| All | | 85 | 70.3[d] | 0.18 | 1 061 687 | 1.18 (0.39, 2.31) | <0 (<0, 348.40) |
| $^{226}$Ra for uterine bleeding [I4]: mortality[b] | | 37 | 23 | 2.3 | 109 911 | 0.41 (–0.69, 1.51) | n.a. |
| United Kingdom X-ray for uterine bleeding [D7] | | 18 | 15.6 | 5.3 | 47 144 | 0.02 (–0. 08, 0.12)[c] | 0.10 (–0.20, 0.51) |
| United Kingdom NRRW [M12] | | 10 | 11.6 | 0.006 | ~192 000 | 82.8 (<–1.95, 2583) | n.a. |
| **INTERNAL HIGH-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| Danish and Swedish Thorotrast patients [T30] | | 9 | 4.5 | n.a. | 12 247 | 4.3 (1.1, 24.3)[e] | n.a. |

[a] 90% CI in parentheses derived from fitting models (4) and (5) for the LSS, and derived from published data for the other studies.
[b] Data for "genital organs other than uterus".
[c] Excess relative risk (and 95% CI) was derived from dose–response analysis; excess absolute risk (and 95% CI) was calculated from the observed and expected cancers and the mean dose and person years of follow-up reported in the paper.
[d] All expected numbers calculated by means of fitted relative risk model (4), evaluated at zero dose.
[e] Risk relative to unexposed controls, with 95% CI in parentheses.

**Table 36 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 LSS the exposed group included survivors with doses of 0.005 Sv or more (weighted testicular dose) for incidence or mortality. The studies listed are those for which quantitative estimates of risk could be made

| *Study* | | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk*[a] *at 1 Sv* | *Average excess absolute risk*[a] *($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|---|
| **EXTERNAL LOW-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| LSS [P48] | | | | | | | |
| Age at exposure | <20 years | 18 | 19.1[k] | 0.22 | 270 718 | 0.12 (<0, 1.38) | <0 (<0, 0.42) |
| | 20–40 years | 59 | 60.2[k] | 0.26 | 90 222 | 0.03 (<0, 0.70) | <0 (<0, 1.84) |
| | >40 years | 79 | 78.5[k] | 0.23 | 75 240 | 0.11 (<0, 0.70) | <0 (<0, 2.96) |
| Time since exposure | 12–15 years | 4 | 5.4[k] | 0.24 | 47 208 | <0 (<0, 1.14) | <0 (<0, 325.76) |
| | 15–30 years | 44 | 48.2[k] | 0.24 | 196 069 | <0 (<0, 0.31) | <0 (<0, 0.38) |
| | >30 years | 108 | 103.4[k] | 0.22 | 192 903 | 0.36 (<0, 0.93) | <0 (<0, 2207.9) |
| All | | 156 | 157.3[k] | 0.23 | 436 180 | 0.12 (<0, 0.51) | <0 (<0, 0.38) |
| Canadian National Dose Registry [S8] | | 232 | 279 | 0.115 | n.a. | 0.1 (<0, 3.5)[j] | n.a. |

| *Study* | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|
| Capenhurst uranium facility, United Kingdom [M4] | 9 | 16.72 | 0.098 5 | 40 933 | –1.31 (<–1.31, 12.76) | n.a. |
| Springfields uranium workers, United Kingdom [M5] | 69 | 89.79 | 0.022 8 | 190 795 | 0.41 (<–2.90, 9.27) | n.a. |
| **Mortality** | | | | | | |
| LSS [P9] | | | | | | |
| Age at exposure <20 years | 5 | 9.3[k] | 0.19 | 415 772 | <0 (<0, >10 000) | <0 (<0, 45.63) |
| 20–40 years | 18 | 19.2[k] | 0.22 | 123 547 | <0 (<0, 1.10) | <0 (<0, 473.90) |
| >40 years | 30 | 28.9[k] | 0.20 | 127 550 | 1.01 (0.01, 2.78) | <0 (<0, 910.84) |
| Time since exposure 12–15 years | 4 | 5.0[k] | 0.20 | 202 966 | <0 (<0, 0.38) | <0 (<0, 59.26) |
| 15–30 years | 10 | 15.2[k] | 0.20 | 227 492 | <0 (<0, 1.33) | <0 (<0, 184.91) |
| >30 years | 39 | 36.3[k] | 0.20 | 236 411 | 0.69 (<0, 0.97) | <0 (<0, 623.82) |
| All | 53 | 54.9[k] | 0.20 | 666 869 | 0.40 (<0, 1.31) | <0 (<0, 298.22) |
| Ankylosing spondylitis [W8][b] | 88 | 64.7 | 2.18 | n.a. | 0.14 (0.02, 0.28)[c,e] | n.a. |
| Peptic ulcer [C4] | 30 | 24.2 | 0.1 | 41 779 | –1.60 (<–1.60, 4.50)[e,h,l] | n.a. |
| Nuclear workers in Canada, United Kingdom and United States [C3] | 256 | n.a. | 0.04 | n.a. | <0[d] | n.a. |
| United Kingdom NRRW [M12] | 211 | 214.6 | 0.033 | ~1 871 000 | 0.29 (–1.13, 2.95) | n.a. |
| Nuclear power industry workers in the United States [H44] | 14 | 23.2 | 0.026 | 698 041 | –2.50 (<–2.51, 26.4)[e] | n.a. |
| Oak Ridge National Laboratory workers, United States, 1943–1947 [F2] | 150 | 142.0 | n.a. | n.a. | n.a. | n.a. |
| Oak Ridge X-10 and Y-12 plants [F5] | 77 | n.a. | 0.013 | n.a. | 2.06 (<0, 24.6) | n.a. |
| Los Alamos National Laboratory workers, United States [W6] | 53 | 79.0 | ~0.016 | 251 651 | <0[i] | n.a. |
| **INTERNAL HIGH-LET EXPOSURES** | | | | | | |
| **Incidence** | | | | | | |
| $^{224}$Ra TB and ankylosing spondylitis patients [N2] | 16 | ~12 | n.a. | n.a. | ~1.3[g] | n.a. |
| Danish and Swedish Thorotrast patients [T30] | 14 | 10.0 | n.a. | 13 233 | 4.5 (1.6, 16.3)[e,g] | n.a. |
| **Mortality** | | | | | | |
| German Thorotrast patients [V4] | 21 | n.a. | 20.6 mL[f] | n.a. | ~0.9[g] | n.a. |
| United States Thorotrast patients [T30] | 1 | 1.4 | n.a. | 4 127 | 0.2 (0.0, 5.1)[e,g] | n.a. |

[a] 90% CI in parentheses derived from fitting models (4) and (5) for the LSS, and derived from published data for the other studies, unless otherwise stated.
[b] The values given exclude the period within 5 years of first treatment.
[c] Dose–response analysis based on the number of treatment courses given.
[d] Based on a 10-year lag. One-sided p-value for increasing trend = 0.953, based on a normal approximation.
[e] 95% CI in parentheses.
[f] Amount of Thorotrast administered (mL).
[g] Risk relative to unexposed controls.
[h] Excess relative risk and excess absolute risk values were calculated from the mean dose and the observed and expected cancers (or the relative risk and confidence interval) reported in the paper.
[i] Dose response was in the negative direction.
[j] Tabulation and analysis with a 10-year lag. Risk estimate based on a dose–response analysis.
[k] All expected numbers calculated by means of fitted relative risk model (4), evaluated at zero dose.
[l] Based on follow-up of 11 or more years after radiotherapy.

**Table 37 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 LSS the exposed group included survivors with organ doses of 0.005 Sv or more (weighted bladder dose (incidence data), weighted urinary tract dose (mortality data)) for incidence or mortality. The studies listed are those for which quantitative estimates of risk could be made

| *Study* | | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|---|
| **EXTERNAL LOW-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| LSS [P48] | | | | | | | |
| Sex | Males | 132 | 118.3[k] | 0.22 | 436 180 | 0.63 (0.17, 1.25) | 0.47 (<0, 1.60) |
| | Females | 90 | 59.0[k] | 0.20 | 729 607 | 1.74 (0.71, 3.22) | 0.52 (0.12, 1.13) |
| Age at exposure | <20 years | 48 | 38.6[k] | 0.21 | 586 255 | 1.00 (0.16, 2.32) | <0 (<0, 0.46) |
| | 20–40 years | 80 | 61.3[k] | 0.21 | 378 204 | 0.95 (0.23, 2.01) | 0.69 (<0, 1.89) |
| | >40 years | 94 | 79.2[k] | 0.19 | 201 329 | 0.78 (0.14, 1.70) | 2.28 (0.21, 5.01) |
| Time since exposure | 12–15 years | 9 | 9.6[k] | 0.21 | 119 774 | <0 (<0, 1.06) | <0 (<0, 292.76) |
| | 15–30 years | 66 | 52.8[k] | 0.21 | 514 582 | 0.98 (0.17, 2.20) | 0.50 (<0, 1.19) |
| | >30 years | 147 | 116.4[k] | 0.20 | 531 432 | 1.00 (0.44, 1.74) | 1.28 (0.33, 2.50) |
| All | | 222 | 178.1[k] | 0.21 | 1 165 787 | 0.92 (0.46, 1.50) | 0.51 (0.14, 1.02) |
| Cervical cancer case-control [B8][c] | | 273 | 65.8 | 45 | n.a. | 0.07 (0.02, 0.17) | 0.12 (0.04, 0.3) |
| Canadian National Dose Registry – males only [S8] | | 139 | 183 | 0.115 | n.a. | 1.4 (<0, 8.2)[j] | n.a. |
| Capenhurst uranium facility, United Kingdom [M4][b] | | 14 | 14.57 | 0.098 5 | 40 933 | 10.33 (<0, 57.24)[d,m] | n.a. |
| Springfields uranium workers, United Kingdom [M5] | | 57 | 75.15 | 0.022 8 | 190 795 | 2.68 (<–4.11, 14.50)[d,m] | n.a. |
| **Mortality** | | | | | | | |
| LSS [P9] | | | | | | | |
| Sex | Males | 55 | 43.6[k] | 0.19 | 666 869 | 1.03 (0.07, 2.53) | <0 (<0, 313.73) |
| | Females | 43 | 33.6[k] | 0.18 | 1 061 687 | 1.37 (0.15, 3.40) | <0 (<0, 170.04) |
| Age at exposure | <20 years | 12 | 10.9[k] | 0.19 | 885 656 | <0 (<0, 2.28) | <0 (<0, 43.45) |
| | 20–40 years | 24 | 16.6[k] | 0.19 | 514 903 | 1.52 (<0, 4.72) | <0 (<0, 176.04) |
| | >40 years | 62 | 50.1[k] | 0.18 | 327 997 | 1.36 (0.34, 2.89) | <0 (<0, 848.46) |
| Time since exposure | 12–15 years | 14 | 12.9[k] | 0.18 | 504 112 | <0 (<0, 2.73) | <0 (<0, 118.39) |
| | 15–30 years | 30 | 25.7[k] | 0.19 | 592 956 | 0.87 (<0, 2.87) | <0 (<0, 203.71) |
| | >30 years | 54 | 38.7[k] | 0.19 | 631 488 | 1.76 (0.51, 3.73) | <0 (<0, 334.58) |
| All | | 98 | 77.2[k] | 0.19 | 1 728 556 | 1.17 (0.36, 2.30) | <0 (<0, 226.53) |
| Benign gynaecological disorders [I4][e] | | 19 | 9 | 6 | 71 958 | 0.20 (0.08, 0.35) | 0.24 (0.1, 0.4)[b] |
| Metropathia haemorrhagica [D7][f] | | 20 | 6.65 | 5.2 | 47 144 | 0.40 (0.15, 0.66)[l,p] | 0.54 (0.23, 0.99)[b,l] |
| Ankylosing spondylitis [W8][g] | | 71 | 46.1 | 2.18 | 287 095 | 0.24 (–0.09, 0.41)[h,l] | 0.39 (0.19, 0.54)[b,l] |
| Peptic ulcer [C4] | | 13 | 8.8 | 0.2 | 41 779 | 2.5 (<0, 17.2)[i,l,o] | n.a. |
| Los Alamos National Laboratory workers, United States [W6] | | 18 | 30.1 | ~0.016 | 251 651 | <0[d] | n.a. |
| Nuclear industry workers in Japan [I14] | | 27 | 23.4 | 0.015 | ~1 390 000 | <0[d] | n.a. |

| *Study* | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|
| Nuclear workers in Canada, United Kingdom and United States [C3] | 104 | n.a. | 0.04 | 2 142 526 | <0[d] | n.a. |
| United Kingdom NRRW [M12] | 110 | 130.8 | 0.031 | 2 063 300 | –0.33 (–1.28, 1.61)[j] | n.a. |
| **INTERNAL HIGH-LET EXPOSURES** | | | | | | |
| **Incidence** | | | | | | |
| Danish and Swedish Thorotrast patients [T30] | 8 | 6.7 | n.a. | 25 480 | 0.8 (0.3, 1.9)[l,n] | n.a. |
| **Mortality** | | | | | | |
| United States Thorotrast patients [T30] | 3 | 0.8 | n.a. | 8 740 | ∞ (0.2, ∞)[l,n] | n.a. |

[a] 90% CI in parentheses derived from fitting models (4) and (5) for the LSS, and derived from published data for the other studies, unless otherwise stated.
[b] Estimates based on method described in the introduction to chapter III of annex I in the UNSCEAR 2000 Report [U2].
[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 underlying cancer incidence estimated using the cervical cancer cohort study [B11].
[d] Based on a 10-year lag. Trend not statistically significant.
[e] The observed and expected numbers of cases are for 10-year survivors. The estimated number of expected cases incorporated an adjustment based on the Poisson regression model given in reference [I4].
[f] The values given exclude the period within 5 years of irradiation.
[g] The values given exclude the period within 5 years of first treatment.
[h] Dose–response analysis based on the number of treatment courses given.
[i] Excess relative risk and excess absolute risk values were calculated from the mean dose and the observed and expected cancers (or the relative risk and confidence interval) reported in the paper.
[j] Tabulation and analysis with a 10-year lag. Risk estimate based on a dose–response analysis.
[k] All expected numbers calculated by means of fitted relative risk model (4), evaluated at zero dose.
[l] 95% CI in parentheses.
[m] Males only.
[n] Risk relative to unexposed controls.
[o] Based on follow-up of 11 or more years after radiotherapy.
[p] Risk estimate based on a dose–response analysis.

**Table 38 Risk estimates for cancer incidence and mortality from studies of radiation exposure: kidney 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 LSS the exposed group included survivors with doses of 0.005 Sv or more (weighted bladder dose (incidence data), weighted urinary tract dose (mortality data)) for incidence or mortality. For case-control studies, the observed number of cases covers both exposed and unexposed persons. The studies listed are those for which quantitative estimates of risk could be made

| *Study* | | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|---|
| **EXTERNAL LOW-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| LSS [P48] | | | | | | | |
| Sex | Males | 34 | 40.2[b] | 0.22 | 436 180 | <0 (<0, 0.42) | 0.18 (0.02, 0.61) |
| | Females | 36 | 30.6[b] | 0.20 | 729 607 | 1.04 (0.02, 2.83) | <0 (<0, 244.95) |
| Age at exposure | <20 years | 23 | 22.7[b] | 0.21 | 586 255 | 0.75 (<0, 2.19) | 0.31 (0.08, 0.74) |
| | 20–40 years | 27 | 22.8[b] | 0.21 | 378 204 | 0.23 (<0, 1.94) | <0 (<0, 304.44) |
| | >40 years | 20 | 28.9[b] | 0.19 | 201 329 | <0 (<0, <0) | <0 (<0, <0) |
| Time since exposure | 12–15 years | 2 | 4.6[b] | 0.21 | 119 774 | <0 (<0, 0.33) | <0 (<0, 92.43) |
| | 15–30 years | 23 | 20.6[b] | 0.21 | 514 582 | 0.66 (<0, 2.38) | 0.47 (0.13, 0.96) |
| | >30 years | 45 | 48.3[b] | 0.20 | 531 432 | <0 (<0, 0.71) | 0.10 (<0, 0.69) |
| All | | 70 | 72.1[b] | 0.21 | 1 165 787 | 0.16 (<0, 0.78) | 0.28 (0.09, 0.58) |
| Cervical cancer cohort [B11] | | 70 | 67 | 2.0 | 623 798 | 0.02 (–0.06, 0.16) | 0.02 (–0.10, 0.17) |

| *Study* | | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|---|
| Cervical cancer case-control [B8] | | 148 | n.a. | 2.0 | n.a. | 0.71 (0.03, 2.24) | 1.10 (0.05, 3.50) |
| Springfields uranium workers, United Kingdom [M5] | | 14[c] | 22.31[c] | 0.022 8 | 190 795 | 19.85 (<–14.57, 108.30)[c,h] | n.a. |
| **Mortality** | | | | | | | |
| LSS [P9] | | | | | | | |
| Sex | Males | 18 | 23.8[b] | 0.19 | 666 869 | <0 (<0, >10 000) | <0 (<0, 114.09) |
| | Females | 21 | 15.9[b] | 0.18 | 1 061 687 | 1.17 (<0, 4.28) | <0 (<0, 71.62) |
| Age at exposure | <20 years | 8 | 7.8[b] | 0.19 | 885 656 | <0 (<0, >10 000) | <0 (<0, 39.84) |
| | 20–40 years | 17 | 11.4[b] | 0.19 | 514 903 | 0.86 (<0, 4.13) | <0 (<0, 106.20) |
| | >40 years | 14 | 20.3[b] | 0.18 | 327 997 | <0 (<0, <0) | <0 (<0, 198.97) |
| Time since exposure | 12–15 years | 4 | 4.0[b] | 0.18 | 504 112 | <0 (<0, 2.02) | <0 (<0, 25.61) |
| | 15–30 years | 12 | 11.0[b] | 0.19 | 592 956 | 1.25 (<0, 4.60) | <0 (<0, 76.09) |
| | >30 years | 23 | 22.0[b] | 0.19 | 631 488 | <0 (<0, 1.29) | <0 (<0, 150.04) |
| All | | 39 | 36.2[b] | 0.19 | 1 728 556 | 0.35 (<0, 1.51) | <0 (<0, 88.31) |
| Ankylosing spondylitis [W8] | | 35 | 21.6 | 6.08 | 378 014 | 0.10 (0.02, 0.20) | 0.06 (0.01, 0.12) |
| Metropathia haemorrhagica [D7] | | 5 | 4.19 | 0.4 | 47 144 | 0.48 (–1.53, 4.45)[k] | 0.43 (–1.36, 3.96)[k] |
| Peptic ulcer [C4] | | 7 | 5.3 | 14.2 | 41 779 | 0.12 (<0, 0.97)[d,i,j] | n.a. |
| Nuclear workers in Canada, United Kingdom and United States [C3] | | 34 | 37.3 | 0.04 | 2 142 526 | <0 | n.a. |
| United Kingdom NRRW [M12] | | 67 | 73.1 | 0.031 | 2 063 300 | <–1.95 (<–1.95, 0.96)[f] | n.a. |
| Nuclear power industry workers in the United States [H44] | | 14 | 17.7 | 0.026 | 698 041 | 48.8 (–1.77, 315)[i] | n.a. |
| Oak Ridge National Laboratory, United States, X-10 and Y-12 plants [F5] | | 35 | n.a. | 0.013 | n.a. | 2.6 (<0, 10.9) | n.a. |
| Los Alamos National Laboratory workers, United States [W6] | | 17 | 28.8 | ~0.016 | 251 651 | >0[e] | n.a. |
| Nuclear industry workers in Japan [I14] | | 32 | 37.4 | 0.015 | ~1 390 000 | <0 | <0 |
| **INTERNAL LOW-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| Swedish $^{131}$I for hyperthyroidism [H6] | | 66 | 47.5 | 0.05 | 139 018 | 7.8 (1.7, 15) | 27 (6, 52) |
| **INTERNAL HIGH-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| Danish and Swedish Thorotrast patients [T30] | | 12 | 4.4 | n.a. | 25 480 | 5.7 (1.9, 21)[g] | n.a. |
| **Mortality** | | | | | | | |
| United States Thorotrast patients [T30] | | 1 | 0.6 | n.a. | 8 740 | ∞ (0.1, ∞)[g] | n.a. |

[a] 90% CI in parentheses derived from fitting models (4) and (5) for the LSS, and derived from published data for the other studies.
[b] All expected numbers calculated by means of fitted relative risk model (4), evaluated at zero dose.
[c] Kidney and ureter.
[d] Excess relative risk value was calculated from the mean dose and the relative risk and confidence interval reported in the paper.
[e] Dose–response trend was in the positive direction but not statistically significant.
[f] Tabulation and analysis with a 10-year lag. Risk estimate based on a dose–response analysis.
[g] Risk relative to unexposed controls, with 95% CI.
[h] Males only.
[i] 95% CI in parentheses.
[j] Based on follow-up of 11 or more years after radiotherapy.
[k] Estimates (with 95% CI) based on method described in the introduction to chapter III of annex I in the UNSCEAR 2000 Report [U2].

**Table 39 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 LSS the exposed group included survivors with doses of 0.005 Sv or more (weighted brain dose) for incidence or mortality. For case-control studies, the observed number of cases covers both exposed and unexposed persons. The studies listed are those for which quantitative estimates of risk could be made

| *Study* | | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|---|
| **EXTERNAL LOW-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| LSS [P48][d] | | | | | | | |
| Sex | Males | 46 | 34.9[e] | 0.26 | 436 180 | 1.54 (0.66, 2.87) | 1.21 (0.58, 2.03) |
| | Females | 91 | 94.9[e] | 0.24 | 729 608 | <0 (<0, 0.46) | 0.01 (<0, 0.50) |
| Age at exposure | <20 years | 50 | 49.2[e] | 0.25 | 586 255 | 0.88 (0.28, 1.78) | 0.68 (0.24, 1.28) |
| | 20–40 years | 48 | 41.3[e] | 0.26 | 378 204 | 0.64 (<0, 1.82) | 0.48 (<0, 1.43) |
| | >40 years | 39 | 37.7[e] | 0.24 | 201 330 | <0 (<0, 0.51) | <0 (<0, 0.28) |
| Time since exposure | 12–15 years | 9 | 4.7[e] | 0.26 | 119 774 | 2.20 (<0, 11.11) | <0 (<0, 226.13) |
| | 15–30 years | 46 | 41.6[e] | 0.25 | 514 582 | 0.42 (<0, 1.44) | <0 (<0, 357.41) |
| | >30 years | 82 | 80.1[e] | 0.24 | 531 433 | 0.57 (0.10, 1.24) | 0.96 (0.26, 1.83) |
| All | | 137 | 126.9[e] | 0.25 | 1 165 788 | 0.55 (0.16, 1.07) | 0.57 (0.23, 1.01) |
| LSS [P33] | | | | | | | |
| All nervous system tumours | | 228 | n.a. | 0.26 | 1 989 297 | 1.2 (0.6, 2.1)[b] | n.a. |
| Glioma | | 43 | n.a. | 0.26 | | 0.56 (–0.2, 2.0)[b] | n.a. |
| Meningioma | | 88 | n.a. | 0.26 | | 0.64 (–0.01, 1.8)[b] | 0.14 (0.00, 0.45)[b] |
| Schwannoma | | 55 | n.a. | 0.26 | | 4.5 (1.9, 9.2)[b] | 0.67 (0.3, 1.1)[b] |
| LSS [P33] | | | | | | | |
| Meningioma | | | | | | | |
| Sex | Males | 14 | n.a. | n.a. | 745 157 | 1.6 (–0.04, 7.1)[b] | n.a. |
| | Females | 74 | n.a. | n.a. | 1 244 140 | 0.4 (–0.2, 1.7)[b] | n.a. |
| Age at exposure | <20 years | n.a. | n.a. | n.a. | 975 373 | 1.3 (0.01, 4.5)[b] | n.a. |
| | 20–39 years | n.a. | n.a. | n.a. | 645 557 | 0.5 (–0.05, 2.8)[b] | n.a. |
| | ≥40 years | n.a. | n.a. | n.a. | 358 367 | 0.3 (<–0.1, 2.0)[b] | n.a. |
| LSS [P33] | | | | | | | |
| Schwannoma | | | | | | | |
| Sex | Males | 23 | n.a. | n.a. | 745 157 | 8.0 (2.7, 21)[b] | n.a. |
| | Females | 32 | n.a. | n.a. | 1 244 140 | 2.3 (0.3, 7.0)[b] | n.a. |
| Age at exposure | <20 years | | n.a. | n.a. | 975 373 | 6.0 (2.1, 14)[b] | n.a. |
| | 20–39 years | | n.a. | n.a. | 645 557 | 2.6 (<–0.2, 10)[b] | n.a. |
| | ≥40 years | | n.a. | n.a. | 358 367 | 3.3 (0.33, 11)[b] | n.a. |
| Israel tinea capitis [R17] | | 60 | n.a. | 1.5 | 283 930 | 4.9[c] | n.a. |
| Glioma | | 7 | n.a. | | | 1.6[c] | n.a. |
| Meningioma | | 19 | n.a. | | | 5.7[c] | n.a. |
| Schwannoma | | 22 | n.a. | | | 21.4[c] | n.a. |

| *Study* | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|
| Israel tinea capitis [S48] | | | | | | |
| Malignant brain tumours | 44 | n.a. | 1.5 | 1 069 450 | 1.98 (0.73, 4.69) | 0.31 (0.12, 0.53) |
| Benign meningioma | 81 | n.a. | 1.5 | 1 069 043 | 4.63 (2.43, 9.12) | 0.48 (0.28, 0.73) |
| New York tinea capitis [S68] | | | | | | |
| Brain cancer | 7 | 2.34 | 1.4 | 125 357 | 1.1 (0.1, 2.8)[b] | n.a. |
| All intracranial tumours | 16 | 1.6 | 1.4 | 125 357 | 5.6 (3.0, 9.4)[b] | n.a. |
| Swedish pooled skin haemangioma [K15] | 83 | 58.0 | 0.07 | 913 402 | 2.7 (1.0, 5.6)[b] | 2.1 (0.3, 4.4)[b] |
| Childhood cancer survivors [L24] | | | 6.2 | | | |
| All brain tumours | 22 | n.a. | | n.a. | 0.19 (0.03, 0.85)[b] | n.a. |
| Malignant tumours | 12 | n.a. | | n.a. | 0.07 (<0, 0.62)[b] | n.a. |
| Benign tumours | 10 | n.a. | | n.a. | n.a. | n.a. |
| Springfields uranium workers, United Kingdom [M5] | 12 | 18.76 | 0.022 8 | 190 795 | –1.96 (<–2.00, 9.31)[b] | n.a. |
| **Mortality** | | | | | | |
| LSS [P9][d] | | | | | | |
| Sex Males | 9 | 4.0[e] | 0.22 | 666 870 | 5.87 (1.55, 17.94) | <0 (<0, 46.43) |
| Females | 10 | 8.9[e] | 0.21 | 1 061 688 | 0.78 (<0, 4.62) | <0 (<0, 29.00) |
| Age at exposure <20 years | 11 | 4.8[e] | 0.21 | 885 656 | 5.72 (1.56, 17.04) | <0 (<0, <0) |
| >20 years | 8 | 7.5[e] | 0.22 | 842 902 | 0.77 (<0, 4.88) | <0 (<0, 35.70) |
| Time since exposure 5–30 years | 4 | 3.8[e] | 0.22 | 1 097 070 | <0 (<0, >10 000) | <0 (<0, 14.96) |
| >30 years | 15 | 9.9[e] | 0.22 | 631 488 | 2.56 (0.54, 6.89) | <0 (<0, 72.60) |
| All | 19 | 12.2[e] | 0.22 | 1 728 558 | 2.86 (0.83, 6.76) | <0 (<0, 35.75) |
| Pituitary adenoma (United Kingdom) [B13] | 5 | 0.5 | 45 | 3 760 | 0.20 (0.07, 0.45)[c] | 0.27 (0.09, 0.59)[c] |
| Nuclear workers in Canada, United Kingdom and United States [C3] | 122 | n.a. | 0.04 | 2 142 526 | <0 | n.a. |
| United Kingdom NRRW [M12] | 111 | 114.2 | 0.031 | 2 063 300 | –0.54 (<–1.95, 4.26) | n.a. |
| Nuclear power industry workers in the United States [H44] | 23 | 27.0 | 0.026 | 698 041 | –2.50 (<–2.51, 27.1)[b] | n.a. |
| Canadian National Dose Registry [S8] | 105[c] | 133.2 | 0.006 6 | 2 667 903 | <0 | <0 |
| Nuclear power station workers in France [R54][d] | 16 | 10.3 | 0.018 | 261 418 | –4.1 (–9.9, 28.9)[h] | n.a. |
| **INTERNAL HIGH-LET EXPOSURES** | | | | | | |
| **Mortality** | | | | | | |
| United States Thorotrast patients [T30] | 21 | 0.6 | n.a. | 8 740 | 1.3 (0.6, 3.7)[b,g] | n.a. |

[a] Some risk estimates are based on formal dose–response analyses (for example for the LSS [P9, P48], derived from fitting models (4) and (5)); others are simply excess relative risk or absolute risk divided by mean dose. All CIs shown are 90% CI unless otherwise stated.
[b] 95% CI.
[c] Data are for all brain and nervous system tumours combined; estimates based on method described in the introduction to chapter III of annex I in the UNSCEAR 2000 Report [U2].
[d] Data are for all brain and nervous system tumours combined.
[e] All expected numbers calculated by means of fitted relative risk model (4), evaluated at zero dose.
[f] Males only.
[g] Risk relative to unexposed controls, with 95% CI.
[h] Based on a 10-year latent period.

**Table 40 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 LSS the exposed group included survivors with organ doses of 0.005 Sv (weighted thyroid dose) or more for incidence or mortality. The studies listed are those for which quantitative estimates of risk could be made

| *Study* | | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|---|
| **EXTERNAL LOW-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| LSS [P48] | | | | | | | |
| Sex | Males | 48 | 41.5[l] | 0.26 | 436 180 | 0.78 (0.15, 1.77) | 1.03 (0.46, 1.79) |
| | Females | 217 | 144.1[l] | 0.24 | 729 608 | 1.89 (1.28, 2.65) | 3.75 (2.73, 4.89) |
| Age at exposure | <20 years | 105 | 52.3[l] | 0.24 | 586 255 | 3.93 (2.57, 5.81) | 3.07 (2.14, 4.14) |
| | 20–40 years | 87 | 65.5[l] | 0.26 | 378 204 | 0.99 (0.34, 1.93) | 1.46 (0.49, 2.69) |
| | >40 years | 73 | 69.0[l] | 0.24 | 201 330 | 0.29 (<0, 0.95) | 0.86 (<0, 2.84) |
| Time since exposure | 12–15 years | 21 | 13.0[l] | 0.25 | 119 774 | 3.24 (1.10, 7.28) | 2.85 (1.17, 5.22) |
| | 15–30 years | 115 | 84.4[l] | 0.25 | 514 582 | 1.35 (0.69, 2.23) | 2.04 (1.18, 3.07) |
| | >30 years | 129 | 88.2[l] | 0.24 | 531 433 | 1.61 (0.93, 2.52) | 2.31 (1.34, 3.48) |
| All | | 265 | 186.4[l] | 0.25 | 1 165 788 | 1.59 (1.10, 2.19) | 2.30 (1.67, 3.02) |
| TB, adenitis screening [H22, S14] | | | | | | | |
| 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** | | | | | | | |
| 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 [S14, S68] | | 2 | 2.04 | 0.06 | 78 056 | –0.3 (–14.0, 37.3)[b,k] | n.a. |
| Rochester thymic irradiation [S18][e] | | 37 | 1.5 | 1.36 | 85 204 | 9.0 (4.2, 21.7) | 2.9 (2.1, 3.9)[b] |
| Childhood cancer [T5][f] | | 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 (1.3, 10.2)[k] | 0.9 (0.2, 1.9)[k] |
| Gothenburg skin haemangioma [L4] | | 15 | 8 | 0.12 | 370 517 | 7.5 (0.4, 18.1)[k] | 1.6 (0.09, 3.9)[k] |
| **Screening studies of children** | | | | | | | |
| Lymphoid hyperplasia screening [P5, S14][e,g] | | 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 [M13, S14] | | 16 | 1.1[b] | 2.9 | 44 310 | 4.5 (2.7, 7.0)[b] | 1.2 (0.7, 1.8)[b] |
| Michael Reese Hospital, tonsils [S21][h] | | 309 | 110.4 | 0.6 | 88 101 | 3.0 (2.6, 3.5)[b] | 37.6 (32, 43)[b] |
| Tonsils/thymus/acne screening [D9, S14] | | 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** | | | | | | | |
| LSS<br>Israeli tinea capitis<br>Rochester thymic irradiation<br>Lymphoid hyperplasia screening<br>Michael Reese Hospital, tonsils [R6] | | 436 | n.a. | n.a. | n.a. | 7.7 (2.1, 28.7)[k] | 4.4 (1.9, 10.1)[k] |
| **Studies of adults** | | | | | | | |
| Cervical cancer case-control [B8][d] | | 43 | 18.8 | 0.11 | n.a. | 12.3 (<0, 76)[b] | 6.9 (<0, 39.2)[b] |
| Cervical cancer cohort [B11][d,i] | | 16 | 12 | 0.11 | 178 243 | 2.5 (<0, 6.8)[b] | 0.9 (<0, 2.5)[b] |
| Stanford thyroid [H19] | | 6 | 0.4 | 45 | 17 700 | 0.3 (0.1, 0.7)[b] | 0.07 (0.03, 0.1)[b] |
| Canadian National Dose Registry [S8] | | 129 | 92.6 | 0.066 2 | 2 667 903 | 5.9 (2.5, 9.9)[j] | 2.1 (0.9, 3.4) |

| *Study* | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|
| Chinese medical x-ray workers [W3] | | | | | | |
| Employed before 1970 | 13 | 6.32 | 0.551 | 357 753 | 1.9 (0.3, 4.4)[j] | 0.3 (0.15, 0.8) |
| Employed only 1970–1980 | 1 | 2.54 | 0.082 | 337 133 | <0 | <0 |
| **INTERNAL LOW-LET EXPOSURES** | | | | | | |
| **Incidence** | | | | | | |
| Diagnostic $^{131}$I [D42] | 36 | 39.5 | 0.94 | ~648 000 | <0 | <0 |
| Diagnostic $^{131}$I [H14] | 67 | 49.6 | 1.1 | 653 093 | 0.25 (0, 2.7)[p] | n.a. |
| Russian Federation–Belarus Chernobyl case-control study [C2] | 276 | n.a. | 0.37, 0.04[m] | n.a. | 4.9 (2.2, 7.5)[n] | n.a. |
| Ukraine–Belarus Chernobyl cohort study [J9] | 1 185 | n.a. | n.a. | ~19 440 000 | 18.9 (11.1, 26.7)[o] | 2.66 (2.19, 3.13)[o] |
| **EXTERNAL LOW-LET EXPOSURES** | | | | | | |
| **Mortality** | | | | | | |
| LSS [P9] | | | | | | |
| Sex | Males | 6 | 7.4[l] | 0.22 | 666 870 | 0.46 (<0, 2.96) | <0 (<0, 24.90) |
| | Females | 32 | 29.7[l] | 0.21 | 1 061 688 | <0 (<0, 0.22) | <0 (<0, 0.09) |
| Age at exposure | <20 years | 5 | 3.7[l] | 0.21 | 885 656 | 1.67 (<0, 7.67) | <0 (<0, 12.88) |
| | 20–40 years | 14 | 14.2[l] | 0.23 | 514 903 | <0 (<0, 0.87) | <0 (<0, 0.23) |
| | >40 years | 19 | 19.7[l] | 0.21 | 327 999 | <0 (<0, <0) | <0 (<0, 0.01) |
| Time since exposure | 12–15 years | 4 | 6.4[l] | 0.21 | 504 112 | <0 (<0, 2.03) | <0 (<0, <0) |
| | 15–30 years | 13 | 9.3[l] | 0.22 | 592 958 | <0 (<0, 3.17) | 0.12 (<0, 0.41) |
| | >30 years | 21 | 21.2[l] | 0.21 | 631 488 | <0 (<0, 0.45) | <0 (<0, 97.90) |
| All | | 38 | 37.1[l] | 0.21 | 1 728 558 | <0 (<0, 0.42) | <0 (<0, 43.97) |

*a* 90% CI in parentheses derived from fitting models (4) and (5) for the LSS, and derived from published data for the other studies, unless otherwise stated.
*b* Estimates based on method described in the introduction to chapter III of annex I in the UNSCEAR 2000 Report [U2].
*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 reference [S14].
*e* Known dose. Person-years and expected number of cases estimated from data given in reference [S14].
*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 reference [S21]. Results are based on the new dosimetry described in reference [S21]. The large excess absolute risk in this study illustrates the impact of screening on thyroid cancer risk estimates. As described in reference [S21], a special thyroid screening programme in this cohort was initiated in 1974. This screening led to a large increase in the number of cancer 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 ($10^4$ PY Gy)$^{-1}$.
*i* Excludes cases diagnosed during first 10 years of follow-up.
*j* Excess relative risk and excess absolute risk values were calculated from the mean dose and the observed and expected cancers (or the relative risk and confidence interval) reported in the paper.
*k* 95% CI in parentheses.
*l* All expected numbers calculated by means of fitted relative risk model (4), evaluated at zero dose.
*m* Median doses to all subjects (cases, controls) in Belarus, Russian Federation, respectively.
*n* Fitted using linear–quadratic model for odds ratio over full dose range, 95% CI.
*o* Linear coefficient of linear–quadratic model fit, 95% CI.
*p* Trend estimate (with 95% CI) is for exposure in childhood and adolescence among those referred for diagnosis with $^{131}$I without suspicion of thyroid tumour; the overall trend (among all ages at exposure, with or without suspicion of thyroid tumour at diagnosis) is not statistically significant (see table 28 of annex I in the UNSCEAR 2000 Report [U2]).

**Table 41 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 LSS the exposed group included survivors with doses of 0.005 Gy or more (unweighted bone marrow dose) for incidence and 0.005 Sv or more (weighted bone marrow dose) for mortality. The studies listed are those for which quantitative estimates of risk could be made

| *Study* | | *Observed cases* | *Expected cases* | *Mean dose (Sv)*[a] | *Person-years* | *Average excess relative risk*[b] *at 1 Sv* | *Average excess absolute risk*[b] *($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|---|
| **EXTERNAL LOW-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| LSS [P4] | | | | | | | |
| Sex | Males | 41 | n.a. | 0.26 | 412 371 | 0.44 (–0.16, 1.42) | 0.46 (0.04, 1.16) |
| | Females | 35 | n.a. | 0.25 | 664 481 | –0.22 (<–0.22, 0.40) | 0.00 (<0, 0.28) |
| Age at exposure | <20 years | 17 | n.a. | 0.26 | 478 108 | 0.45 (<0, 2.16) | 0.18 (<0, 0.61) |
| | 20–40 years | 34 | n.a. | 0.26 | 346 807 | –0.12 (<–0.12, 0.73) | 0.03 (<0, 0.63) |
| | >40 years | 25 | n.a. | 0.24 | 251 938 | 0.09 (<0, 1.04) | –0.11 (<–0.11, 1.72) |
| Time since exposure | 12–15 years | 7 | n.a. | 0.25 | 369 152 | 0.33 (<0, 2.14) | 0.24 (–0.01, 0.70) |
| | 15–30 years | 34 | n.a. | 0.25 | 436 877 | 0.33 (<0, 1.44) | 0.09 (<0, 0.71) |
| | >30 years | 35 | n.a. | 0.25 | 270 824 | –0.22 (<–0.22, 0.45) | –0.17 (<–0.17, 2.28) |
| All | | 76 | n.a. | 0.25 | 1 076 850 | 0.08 (<0, 0.62) | 0.12 (<0, 0.40) |
| Cervical cancer case-control [B8][d] | | 94 | 37.5 | 7.10 | n.a. | 0.21 (–0.03, 0.93)[c] | n.a. |
| Benign lesions in locomotor system [D2] | | 81 | 80.3 | 0.39 | 392 900 | 0.02[c] | 0.05[c] |
| Canadian National Dose Registry [S8] | | 133 | 188.3 | 0.066 2 | 2 667 903 | 6.6 (<0, 28.3)[p] | n.a. |
| United States case-control: occupational exposure [E10] | | 114 | n.a. | 0.015 | n.a. | ($p = 0.66$)[h] | n.a. |
| Springfields uranium workers, United Kingdom [M5] | | 20 | 25.39 | 0.022 8 | 190 795 | 20.62 (<–5.69, 86.62)[r] | n.a. |
| **Mortality** | | | | | | | |
| LSS [P1][q] | | | | | | | |
| Sex | Males | 74 | | | | 0.25 (<0, 6.41) | 0.18 (<0, 0.81) |
| | Females | 88 | | | | –0.06 (<0, 0.22) | –0.12 (<0, 0.47) |
| Total | | 162 | n.a. | 0.25 | n.a. | 0.01 (<0, 0.42) | 0.01 (<0, 0.23) |
| Benign lesions in locomotor system [D2] | | 50 | 56.9 | 0.39 | 439 400 | –0.31[c] | –0.40[c] |
| Ankylosing spondylitis [W8][e] | | 37 | 21.3 | 4.38 | 287 095 | 0.17[c] | 0.77[c] |
| Benign gynaecological disorders [I1] | | 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)[b] | –0.04 (<–0.2, 5.4)[b] |
| Peptic ulcer [C4] | | 14 | 7.1 | 1.6[a] | 41 779 | 0.65 (<0, 3.28)[j,o,t] | n.a. |
| Nuclear workers in Canada, United Kingdom and United States [C3] | | 135 | n.a. | 0.04 | 2 142 526 | <0[g] | <0 |
| United Kingdom NRRW [M12] | | 84 | 80.2 | 0.031 | 2 063 300 | 0.03 (–1.33, 3.06)[p] | n.a. |
| Nuclear power industry workers in the United States [H44] | | 14 | n.a. | 0.026 | 698 041 | 61.3 (–2.51, 313)[j] | n.a. |
| Oak Ridge National Laboratory workers, United States, 1943–1947 [F2] (lympho-sarcoma, reticulosarcoma, ICD8-200) | | 39 | 45.8 | n.a. | n.a. | <0 | <0 |

| *Study* | *Observed cases* | *Expected cases* | *Mean dose (Sv)*[a] | *Person-years* | *Average excess relative risk*[b] *at 1 Sv* | *Average excess absolute risk*[b] *($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|
| Los Alamos National Laboratory workers, United States [W6] | 46[f] | n.a. | ~0.016 | 251 651 | >0[g] | n.a. |
| Nuclear industry workers in Japan [I14] | 46 | 57.3 | 0.015 | ~1 390 000 | <0 | <0 |
| | | | | | | |
| *Study* | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk at 1 Sv* | |
| **INTERNAL LOW-LET EXPOSURES** | | | | | | |
| **Mortality** | | | | | | |
| United States thyrotoxicosis [R3][i] | 74 | n.a. | 0.042 | 735 255 | 0.6[s] | |
| | | | | | | |
| *Study* | *Observed cases* | *Expected cases* | *Mean dose (Gy)* | *Person-years* | *Average relative risk* | |
| **INTERNAL HIGH-LET EXPOSURES** | | | | | | |
| **Incidence** | | | | | | |
| Danish and Swedish Thorotrast patients [T30] | 4 | 2.7 | n.a. | 25 480 | 1.6 (0.3, 11.4)[j,k] | |
| $^{224}$Ra ankylosing spondylitis patients [W9] | 2 | 0.9–1.8 | n.a. | n.a. | ~2[l] | |
| **Mortality** | | | | | | |
| German Thorotrast patients [V4] | 15 | n.a. | 0.83[m] | n.a. | ~2.5[n] | |

[a] Mean dose to red bone marrow.
[b] 90% CI in parentheses derived from published data for the LSS and for the other studies.
[c] Estimates based on method described in the introduction to chapter III of annex I in the UNSCEAR 2000 Report [U2].
[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 5 years of first treatment. Mean dose to bone marrow taken from reference [W2].
[f] Includes deaths from multiple myeloma.
[g] Not statistically significantly different from zero.
[h] *p*-value from test for trend in risk with dose.
[i] Some patients from the United Kingdom were included in this analysis [R3].
[j] 95% CI in parentheses.
[k] Risk relative to an unexposed control group, in which 3 cases were observed compared with 3.3 expected [T30].
[l] Risk relative to an unexposed control group, in which 1 case was observed compared with 1.0–2.3 expected.
[m] Dose to bone marrow (Gy) over 10 years based on estimated mean of 20.8 mL injected Thorotrast derived from hospital records, and using dosimetry from reference [K42].
[n] Crude relative risk, based on 5 cases in an unexposed control group.
[o] Excess relative risk and excess absolute risk values were calculated from the mean dose and the observed and expected cancers (or the relative risk and confidence interval) reported in the paper.
[p] Tabulation and analysis with a 10-year lag. Risk estimate based on a dose–response analysis.
[q] Includes deaths from Hodgkin's disease.
[r] Males only.
[s] Non-significant trend with dose ($p > 0.5$).
[t] Based on follow-up of 11 or more years after radiotherapy.

**Table 42 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 LSS the exposed group included survivors with doses of 0.005 Gy or more (unweighted bone marrow dose) for incidence. The studies listed are those for which quantitative estimates of risk could be made

| *Study* | *Observed cases* | *Expected cases* | *Mean dose (Sv)*[a] | *Person-years* | *Average excess relative risk*[b] *at 1 Sv* | *Average excess absolute risk*[b] *($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|
| **EXTERNAL LOW-LET EXPOSURES** | | | | | | |
| **Incidence** | | | | | | |
| LSS [P4] | 10 | 9.02 | 0.23 | 1 076 500 | 0.43 (1.6, 3.5) | 0.04 (0.1, 0.3) |
| Cervical cancer cohort [K1] | 15 | 15.5 | 7 | 532 740 | –0.005 (–0.06, 0.08) | –0.001 (–0.02, 0.02) |
| Cervical cancer case-control [B8][c] | 14 | n.a. | 7.10 | n.a. | n.a. | n.a. |
| Benign lesions in locomotor system [D2] | 17 | 22.3 | 0.39 | 392 900 | 0.30 (–1.01, 7.38)[d, e] | n.a. |
| Canadian National Dose Registry [S8] | 79 | n.a. | 0.066 2 | 2 667 903 | 64.8 (<0, 591.3)[m] | n.a. |
| **Mortality** | | | | | | |
| Benign lesions in locomotor system [D2] | 21 | 15.4 | 0.39 | 439 400 | 0.93[f] | 0.33[f] |
| Metropathia haemorrhagica [D7] | 4 | 1.21 | 1.3 | 47 144 | 1.77 (–0.08, 5.74)[e, f] | 0.45 (–0.02, 1.48)[e, f] |
| Ankylosing spondylitis [W8][g] | 13 | 7.9 | 4.38 | 287 095 | 0.15[f] | 0.04[f] |
| Benign gynaecological disorders [I1] | 10 | 6.6 | 1.19 | 246 821 | 0.43[f] | 0.12[f] |
| Nuclear workers in Canada, United Kingdom and United States [C3] | 43 | n.a. | 0.040 2 | 2 124 526 | >0[h] | n.a. |
| United Kingdom NRRW [M12] | 21 | n.a. | 0.031 | 2 063 300 | <–1.95 (<–1.95, 2.84) | n.a. |
| Los Alamos National Laboratory workers, United States [W6] | 10 | n.a. | ~0.016 | 251 651 | >0[i] | n.a. |
| **INTERNAL LOW-LET EXPOSURES** | | | | | | |
| **Mortality** | | | | | | |
| United States thyrotoxicosis [R3][o] | 12 | n.a. | 0.042 | 735 255 | –1.0[p] | n.a. |
| **INTERNAL HIGH-LET EXPOSURES** | | | | | | |
| **Incidence** | | | | | | |
| Danish Thorotrast patients [A5] | 1 | 0.65 | n.a. | 19 365 | 1.60 (0.06, 40.40)[e, j] | n.a. |
| Danish and Swedish Thorotrast patients [T30] | 1 | 1.0 | n.a. | 25 480 | 1.5 (0.1, 81.8)[e, n] | n.a. |
| **Mortality** | | | | | | |
| German Thorotrast patients [V4] | 2 | n.a. | 0.83[k] | n.a. | 0.8 | n.a. |
| United States Thorotrast patients [T30] | 1 | 0.2 | n.a. | 8 740 | ∞ (0.0, ∞)[e, n] | n.a. |

[a] Mean dose to red bone marrow.
[b] 90% CI in parentheses derived from published data for the LSS and for the other studies.
[c] Based on 1-year survivors. The observed and expected numbers cover both exposed and unexposed persons.
[d] Estimates derived from published data, as given in reference [L20].
[e] 95% CI in parentheses.
[f] Estimates based on method described in the introduction to chapter III of annex I in the UNSCEAR 2000 Report [U2].
[g] The values given exclude the period within 5 years of treatment. Mean dose to bone marrow taken from reference [W2].
[h] Trend not statistically significantly different from zero.
[i] Trend statistically significantly different from 0 ($0.01 < p < 0.05$).
[j] Relative risk based on comparison with control group in which 1 case occurred with 1.04 expected.
[k] Dose to bone marrow (Gy) over 10 years based on estimated mean of 20.8 mL injected Thorotrast derived from hospital records, and using dosimetry from reference [K42].
[l] Crude relative risk based on comparison with (unexposed) control group in which 2 cases occurred.
[m] Tabulation and analysis with a 10-year lag. Risk estimate based on a dose–response analysis.
[n] Risk relative to unexposed control group.
[o] Some patients from the United Kingdom were included in this analysis [R3].
[p] Non-significant trend with dose ($p > 0.5$).

**Table 43 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 LSS the exposed group included survivors with doses of 0.005 Gy or more (unweighted bone marrow dose) for incidence and 0.005 Sv or more (weighted bone marrow dose) for mortality. The studies listed are those for which quantitative estimates of risk could be made

| *Study* | *Observed cases* | *Expected cases* | *Mean dose (Sv)*[a] | *Person-years* | *Average excess relative risk*[b] *at 1 Sv* | *Average excess absolute risk*[b] *($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|
| **EXTERNAL LOW-LET EXPOSURES** | | | | | | |
| **Incidence** | | | | | | |
| LSS [P4] | | | | | | |
| Sex Males | 12 | 9.2 | 0.26 | 412 400 | 0.17 | 0.26 |
| Females | 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, 21.7)[c] | 0.05 (<–0.05, 0.4)[c] |
| Cervical cancer case-control [B8][d] | 56 | n.a. | 7.10 | n.a. | –0.10 (<0, 0.23)[c] | n.a. |
| Benign lesions in locomotor system [D2] | 65 | 67.5 | 0.39 | 392 900 | –0.09[c] | –0.16[c] |
| Springfields uranium workers, United Kingdom [M5] | 10 | 12.36 | 0.022 8 | 190 795 | 7.66 (<–17.18, 109.52)[n] | n.a. |
| **Mortality** | | | | | | |
| LSS [P1] | | | | | | |
| Sex Males | 16 | 14 | 0.23 | 614 997 | 1.13 (<0, 6.41) | 0.15 (<0, 0.51) |
| Females | 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 locomotor system [D2] | 80 | 63.8 | 0.39 | 439 400 | 0.65[c] | 0.95[c] |
| Ankylosing spondylitis [W8][e] | 22 | 13.6 | 4.38 | 287 095 | n.a. | n.a. |
| Benign gynaecological disorders [I1] | 14 | 12.4 | 1.19 | 246 821 | 0.11 (<–0.2, 0.6)[c] | 0.05 (<–0.1, 0.3)[c] |
| Peptic ulcer [C4] | 4 | 3.5 | 1.6 | 41 779 | –0.61 (<–0.61, 1.38)[f,k,p] | n.a. |
| Metropathia haemorrhagica [D7][g] | 9 | 3.5 | 1.3 | 47 144 | 1.23 (0.15, 3.02)[c,k] | 0.90 (0.11, 2.22)[c,k] |
| Nuclear workers in Canada, United Kingdom and United States [C3] | 44 | n.a. | 0.04 | 2 142 526 | 4.2 (0.3, 14.4) | n.a. |
| United Kingdom NRRW [M12] | 35 | 45.8 | 0.031 | 2 063 300 | 4.1 (0.03, 14.8)[m] | n.a. |
| Nuclear industry workers in Japan [I14] | 20 | 17.8 | 0.015 3 | ~1 390 000 | n.a. | n.a. |
| United States four-cohort analysis [W7] | 98 | n.a. | n.a. | n.a. | 0.66 (–2.35, 3.67)[m] | n.a. |
| **INTERNAL LOW-LET EXPOSURES** | | | | | | |
| **Incidence** | | | | | | |
| Diagnostic $^{131}$I [H8] | 50 | 45.9 | 0.000 19[h] | 527 056 | n.a. | n.a. |
| Swedish $^{131}$I hyperthyroid [H6] | 21 | 20.0 | 0.06 | 139 018 | n.a. | n.a. |
| **Mortality** | | | | | | |
| United States thyrotoxicosis [R3] | 28[i] | n.a. | 0.042 | 735 255 | 11.0[j] | n.a. |

| *Study* | *Observed cases* | *Expected-cases* | *Mean dose* | *Person-years* | *Average relative risk at 1 Sv* |
|---|---|---|---|---|---|
| **INTERNAL HIGH-LET EXPOSURES** | | | | | |
| **Incidence** | | | | | |
| Danish Thorotrast patients [A5] | 4 | 0.95 | n.a. | 19 365 | 4.34 (0.85, 31.3)[k,l] |
| Danish and Swedish Thorotrast patients [T30] | 5 | 1.7 | n.a. | 25 480 | 3.7 (0.5, 30.9)[k,o] |
| **Mortality** | | | | | |
| United States Thorotrast patients [T30] | 1 | 0.4 | n.a. | 8 740 | 1.8 (0.1, 51.6)[k,o] |

*a* Mean dose to red bone marrow.
*b* 90% CI in parentheses derived from published data for the LSS and using exact Poisson methods for the other studies.
*c* Estimates based on method described in the introduction to chapter III of annex I in the UNSCEAR 2000 Report [U2].
*d* Based on 1-year survivors. The observed number of cases covers both exposed and unexposed persons.
*e* The values given exclude the period within 5 years of first treatment. Mean dose to bone marrow taken from reference [W2].
*f* Excess relative risk value was calculated from the mean dose and the relative risk and confidence interval reported in the paper.
*g* The values given exclude the period within 5 years of irradiation.
*h* Mean dose to bone marrow given in reference [H12].
*i* Some patients from the United Kingdom were included in this analysis [R3].
*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 2 cases were observed compared with 2.1 expected.
*m* Tabulation and analysis with a 10-year lag. Risk estimate based on a dose–response analysis.
*n* Males only.
*o* Risk relative to unexposed controls.
*p* Based on follow-up of 11 or more years after radiotherapy.

**Table 44 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 LSS the exposed group included survivors with doses of 0.005 Gy or more (unweighted bone marrow dose) for incidence and 0.005 Sv or more (weighted bone marrow dose) for mortality. The studies listed are those for which quantitative estimates of risk could be made

| *Study* | | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|---|
| **EXTERNAL LOW-LET EXPOSURES** | | | | | | | |
| **Incidence** | | | | | | | |
| LSS [P4] | | | | | | | |
| Sex | Males | 71 | n.a. | 0.26 | 412 371 | 4.66 (3.07, 6.88) | 4.14 (3.06, 5.39) |
| | Females | 70 | n.a. | 0.25 | 664 481 | 5.05 (3.24, 7.61) | 2.41 (1.71, 3.23) |
| Age at exposure | <20 years | 46 | n.a. | 0.26 | 478 108 | 8.27 (4.95, 13.66) | 2.79 (1.99, 3.74) |
| | 20–40 years | 46 | n.a. | 0.26 | 346 807 | 3.59 (2.01, 5.97) | 2.69 (1.70, 3.90) |
| | >40 years | 49 | n.a. | 0.24 | 251 938 | 3.98 (2.32, 6.45) | 4.68 (3.10, 6.57) |
| Time since exposure | 12–15 years | 57 | n.a. | 0.25 | 369 152 | 13.78 (8.67, 22.24) | 5.19 (3.97, 6.60) |
| | 15–30 years | 51 | n.a. | 0.25 | 436 877 | 4.37 (2.53, 7.16) | 2.41 (1.55, 3.45) |
| | >30 years | 33 | n.a. | 0.25 | 270 824 | 0.88 (0.17, 2.02) | 1.09 (0.33, 2.19) |
| All | | 141 | n.a. | 0.25 | 1 076 850 | 4.84 (3.59, 6.44) | 3.08 (2.47, 3.77) |
| Cervical cancer case-control [B5][b,c] | | 141 | n.a. | 7.2 | n.a. | 0.74 (0.1, 3.8) | 0.50 (0.1, 2.6) |
| Cancer of the uterine corpus [C8][c,d] | | 118 | n.a. | 5.4 | n.a. | 0.10 (<0.0, 0.23)[e] | n.a. |
| Benign lesions in locomotor system [D2] | | 116 | 98.5 | 0.39 | 392 900 | 0.70 (–0.43, 3.48)[e,f] | 1.14[g] |
| Hodgkin's disease [K20][c,h] | | 60 | n.a. | n.a. | n.a. | 0.24 (0.04, 0.43)[e,f] | n.a. |
| Breast cancer therapy [C9][i] | | 38 | n.a. | 7.5 | n.a. | 0.19 (0.00, 0.6) | 0.89 (0.00, 3.0) |

| *Study* | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|
| United Kingdom childhood cancers [H21][h] | 26 | n.a. | n.a. | n.a. | 0.24 (0.01, 1.28)[e,f] | n.a. |
| International childhood cancer [T7][j,k] | 25 | n.a. | 10 | n.a. | 0.0 (0.0, 0.004) | n.a. |
| Chernobyl recovery operation workers in Russian Federation [K3][l] | 25 | n.a. | 0.105 | n.a. | 15.6 (–24.9, 56.1) | n.a. |
| Testicular cancer [T24] | 22 | n.a. | 12.6 | n.a. | 0.37 (0.12, 1.3)[e] | n.a. |
| Canadian National Dose Registry [S8][c,m] | 72 | 101.8 | 0.066 2 | 2 667 903 | 2.7 (<0, 18.8)[n,v] | n.a. |
| Chinese medical X-ray workers [W3] | | | | | | |
| — Employed before 1970 | 33 | 13.95 | 0.551 | 357 753 | 2.5 (1.2, 4.1)[o] | 1.0 (0.5, 1.6) |
| — Employed only 1970–1980 | 11 | 6.35 | 0.082 | 337 133 | 8.9 (–1.1, 25) | 1.7 (–0.2, 4.6) |
| **Mortality** | | | | | | |
| LSS [P10] | | | | | | |
| Sex Males | 98 | 55.4[qq] | 0.23 | 682 048 | 4.07 (2.75, 5.84) | 3.23 (2.41, 4.18) |
| Females | 91 | 52.2[qq] | 0.22 | 1 075 920 | 3.96 (2.57, 5.87) | <0 (<0, 291.33) |
| Age at exposure <20 years | 68 | 29.5[qq] | 0.23 | 916 830 | 6.63 (4.21, 10.26) | <0 (<0, 271.86) |
| 20–40 years | 66 | 41.9[qq] | 0.23 | 520 263 | 3.07 (1.81, 4.87) | 2.39 (1.56, 3.39) |
| >40 years | 55 | 35.8[qq] | 0.21 | 320 874 | 3.15 (1.74, 5.24) | 3.46 (2.12, 5.09) |
| Time since exposure 12–15 years | 58 | 18.3[qq] | 0.23 | 465 730 | 10.24 (6.34, 16.59) | 3.92 (2.90, 5.13) |
| 15–30 years | 51 | 29.4[qq] | 0.23 | 586 805 | 3.82 (2.13, 6.40) | 1.87 (1.19, 2.69) |
| >30 years | 80 | 61.0[qq] | 0.22 | 705 433 | 1.97 (1.09, 3.18) | <0 (<0, 396.31) |
| All | 189 | 107.7[qq] | 0.22 | 1 757 967 | 4.02 (3.02, 5.26) | 2.31 (1.85, 2.82) |
| Benign lesions in locomotor system [D2] | 115 | 95.5 | 0.39 | 439 400 | 0.52[g] | 1.14[g] |
| Ankylosing spondylitis [W2][c,p] | 53 | 17.0 | 4.38 | 245 413 | 0.02 (–0.07, 0.29)[e,f] | n.a. |
| Benign gynaecological disorders [I1][c] | 47 | 27.6 | 1.19 | 246 821 | 2.97 (2.2, .0) | 1.25 (0.9, 1.7) |
| Massachusetts TB fluoroscopy [D4][c] | 17 | 18 | 0.09 | 157 578 | <–0.2 (<–0.2, 4.5)[g] | <–0.2 (<–0.2, 5.1)[g] |
| Israeli tinea capitis [R5][k,r] | 14 | 6 | 0.3 | 279 901 | 4.44 (1.7, 8.7)[g] | 0.95 (0.4, 1.9)[g] |
| Stockholm skin haemangioma [L6][k] | 14 | ~11 | 0.2 | 373 542 | 1.6 (–0.6, 5.5)[e,s] | n.a. |
| Metropathia haemorrhagica [D7][t] | 12 | 5.86 | 1.3 | 53 144 | 0.74 (–0.11, 1.59)[e,tt] | 0.89 (0.05, 2.19)[e,g] |
| Peptic ulcer [C4][c] | 10 | 7.1 | 1.6 | 41 779 | 0.91 (<0, 4.38)[e,o,ss] | n.a. |
| IARC 15-country nuclear worker study [C41][c] | 196 | n.a. | 0.019 4 | 5 192 710 | 1.93 (<0, 8.47)[e] | n.a. |
| Nuclear workers in Canada, United Kingdom and United States [C3][c] | 119 | n.a. | 0.04 | 2 142 526 | 2.18 (0.13, 5.7)[u] | n.a. |
| United Kingdom NRRW [M12][c] | 89 | 91.1 | 0.031 | 2 063 300 | 2.55 (–0.03, 7.16)[v] | n.a. |
| Nuclear power industry workers in the United States [H44][c] | 26 | n.a. | 0.026 | 698 041 | 5.67 (–2.56, 30.4)[e] | n.a. |
| Mayak workers [S28] | 66 | 39.5 | 0.81 | 720 000 | 1.0 (0.5, 2.0) | n.a. |
| Oak Ridge National Laboratory, United States, X-10 and Y-12 plants [F5] | 50 | n.a. | 0.013 | n.a. | <0 (<0–6.5) | n.a. |
| Los Alamos National Laboratory workers, United States [W6] | 44 | 43.6 | ~0.016 | 251 651 | ~0[w] | n.a. |
| Portsmouth shipyard workers, United States [S56, Y10] | 34 | 38.6 | 0.020 | 303 892 | 10.88 (–0.90, 38.77)[e,ll] | 33.8 (16.8, 50.7)[mm] |

| *Study* | *Observed cases* | *Expected cases* | *Mean dose (Sv)* | *Person-years* | *Average excess relative risk[a] at 1 Sv* | *Average excess absolute risk[a] ($10^4$ PY Sv)$^{-1}$* |
|---|---|---|---|---|---|---|
| Nuclear industry workers in Japan [I14][x] | 28 | 30.9 | 0.015 | ~540 000 | 0.01 (–10.0, 10.0) | n.a. |
| Japanese radiological technologists [A4] | 20 | 15.3 | 0.466 | 270 585 | 0.7 (–0.4, 2.1)[o] | 0.4 (–0.2, 1.2) |
| Nuclear power station workers in France [R54][c] | 5 | 7.2 | 0.018 | 261 418 | 6.8 (–8.4, 62.2)[z] | n.a. |
| Yangjiang background radiation [T14, T16] | 33 | 29.7 | n.a.[y] | 1 246 340 | 1.61 (<0, 28.4)[e,z] | n.a. |
| **INTERNAL LOW-LET EXPOSURES** | | | | | | |
| **Incidence** | | | | | | |
| Chernobyl-related exposure in Belarus, Russian Federation and Ukraine [D52] | 421 | n.a. | 0.006 3[nn] | n.a. | 32.4 (9.78, 84.0)[e] | n.a. |
| Chernobyl-related exposure in Ukraine [N6] | 98 | n.a. | 0.004 5 | n.a. | 2.5 (1.1, 5.4)[e,oo] | n.a. |
| **Mortality** | | | | | | |
| Extended Techa River Cohort [K49, K50][c] | 49 | 18.1 | 0.30 Sv | 865 812 | 6.5 (1.8, 24)[e] | 2.9 (0.8, 4.4)[e,pp] |
| Extended Techa River cohort: leukaemia case-control study [O13][c] | 60 | n.a. | 0.38 Sv[nn] | n.a. | 4.6 (1.7, 12.3)[e] | n.a. |
| Semipalatinsk: leukaemia case-control study [A23][c] | 22 | n.a. | 0.89 Sv (median) | n.a. | ~ 0.1 | n.a. |
| Thyroid cancer patients [R38] | 12 | 6.3 | 6 GBq[q] | n.a. | 0.39 (n.a, 1.54)[e] (GBq)$^{-1}$ | 8 ($10^4$ PY GBq)$^{-1}$ |
| United States thyrotoxicosis [R3][c,aa] | 82 | n.a. | 0.042 Sv | 735 255 | –1.0[rr] | n.a. |

| *Study* | *Observed cases* | *Expected cases* | *Mean dose* | *Person-years* | *Average relative risk* |
|---|---|---|---|---|---|
| **INTERNAL HIGH-LET EXPOSURES** | | | | | |
| **Incidence** | | | | | |
| Danish and Swedish Thorotrast patients [T30][c] | 28 | 1.8 | n.a. | 25 480 | 15.2 (4.4, 149.6)[e,bb] |
| $^{224}$Ra ankylosing spondylitis patients [W15] | 13 | 4.2 | n.a. | 32 800 | 2.4[cc] |
| Uranium in drinking water – Finland [A25] | 35 | n.a. | 0.06 Bq/L[dd] | n.a. | 0.91 (0.73, 1.13)[e] |
| **Mortality** | | | | | |
| Radon-exposed miners [D10] | 69 | 59.5 | 155 WLM[ee] | 1 085 000 | n.a. |
| German Thorotrast patients [V4] | 42[c] | n.a. | 0.83[ff] | n.a. | 4.9[gg] |
| Japanese Thorotrast patients (combined data) [M14] | 10 | n.a. | 0.68[hh] | 10 685 | 12.5 (4.5, 34.7)[e] |
| United States Thorotrast patients [T30] | 8 | 1.1 | n.a. | 8 740 | 16.8 (0.6, 211.7)[e,bb] |
| Portuguese Thorotrast patients [D27][ii] | 6 | 0.73 | 0.80[jj] | 13 283 | 10.2 (1.24, 471)[e,kk] |

[a] 90% CI in parentheses derived from published data for the LSS and for the other studies; for latest LSS mortality data [P10] the 90% CIs are derived from models (4) and (5) fitted to the data.

[b] 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 reference [B9]. The excess absolute risk estimate uses incidence estimates from the cohort study [B11].

[c] Excludes cases of chronic lymphoblastic leukaemia.

[d] Risk estimate based on a linear dose–response model fitted to data for all radiation types [C8].

[e] 95% CI in parentheses.

[f] Estimates derived from analysis based on published data, as given in reference [L20].

[g] Estimates based on method described in the introduction to chapter III of annex I in the UNSCEAR 2000 Report [U2].

[h] The observed number of cases covers both exposed and unexposed persons. Risk estimate based on analysis in references [L9, L20].

[i] The excess absolute risk for this study is computed on the basis of annual incidence rate estimates and average follow-up times reported in reference [C9].

[j] The observed number of cases covers both exposed and unexposed persons. Risk estimates based on an unmatched analysis of data given in reference [T5].

[k] Population exposed as children.

*l* Excludes cases of chronic lymphoblastic leukaemia. Results are not restricted according to the date of starting work.
*m* Observed and expected values are for leukaemia excluding chronic lymphoblastic leukaemia.
*n* Values specific to males.
*o* Excess relative risk and excess absolute risk values were calculated from the mean dose and the observed and expected cancers (or the relative risk and confidence interval) reported in the paper.
*p* The values given exclude the 1-year period following the treatment.
*q* Mean cumulative $^{131}$I activity.
*r* 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 [R7].
*s* Based on those with doses above 0.1 Sv.
*t* The values given exclude the period within 2 years of irradiation.
*u* Doses lagged by 2 years.
*v* Tabulation and analysis with a 2-year lag. Risk estimate based on a dose–response analysis.
*w* Dose–response trend was approximately zero.
*x* The values given are based on the prospective study population followed over 1991–1997 [I14].
*y* Mean annual effective dose = 6.4 mSv.
*z* Based on a 2-year latent period.
*aa* Some patients from the United Kingdom were included in this analysis [R3].
*bb* Risk relative to unexposed controls, adjusted for sex, age and calendar period [T30].
*cc* In the control group, 7 leukaemias were observed, compared with 5.4 expected [W15].
*dd* Median activity concentration of uranium in well water for the reference group [A25].
*ee* Mean cumulative radon exposure.
*ff* Dose to bone marrow (Gy) over 10 years based on estimated mean of 20.8 mL injected Thorotrast derived from hospital records, and using dosimetry from reference [K41].
*gg* Crude relative risk, based on 7 cases in the control group.
*hh* Dose to bone marrow (Gy) over 10 years based on estimated mean of 17 mL injected Thorotrast derived from hospital records, and using dosimetry from reference [K41].
*ii* Results presented are based on follow-up over the period 5 or more years after first examination [D27].
*jj* Dose to bone marrow (Gy) over 10 years based on estimated mean of 20 mL injected Thorotrast derived from hospital records, and using dosimetry from reference [K42].
*kk* Based on 1 death in the control group, compared with 1.25 expected [D27].
*ll* Based on the analysis of reference [Y10].
*mm* Based on the analysis of reference [S56].
*nn* Value for controls.
*oo* Relative risk among those with doses of 10 mSv or more relative to those with less than 2 mSv.
*pp* Value at age 70 years.
*qq* All expected numbers calculated by means of fitted relative risk model (4), evaluated at zero dose.
*rr* Non-significant trend with dose ($p > 0.5$).
*ss* Based on follow-up of 11 or more years after radiotherapy.
*tt* Risk estimate based on a dose–response analysis.

**Table 45 Coefficients of solid cancer mortality models, fitted to current data for the survivors of the atomic bombings in Japan** [P10]

All models are fitted by Poisson maximum-likelihood, using adjustments for dosimetric error as described in appendix B and assuming 35% GSD errors. $D$ = radiation dose (Sv), $a$ = attained age, $e$ = age at exposure, $s$ = sex, $c$ = city.

**Generalized ERR model (adjustment for attained age, years since exposure), linear dose response**

$$h_0(a,e,c,s)\cdot\left[1+\alpha\cdot D\cdot\exp[\kappa_1\cdot 1_{s=female}+\kappa_2\cdot\ln[a-e]+\kappa_3\cdot\ln[a]]\right]$$

| | |
|---|---|
| $\alpha$ = | 601.02 Sv$^{-1}$ |
| $\kappa_1$ = | 0.603 5 |
| $\kappa_2$ = | 0.990 3 |
| $\kappa_3$ = | –2.635 |

**Generalized ERR model (adjustment for age at exposure), linear dose response**

$$h_0(a,e,c,s)\cdot\left[1+\alpha\cdot D\cdot\exp[\kappa_1\cdot 1_{s=female}+\kappa_2\cdot\ln[e]]\right]$$

| | |
|---|---|
| $\alpha$ = | 2.302 73 Sv$^{-1}$ |
| $\kappa_1$ = | 0.733 5 |
| $\kappa_2$ = | –0.619 5 |

**Generalized ERR model (adjustment for attained age, years since exposure), linear–quadratic dose response**

$$h_0(a,e,c,s)\cdot\left[1+(\alpha\cdot D+\beta\cdot D^2)\cdot\exp[\kappa_1\cdot 1_{s=female}+\kappa_2\cdot\ln[a-e]+\kappa_3\cdot\ln[a]]\right]$$

| | |
|---|---|
| $\alpha$ = | 408.285 Sv$^{-1}$ |
| $\beta/\alpha$ = | 0.292 23 Sv$^{-1}$ |
| $\kappa_1$ = | 0.663 |
| $\kappa_2$ = | 0.987 1 |
| $\kappa_3$ = | –2.636 |

| Generalized EAR model, linear dose response |
|---|
| $h_0(a,e,c,s)+\alpha\cdot D\cdot\exp[\kappa_1\cdot\ln[a-e]+\kappa_2\cdot\ln[a]]$ |
| $\alpha =$ 1.128 34 × $10^{-8}$ $Sv^{-1}$ $a^{-1}$ |
| $\kappa_1 =$ 0.658 6 |
| $\kappa_2 =$ 2.357 |
| **Generalized EAR model, linear–quadratic dose response** |
| $h_0(a,e,c,s)+(\alpha\cdot D+\beta\cdot D^2)\cdot\exp[\kappa_1\cdot\ln[a-e]+\kappa_2\cdot\ln[a]]$ |
| $\alpha =$ 7.745 27 × $10^{-9}$ $Sv^{-1}$ $a^{-1}$ |
| $\beta/\alpha =$ 0.398 406 $Sv^{-1}$ |
| $\kappa_1 =$ 0.656 5 |
| $\kappa_2 =$ 2.340 |

**Table 46 Coefficients of leukaemia mortality models, fitted to current data for the survivors of the atomic bombings in Japan** [P10]

All models are fitted by Poisson maximum-likelihood, using adjustments for dosimetric error as described in appendix B and assuming 35% GSD errors. $D$ = radiation dose (Sv), $a$ = attained age, $e$ = age at exposure, $s$ = sex, $c$ = city.

| Generalized ERR model, quadratic dose response |
|---|
| $h_0(a,e,c,s)\cdot\left[1+\beta\cdot D^2\cdot\exp[\kappa_1\cdot\ln[a]]\right]$ |
| $\beta =$ 1 012.92 $Sv^{-2}$ |
| $\kappa_1 =$ –1.555 |
| **Generalized ERR model, linear–quadratic dose response** |
| $h_0(a,e,c,s)\cdot\left[1+(\alpha\cdot D+\beta\cdot D^2)\cdot\exp[\kappa_1\cdot\ln[a]]\right]$ |
| $\alpha =$ 864.552 $Sv^{-1}$ |
| $\beta/\alpha =$ 1.180 92 $Sv^{-1}$ |
| $\kappa_1 =$ –1.647 |
| **Generalized EAR model, quadratic dose response** |
| $h_0(a,e,c,s)+\beta\cdot D^2\cdot\exp[\kappa_1\cdot 1_{s=female}+\kappa_2\cdot\ln[a-e]]$ |
| $\beta =$ 1.445 75 × $10^{-3}$ $Sv^{-2}$ $a^{-1}$ |
| $\kappa_1 =$ –0.521 984 |
| $\kappa_2 =$ –0.666 2 |
| **Generalized EAR model, linear–quadratic dose response** |
| $h_0(a,e,c,s)+(\alpha\cdot D+\beta\cdot D^2)\cdot\exp[\kappa_1\cdot 1_{s=female}+\kappa_2\cdot\ln[a-e]]$ |
| $\alpha =$ 7.516 50 × $10^{-4}$ $Sv^{-1}$ $a^{-1}$ |
| $\beta/\alpha =$ 1.034 55 $Sv^{-1}$ |
| $\kappa_1 =$ –0.525 26 |
| $\kappa_2 =$ –0.614 1 |

**Table 47 Coefficients of oesophageal cancer incidence models, fitted to current data for the survivors of the atomic bombings in Japan** [P48] **(using DS02 stomach dose)**

All models are fitted by Poisson maximum-likelihood and adjusted for 35% GSD errors, truncated, using adjustment factors derived from DS86 [P2]. $D$ = radiation dose (Sv), $a$ = attained age, $e$ = age at exposure, $s$ = sex, $c$ = city.

| Generalized ERR model, linear dose response |
|---|
| $h_0(a,e,c,s)\cdot\left[1+\alpha\cdot D\right]$ |
| $\alpha =$ 0.527 82 $Sv^{-1}$ |
| **Generalized EAR model, linear dose response** |
| $h_0(a,e,c,s)+\alpha\cdot D$ |
| $\alpha =$ $1.452\,93\times10^{-5}$ $Sv^{-1}$ $a^{-1}$ |

**Table 48 Coefficients of stomach cancer incidence models, fitted to current data for the survivors of the atomic bombings in Japan** [P48] **(using DS02 stomach dose)**

All models are fitted by Poisson maximum-likelihood and adjusted for 35% GSD errors, truncated, using adjustment factors derived from DS86 [P2]. $D$ = radiation dose (Sv), $a$ = attained age, $e$ = age at exposure, $s$ = sex, $c$ = city.

| Generalized ERR model, linear dose response |
|---|
| $h_0(a,e,c,s)\cdot\left[1+\alpha\cdot D\cdot\exp[\kappa_1\cdot\ln[a]]\right]$ |
| $\alpha =$ $4.025\,03\times10^{3}$ $Sv^{-1}$ |
| $\kappa_1 =$ –2.253 |
| **Generalized EAR model, linear dose response** |
| $h_0(a,e,c,s)+\alpha\cdot D\cdot\exp[\kappa_1\cdot\ln[a]]$ |
| $\alpha =$ $3.969\,25\times10^{-7}$ $Sv^{-1}$ $a^{-1}$ |
| $\kappa_1 =$ 1.828 |

**Table 49 Coefficients of colon cancer incidence models, fitted to current data for the survivors of the atomic bombings in Japan** [P48] **(using DS02 colon dose)**

All models are fitted by Poisson maximum-likelihood and adjusted for 35% GSD errors, truncated, using adjustment factors derived from DS86 [P2]. $D$ = radiation dose (Sv), $a$ = attained age, $e$ = age at exposure, $s$ = sex, $c$ = city.

| Generalized ERR model, linear dose response |
|---|
| $h_0(a,e,c,s)\cdot\left[1+\alpha\cdot D\cdot\exp[\kappa_1\cdot\ln[a]]\right]$ |
| $\alpha =$ $1.480\,80\times10^{6}$ $Sv^{-1}$ |
| $\kappa_1 =$ –3.526 |
| **Generalized EAR model, linear dose response** |
| $h_0(a,e,c,s)+\alpha\cdot D\cdot\exp[\kappa_1\cdot\ln[a-e]]$ |
| $\alpha =$ $2.875\,27\times10^{-9}$ $Sv^{-1}$ $a^{-1}$ |
| $\kappa_1 =$ 3.204 |

**Table 50 Coefficients of liver cancer incidence models, fitted to current data for the survivors of the atomic bombings in Japan** [P48] **(using DS02 liver dose)**

All models are fitted by Poisson maximum-likelihood and adjusted for 35% GSD errors, truncated, using adjustment factors derived from DS86 [P2]. $D$ = radiation dose (Sv), $a$ = attained age, $e$ = age at exposure, $s$ = sex, $c$ = city.

| **Generalized ERR model, linear dose response** | |
|---|---|
| $h_0(a,e,c,s)\cdot[1+\alpha\cdot D]$ | |
| $\alpha =$ | $3.951\,06\times10^{-1}$ Sv$^{-1}$ |
| **Generalized EAR model, linear dose response** | |
| $h_0(a,e,c,s)+\alpha\cdot D\cdot\exp[\kappa_1\cdot\ln[a]]$ | |
| $\alpha =$ | $1.037\,36\times10^{-10}$ Sv$^{-1}$ a$^{-1}$ |
| $\kappa_1 =$ | 3.479 |

**Table 51 Coefficients of lung cancer incidence models, fitted to current data for the survivors of the atomic bombings in Japan** [P48] **(using DS02 lung dose)**

All models are fitted by Poisson maximum-likelihood and adjusted for 35% GSD errors, truncated, using adjustment factors derived from DS86 [P2]. $D$ = radiation dose (Sv), $a$ = attained age, $e$ = age at exposure, $s$ = sex, $c$ = city.

| **Generalized ERR model, linear dose response** | |
|---|---|
| $h_0(a,e,c,s)\cdot\left[1+\alpha\cdot D\cdot\exp[\kappa_1\cdot 1_{s=female}]\right]$ | |
| $\alpha =$ | $3.182\,24\times10^{-1}$ Sv$^{-1}$ |
| $\kappa_1 =$ | 1.480 8 |
| **Generalized EAR model, linear dose response** | |
| $h_0(a,e,c,s)+\alpha\cdot D\cdot\exp[\kappa_1\cdot 1_{s=female}+\kappa_2\cdot\ln[a]]$ | |
| $\alpha =$ | $1.00\,830\times10^{-11}$ Sv$^{-1}$ a$^{-1}$ |
| $\kappa_1 =$ | 0.400 8 |
| $\kappa_2 =$ | 4.211 |

**Table 52 Coefficients of bone cancer incidence models, fitted to current data for the survivors of the atomic bombings in Japan** [P48] **(using DS02 skeletal dose)**

All models are fitted by Poisson maximum-likelihood and adjusted for 35% GSD errors, truncated, using adjustment factors derived from DS86 [P2]. $D$ = radiation dose (Sv), $a$ = attained age, $e$ = age at exposure, $s$ = sex, $c$ = city.

| **Generalized ERR model, quadratic dose response** | |
|---|---|
| $h_0(a,e,c,s)\cdot\left[1+\beta\cdot D^2\cdot\exp[\kappa_1\cdot\ln[a]]\right]$ | |
| $\beta =$ | $6.903\,79\times10^{7}$ Sv$^{-2}$ |
| $\kappa_1 =$ | –4.472 |
| **Generalized EAR model, quadratic dose response** | |
| $h_0(a,e,c,s)+\beta\cdot D^2$ | |
| $\beta =$ | $9.329\,40\times10^{-6}$ Sv$^{-2}$ a$^{-1}$ |

**Table 53 Coefficients of non-melanoma skin cancer incidence models, fitted to current data for the survivors of the atomic bombings in Japan** [P48] **(using DS02 skin dose)**

All models are fitted by Poisson maximum-likelihood and adjusted for 35% GSD errors, truncated, using adjustment factors derived from DS86 [P2]. $D$ = radiation dose (Sv), $a$ = attained age, $e$ = age at exposure, $s$ = sex, $c$ = city.

| **Generalized ERR model, quadratic–exponential dose response** | |
|---|---|
| $h_0(a,e,c,s)\cdot\left[1+\beta\cdot D^2\cdot\exp[\gamma\cdot D+\kappa_1\cdot\ln[a-e]+\kappa_2\cdot\ln[a]]\right]$ | |
| $\beta =$ | $2.615\,26\times10^{3}$ Sv$^{-2}$ |
| $\gamma =$ | –0.272 Sv$^{-1}$ |
| $\kappa_1 =$ | 3.196 |
| $\kappa_2 =$ | –4.595 |
| **Generalized EAR model, quadratic–exponential dose response** | |
| $h_0(a,e,c,s)+\beta\cdot D^2\cdot\exp[\gamma\cdot D+\kappa_1\cdot\ln[a-e]]$ | |
| $\beta =$ | $5.245\,49\times10^{-9}$ Sv$^{-2}$ |
| $\gamma =$ | –0.273 9 Sv$^{-1}$ |
| $\kappa_1 =$ | 2.885 |

**Table 54 Coefficients of female breast cancer incidence models, fitted to current data for the survivors of the atomic bombings in Japan** [P48] **(using DS02 breast dose)**

All models are fitted by Poisson maximum-likelihood and adjusted for 35% GSD errors, truncated, using adjustment factors derived from DS86 [P2]. $D$ = radiation dose (Sv), $a$ = attained age, $e$ = age at exposure, $s$ = sex, $c$ = city.

| **Generalized ERR model, linear dose response** | |
|---|---|
| $h_0(a,e,c,s)\cdot\left[1+\alpha\cdot D\cdot\exp[\kappa_1\cdot\ln[a]]\right]$ | |
| $\alpha =$ | $1.492\,21\times10^{4}$ Sv$^{-1}$ |
| $\kappa_1 =$ | –2.304 |
| **Generalized EAR model, linear dose response** | |
| $h_0(a,e,c,s)+\alpha\cdot D\cdot\exp[\kappa_1\cdot\ln[a-e]]$ | |
| $\alpha =$ | $1.940\,38\times10^{-5}$ Sv$^{-1}$ a$^{-1}$ |
| $\kappa_1 =$ | 1.086 |

**Table 55 Coefficients of urinary bladder cancer incidence models, fitted to current data for the survivors of the atomic bombings in Japan** [P48] **(using DS02 bladder dose)**

All models are fitted by Poisson maximum-likelihood and adjusted for 35% GSD errors, truncated, using adjustment factors derived from DS86 [P2]. $D$ = radiation dose (Sv), $a$ = attained age, $e$ = age at exposure, $s$ = sex, $c$ = city.

| **Generalized ERR model, linear dose response** | |
|---|---|
| $h_0(a,e,c,s)\cdot\left[1+\alpha\cdot D\right]$ | |
| $\alpha =$ | $8.988\,85\times10^{-1}$ Sv$^{-1}$ |
| **Generalized EAR model, linear dose response** | |
| $h_0(a,e,c,s)+\alpha\cdot D\cdot\exp[\kappa_1\cdot\ln[a]]$ | |
| $\alpha =$ | $6.135\,72\times10^{-15}$ Sv$^{-1}$ a$^{-1}$ |
| $\kappa_1 =$ | 5.748 |

**Table 56 Coefficients of brain and CNS cancer incidence models, fitted to current data for the survivors of the atomic bombings in Japan** [P48] **(using DS02 brain dose)**

All models are fitted by Poisson maximum-likelihood and adjusted for 35% GSD errors, truncated, using adjustment factors derived from DS86 [P2]. $D$ = radiation dose (Sv), $a$ = attained age, $e$ = age at exposure, $s$ = sex, $c$ = city.

| **Generalized ERR model, linear dose response** | |
|---|---|
| $h_0(a,e,c,s)\cdot\left[1+\alpha\cdot D\cdot\exp[\kappa_1\cdot\ln[e]]\right]$ | |
| $\alpha =$ | 7.431 45 Sv$^{-1}$ |
| $\kappa_1 =$ | –0.989 7 |
| **Generalized EAR model, linear dose response** | |
| $h_0(a,e,c,s)+\alpha\cdot D$ | |
| $\alpha =$ | $4.923\,82\times10^{-5}$ Sv$^{-1}$ a$^{-1}$ |

**Table 57 Coefficients of thyroid cancer incidence models, fitted to current data for the survivors of the atomic bombings in Japan** [P48] **(using DS02 thyroid dose)**

All models are fitted by Poisson maximum-likelihood and adjusted for 35% GSD errors, truncated, using adjustment factors derived from DS86 [P2]. $D$ = radiation dose (Sv), $a$ = attained age, $e$ = age at exposure, $s$ = sex, $c$ = city.

| **Generalized ERR model, linear dose response** |
|---|
| $h_0(a,e,c,s)\cdot\left[1+\alpha\cdot D\cdot\exp[\kappa_1\cdot\ln[e]+\kappa_2\cdot\ln[a]]\right]$ |
| $\alpha =$ 3.80452 × $10^4$ $Sv^{-1}$ |
| $\kappa_1 =$ –0.4405 |
| $\kappa_2 =$ –2.197 |
| **Generalized EAR model, linear dose response** |
| $h_0(a,e,c,s)+\alpha\cdot D\cdot\exp[\kappa_1\cdot 1_{s=female}+\kappa_2\cdot\ln[e]]$ |
| $\alpha =$ 2.628 70 × $10^{-4}$ Sv–1 $a^{-1}$ |
| $\kappa_1 =$ 1.362 4 |
| $\kappa_2 =$ –0.388 3 |

**Table 58 Coefficients of all other solid cancer incidence models, fitted to current data for the survivors of the atomic bombings in Japan** [P48] **(using DS02 colon dose)**

All models are fitted by Poisson maximum-likelihood and adjusted for 35% GSD errors, truncated, using adjustment factors derived from DS86 [P2]. $D$ = radiation dose (Sv), $a$ = attained age, $e$ = age at exposure, $s$ = sex, $c$ = city.

| **Generalized ERR model, linear dose response** |
|---|
| $h_0(a,e,c,s)\cdot\left[1+\alpha\cdot D\cdot\exp[\kappa_1\cdot\ln[a-e]+\kappa_2\cdot\ln[a]]\right]$ |
| $\alpha =$ 1.432 20 × $10^2$ $Sv^{-1}$ |
| $\kappa_1 =$ 1.645 |
| $\kappa_2 =$ –2.939 |
| **Generalized EAR model, linear dose response** |
| $h_0(a,e,c,s)+\alpha\cdot D\cdot\exp[\kappa_1\cdot\ln[a-e]]$ |
| $\alpha =$ 2.207 51 × $10^{-7}$ $Sv^{-1}$ $a^{-1}$ |
| $\kappa_1 =$ 2.161 |

**Table 59 Risk estimates for solid cancer mortality in various current populations, using generalized ERR and generalized EAR models (models described in table 45)**

Risk estimates are calculated for a population in equilibrium (underlying mortality rates and population structure of current Chinese, Japanese, Puerto Rican, United States and United Kingdom populations) from various models fitted to LSS mortality data [P10], assuming 35% GSD errors

| *Model, modifying terms*[a] | *Test dose, $D_t$ (Sv)* | *Per cent excess cancer deaths ($Sv^{-1}$)* | *Per cent radiation-induced cancer deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/ radiation-induced cancer death (a)* |
|---|---|---|---|---|---|
| **China** | | | | | |
| ERR, *D*, sex, age, years SE[b] | 0.01 | 5.02 | 5.70 | 0.862 | 15.1 |
| | 0.1 | 4.99 | 5.67 | 0.859 | 15.1 |
| | 1.0 | 4.75 | 5.40 | 0.831 | 15.4 |
| ERR, *D*, sex, age AE[c] | 0.01 | 7.38 | 8.31 | 1.096 | 13.2 |
| | 0.1 | 7.28 | 8.19 | 1.086 | 13.3 |
| | 1.0 | 6.44 | 7.27 | 0.999 | 13.7 |
| ERR, $D + D^2$, sex, age, years SE[d] | 0.01 | 3.48 | 3.95 | 0.598 | 15.2 |
| | 0.1 | 3.55 | 4.03 | 0.612 | 15.2 |
| | 1.0 | 4.26 | 4.84 | 0.746 | 15.4 |
| EAR, *D*, age, years SE[e] | 0.01 | 5.43 | 6.12 | 0.859 | 14.0 |
| | 0.1 | 5.40 | 6.09 | 0.856 | 14.1 |
| | 1.0 | 5.12 | 5.78 | 0.828 | 14.3 |
| EAR, $D + D^2$, age, years SE[f] | 0.01 | 3.45 | 3.89 | 0.548 | 14.1 |
| | 0.1 | 3.56 | 4.02 | 0.566 | 14.1 |
| | 1.0 | 4.57 | 5.16 | 0.739 | 14.3 |
| **Japan** | | | | | |
| ERR, *D*, sex, age, years SE[b] | 0.01 | 5.62 | 6.71 | 0.992 | 14.8 |
| | 0.1 | 5.59 | 6.67 | 0.988 | 14.8 |
| | 1.0 | 5.26 | 6.30 | 0.950 | 15.1 |
| ERR, *D*, sex, age AE[c] | 0.01 | 9.06 | 10.69 | 1.390 | 13.0 |
| | 0.1 | 8.88 | 10.49 | 1.372 | 13.1 |
| | 1.0 | 7.61 | 9.03 | 1.236 | 13.7 |
| ERR, $D + D^2$, sex, age, years SE[d] | 0.01 | 3.90 | 4.65 | 0.689 | 14.8 |
| | 0.1 | 3.98 | 4.75 | 0.705 | 14.8 |
| | 1.0 | 4.73 | 5.65 | 0.854 | 15.1 |
| EAR, *D*, age, years SE[e] | 0.01 | 6.49 | 7.70 | 1.145 | 14.9 |
| | 0.1 | 6.44 | 7.65 | 1.140 | 14.9 |
| | 1.0 | 6.03 | 7.17 | 1.094 | 15.2 |
| EAR, $D + D^2$, age, years SE[f] | 0.01 | 4.12 | 4.90 | 0.730 | 14.9 |
| | 0.1 | 4.25 | 5.05 | 0.754 | 14.9 |
| | 1.0 | 5.38 | 6.40 | 0.976 | 15.2 |
| **Puerto Rico** | | | | | |
| ERR, *D*, sex, age, years SE[b] | 0.01 | 4.37 | 5.04 | 0.739 | 14.7 |
| | 0.1 | 4.35 | 5.01 | 0.737 | 14.7 |
| | 1.0 | 4.14 | 4.78 | 0.713 | 14.9 |

| *Model, modifying terms*[a] | *Test dose, $D_t$ (Sv)* | *Per cent excess cancer deaths ($Sv^{-1}$)* | *Per cent radiation-induced cancer deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/ radiation-induced cancer death (a)* |
|---|---|---|---|---|---|
| ERR, *D*, sex, age AE[c] | 0.01 | 6.91 | 7.91 | 1.004 | 12.7 |
| | 0.1 | 6.80 | 7.79 | 0.994 | 12.8 |
| | 1.0 | 5.97 | 6.85 | 0.912 | 13.3 |
| ERR, $D + D^2$, sex, age, years SE[d] | 0.01 | 3.04 | 3.50 | 0.515 | 14.7 |
| | 0.1 | 3.11 | 3.58 | 0.527 | 14.7 |
| | 1.0 | 3.73 | 4.30 | 0.643 | 15.0 |
| EAR, *D*, age, years SE[e] | 0.01 | 5.82 | 6.69 | 0.971 | 14.5 |
| | 0.1 | 5.78 | 6.65 | 0.967 | 14.5 |
| | 1.0 | 5.45 | 6.28 | 0.931 | 14.8 |
| EAR, $D + D^2$, age, years SE[f] | 0.01 | 3.70 | 4.26 | 0.619 | 14.5 |
| | 0.1 | 3.82 | 4.39 | 0.640 | 14.6 |
| | 1.0 | 4.86 | 5.60 | 0.831 | 14.8 |
| **United States** | | | | | |
| ERR, *D*, sex, age, years SE[b] | 0.01 | 5.77 | 6.82 | 1.031 | 15.1 |
| | 0.1 | 5.73 | 6.78 | 1.026 | 15.1 |
| | 1.0 | 5.38 | 6.38 | 0.983 | 15.4 |
| ERR, *D*, sex, age AE[c] | 0.01 | 9.05 | 10.60 | 1.417 | 13.4 |
| | 0.1 | 8.87 | 10.40 | 1.398 | 13.4 |
| | 1.0 | 7.58 | 8.92 | 1.253 | 14.1 |
| ERR, $D + D^2$, sex, age, years SE[d] | 0.01 | 4.01 | 4.74 | 0.719 | 15.2 |
| | 0.1 | 4.10 | 4.84 | 0.735 | 15.2 |
| | 1.0 | 4.86 | 5.75 | 0.887 | 15.4 |
| EAR, *D*, age, years SE[e] | 0.01 | 5.88 | 6.94 | 1.010 | 14.6 |
| | 0.1 | 5.84 | 6.89 | 1.006 | 14.6 |
| | 1.0 | 5.50 | 6.50 | 0.968 | 14.9 |
| EAR, $D + D^2$, age, years SE[f] | 0.01 | 3.74 | 4.41 | 0.644 | 14.6 |
| | 0.1 | 3.86 | 4.55 | 0.665 | 14.6 |
| | 1.0 | 4.91 | 5.80 | 0.864 | 14.9 |
| **United Kingdom** | | | | | |
| ERR, *D*, sex, age, years SE[b] | 0.01 | 6.16 | 7.41 | 1.019 | 13.8 |
| | 0.1 | 6.12 | 7.36 | 1.015 | 13.8 |
| | 1.0 | 5.72 | 6.89 | 0.972 | 14.1 |
| ERR, *D*, sex, age AE[c] | 0.01 | 9.84 | 11.70 | 1.406 | 12.0 |
| | 0.1 | 9.63 | 11.46 | 1.387 | 12.1 |
| | 1.0 | 8.13 | 9.73 | 1.242 | 12.8 |
| ERR, $D + D^2$, sex, age, years SE[d] | 0.01 | 4.29 | 5.15 | 0.711 | 13.8 |
| | 0.1 | 4.38 | 5.26 | 0.727 | 13.8 |
| | 1.0 | 5.16 | 6.21 | 0.877 | 14.1 |
| EAR, *D*, age, years SE[e] | 0.01 | 5.72 | 6.92 | 0.991 | 14.3 |
| | 0.1 | 5.69 | 6.88 | 0.987 | 14.4 |
| | 1.0 | 5.38 | 6.51 | 0.954 | 14.6 |

| *Model, modifying terms*[a] | *Test dose, $D_t$ (Sv)* | *Per cent excess cancer deaths ($Sv^{-1}$)* | *Per cent radiation-induced cancer deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/ radiation-induced cancer death (a)* |
|---|---|---|---|---|---|
| EAR, $D + D^2$, age, years SE[f] | 0.01 | 3.64 | 4.40 | 0.632 | 14.4 |
| | 0.1 | 3.76 | 4.54 | 0.653 | 14.4 |
| | 1.0 | 4.80 | 5.81 | 0.852 | 14.7 |

[a] ERR = generalized excess relative risk, EAR = generalized excess absolute risk, years SE = years since exposure, age AE = age at exposure.
[b] ERR = $\alpha_s\, D\, [a - e]^{\kappa}\, a^{\tau}$, as per model (14) with quadratic coefficient in dose, $\beta$, set to 0 ($a$ = attained age, $e$ = age at exposure, $s$ = sex).
[c] ERR = $\alpha_s\, D\, e^{\kappa}$, as per model (15) with quadratic coefficient in dose, $\beta$, set to 0 ($e$ = age at exposure, $s$ = sex).
[d] ERR = $\alpha_s\, [D+\beta D^2]\, [a - e]^{\kappa}\, a^{\tau}$, as per model (14) ($a$ = attained age, $e$ = age at exposure, $s$ = sex).
[e] EAR = $\alpha\, D\, [a - e]^{\kappa}\, a^{\tau}$, as per model (16) with quadratic coefficient in dose, $\beta$, set to 0 ($a$ = attained age, $e$ = age at exposure).
[f] EAR = $\alpha\, [D+\beta D^2]\, [a - e]^{\kappa}\, a^{\tau}$, as per model (16) ($a$ = attained age, $e$ = age at exposure).

**Table 60 Risk estimates for solid cancer mortality by sex in various current populations, assuming a test dose, $D_t$, of 0.1 Sv, and using generalized ERR and generalized EAR models (models described in table 45)**

Risk estimates are calculated for a population in equilibrium (underlying mortality rates and population structure of current Chinese, Japanese, Puerto Rican, United States and United Kingdom populations) from various models fitted to LSS mortality data [P10], assuming 35% GSD errors

| *Model, modifying terms*[a] | *Sex* | *Per cent excess cancer deaths ($Sv^{-1}$)* | *Per cent radiation-induced cancer deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/ radiation-induced cancer death (a)* |
|---|---|---|---|---|---|
| **China** | | | | | |
| ERR, $D$, sex, age, years SE[b] | Males | 4.52 | 5.33 | 0.747 | 14.0 |
| | Females | 5.48 | 6.03 | 0.976 | 16.2 |
| | Both | 4.99 | 5.67 | 0.859 | 15.1 |
| ERR, $D$, sex, age AE[c] | Males | 6.10 | 7.13 | 0.874 | 12.3 |
| | Females | 8.50 | 9.30 | 1.306 | 14.0 |
| | Both | 7.28 | 8.19 | 1.086 | 13.3 |
| ERR, $D + D^2$, sex, age, years SE[d] | Males | 3.12 | 3.67 | 0.515 | 14.0 |
| | Females | 4.01 | 4.41 | 0.714 | 16.2 |
| | Both | 3.55 | 4.03 | 0.612 | 15.2 |
| EAR, $D$, age, years SE[e] | Males | 4.68 | 5.49 | 0.752 | 13.7 |
| | Females | 6.14 | 6.71 | 0.964 | 14.4 |
| | Both | 5.40 | 6.09 | 0.856 | 14.1 |
| EAR, $D + D^2$, age, years SE[f] | Males | 3.09 | 3.63 | 0.498 | 13.7 |
| | Females | 4.05 | 4.43 | 0.638 | 14.4 |
| | Both | 3.56 | 4.02 | 0.566 | 14.1 |
| **Japan** | | | | | |
| ERR, $D$, sex, age, years SE[b] | Males | 5.03 | 6.31 | 0.836 | 13.2 |
| | Females | 6.13 | 7.03 | 1.135 | 16.2 |
| | Both | 5.59 | 6.67 | 0.988 | 14.8 |
| ERR, $D$, sex, age AE[c] | Males | 7.29 | 9.07 | 1.075 | 11.9 |
| | Females | 10.42 | 11.86 | 1.660 | 14.0 |
| | Both | 8.88 | 10.49 | 1.372 | 13.1 |
| ERR, $D + D^2$, sex, age, years SE[d] | Males | 3.46 | 4.35 | 0.576 | 13.2 |
| | Females | 4.48 | 5.14 | 0.830 | 16.2 |
| | Both | 3.98 | 4.75 | 0.705 | 14.8 |

| *Model, modifying terms*[a] | *Sex* | *Per cent excess cancer deaths ($Sv^{-1}$)* | *Per cent radiation-induced cancer deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/ radiation-induced cancer death (a)* |
|---|---|---|---|---|---|
| EAR, $D$, age, years SE[e] | Males | 5.19 | 6.53 | 0.932 | 14.3 |
| | Females | 7.65 | 8.74 | 1.342 | 15.3 |
| | Both | 6.44 | 7.65 | 1.140 | 14.9 |
| EAR, $D + D^2$, age, years SE[f] | Males | 3.43 | 4.31 | 0.617 | 14.3 |
| | Females | 5.05 | 5.77 | 0.887 | 15.4 |
| | Both | 4.25 | 5.05 | 0.754 | 14.9 |
| **Puerto Rico** | | | | | |
| ERR, $D$, sex, age, years SE[b] | Males | 3.57 | 4.35 | 0.566 | 13.0 |
| | Females | 5.07 | 5.63 | 0.895 | 15.9 |
| | Both | 4.35 | 5.01 | 0.737 | 14.7 |
| ERR, $D$, sex, age AE[c] | Males | 5.20 | 6.32 | 0.723 | 11.4 |
| | Females | 8.28 | 9.14 | 1.244 | 13.6 |
| | Both | 6.80 | 7.79 | 0.994 | 12.8 |
| ERR, $D + D^2$, sex, age, years SE[d] | Males | 2.46 | 3.00 | 0.390 | 13.0 |
| | Females | 3.71 | 4.11 | 0.654 | 15.9 |
| | Both | 3.11 | 3.58 | 0.527 | 14.7 |
| EAR, $D$, age, years SE[e] | Males | 4.77 | 5.81 | 0.825 | 14.2 |
| | Females | 6.72 | 7.44 | 1.098 | 14.8 |
| | Both | 5.78 | 6.65 | 0.967 | 14.5 |
| EAR, $D + D^2$, age, years SE[f] | Males | 3.15 | 3.84 | 0.546 | 14.2 |
| | Females | 4.44 | 4.91 | 0.726 | 14.8 |
| | Both | 3.82 | 4.39 | 0.640 | 14.6 |
| **United States** | | | | | |
| ERR, $D$, sex, age, years SE[b] | Males | 4.50 | 5.53 | 0.746 | 13.5 |
| | Females | 6.93 | 8.00 | 1.298 | 16.2 |
| | Both | 5.73 | 6.78 | 1.026 | 15.1 |
| ERR, $D$, sex, age AE[c] | Males | 6.45 | 7.86 | 0.946 | 12.0 |
| | Females | 11.23 | 12.86 | 1.837 | 14.3 |
| | Both | 8.87 | 10.40 | 1.398 | 13.4 |
| ERR, $D + D^2$, sex, age, years SE[d] | Males | 3.10 | 3.81 | 0.514 | 13.5 |
| | Females | 5.07 | 5.85 | 0.950 | 16.2 |
| | Both | 4.10 | 4.84 | 0.735 | 15.2 |
| EAR, $D$, age, years SE[e] | Males | 5.02 | 6.16 | 0.875 | 14.2 |
| | Females | 6.65 | 7.61 | 1.133 | 14.9 |
| | Both | 5.84 | 6.89 | 1.006 | 14.6 |
| EAR, $D + D^2$, age, years SE[f] | Males | 3.31 | 4.07 | 0.579 | 14.2 |
| | Females | 4.39 | 5.02 | 0.750 | 14.9 |
| | Both | 3.86 | 4.55 | 0.665 | 14.6 |

| *Model, modifying terms*[a] | *Sex* | *Per cent excess cancer deaths ($Sv^{-1}$)* | *Per cent radiation-induced cancer deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/ radiation-induced cancer death (a)* |
|---|---|---|---|---|---|
| **United Kingdom** | | | | | |
| ERR, $D$, sex, age, years SE[b] | Males | 4.78 | 6.00 | 0.729 | 12.2 |
| | Females | 7.46 | 8.72 | 1.301 | 14.9 |
| | Both | 6.12 | 7.36 | 1.015 | 13.8 |
| ERR, $D$, sex, age AE[c] | Males | 7.00 | 8.72 | 0.939 | 10.8 |
| | Females | 12.25 | 14.20 | 1.835 | 12.9 |
| | Both | 9.63 | 11.46 | 1.387 | 12.1 |
| ERR, $D + D^2$, sex, age, years SE[d] | Males | 3.29 | 4.13 | 0.503 | 12.2 |
| | Females | 5.46 | 6.38 | 0.952 | 14.9 |
| | Both | 4.38 | 5.26 | 0.727 | 13.8 |
| EAR, $D$, age, years SE[e] | Males | 4.99 | 6.30 | 0.887 | 14.1 |
| | Females | 6.39 | 7.45 | 1.088 | 14.6 |
| | Both | 5.69 | 6.88 | 0.987 | 14.4 |
| EAR, $D + D^2$, age, years SE[f] | Males | 3.29 | 4.16 | 0.587 | 14.1 |
| | Females | 4.22 | 4.92 | 0.720 | 14.6 |
| | Both | 3.76 | 4.54 | 0.653 | 14.4 |

[a] ERR = generalized excess relative risk, EAR = generalized excess absolute risk, years SE = years since exposure, age AE = age at exposure.
[b] ERR = $\alpha_s\, D\, [a - e]^{\kappa}\, a^{\tau}$, as per model (14) with quadratic coefficient in dose, $\beta$, set to 0 ($a$ = attained age, $e$ = age at exposure, $s$ = sex).
[c] ERR = $\alpha_s\, D\, e^{\kappa}$, as per model (15) with quadratic coefficient in dose, $\beta$, set to 0 ($e$ = age at exposure, $s$ = sex).
[d] ERR = $\alpha_s\, [D+\beta D^2]\, [a - e]^{\kappa}\, a^{\tau}$, as per model (14) ($a$ = attained age, $e$ = age at exposure, $s$ = sex).
[e] EAR = $\alpha\, D\, [a - e]^{\kappa}\, a^{\tau}$, as per model (16) with quadratic coefficient in dose, $\beta$, set to 0 ($a$ = attained age, $e$ = age at exposure).
[f] EAR = $\alpha\, [D+\beta D^2]\, [a - e]^{\kappa}\, a^{\tau}$, as per model (16) ($a$ = attained age, $e$ = age at exposure).

**Table 61 Risk estimates for solid cancer mortality by age-at-exposure group in various current populations, assuming a test dose, $D_t$, of 0.1 Sv and using generalized ERR and generalized EAR models (models described in table 45)**
Risk estimates are calculated for a population in equilibrium (underlying mortality rates and population structure of current Chinese, Japanese, Puerto Rican, United States and United Kingdom populations) from various models fitted to LSS mortality data [P10], assuming 35% GSD errors

| *Model, modifying factors*[a] | *Age at exposure* | *Per cent excess cancer deaths ($Sv^{-1}$)* | *Per cent radiation-induced cancer deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/ radiation-induced cancer death (a)* |
|---|---|---|---|---|---|
| **China** | | | | | |
| ERR, $D$, sex, age, years SE[b] | 0–9 | 10.72 | 12.27 | 2.165 | 17.6 |
| | 10–19 | 8.79 | 10.03 | 1.636 | 16.3 |
| | 20–29 | 6.95 | 7.91 | 1.197 | 15.1 |
| | 30–39 | 5.18 | 5.87 | 0.802 | 13.7 |
| | 40–49 | 3.54 | 3.99 | 0.472 | 11.8 |
| | 50–59 | 2.16 | 2.40 | 0.240 | 10.0 |
| | 60–69 | 1.07 | 1.17 | 0.094 | 8.0 |
| | 70+ | 0.30 | 0.32 | 0.020 | 6.1 |
| | All ages | 4.99 | 5.67 | 0.859 | 15.1 |

| *Model, modifying factors*[a] | *Age at exposure* | *Per cent excess cancer deaths ($Sv^{-1}$)* | *Per cent radiation-induced cancer deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/ radiation-induced cancer death (a)* |
|---|---|---|---|---|---|
| ERR, *D*, sex, age AE[c] | 0–9 | 24.11 | 27.23 | 3.831 | 14.1 |
| | 10–19 | 9.07 | 10.24 | 1.423 | 13.9 |
| | 20–29 | 6.55 | 7.39 | 1.017 | 13.8 |
| | 30–39 | 5.28 | 5.95 | 0.792 | 13.3 |
| | 40–49 | 4.36 | 4.90 | 0.598 | 12.2 |
| | 50–59 | 3.54 | 3.95 | 0.419 | 10.6 |
| | 60–69 | 2.53 | 2.78 | 0.237 | 8.5 |
| | 70+ | 1.09 | 1.17 | 0.073 | 6.3 |
| | All ages | 7.28 | 8.19 | 1.086 | 13.3 |
| ERR, $D + D^2$, sex, age, years SE[d] | 0–9 | 7.63 | 8.72 | 1.543 | 17.7 |
| | 10–19 | 6.25 | 7.13 | 1.165 | 16.3 |
| | 20–29 | 4.94 | 5.62 | 0.853 | 15.2 |
| | 30–39 | 3.69 | 4.17 | 0.571 | 13.7 |
| | 40–49 | 2.52 | 2.84 | 0.337 | 11.9 |
| | 50–59 | 1.54 | 1.71 | 0.171 | 10.0 |
| | 60–69 | 0.76 | 0.83 | 0.067 | 8.0 |
| | 70+ | 0.22 | 0.23 | 0.014 | 6.1 |
| | All ages | 3.55 | 4.03 | 0.612 | 15.2 |
| EAR, *D*, age, years SE[e] | 0–9 | 9.65 | 10.98 | 1.805 | 16.4 |
| | 10–19 | 8.53 | 9.70 | 1.530 | 15.8 |
| | 20–29 | 7.30 | 8.27 | 1.223 | 14.8 |
| | 30–39 | 5.97 | 6.73 | 0.904 | 13.4 |
| | 40–49 | 4.58 | 5.13 | 0.600 | 11.7 |
| | 50–59 | 3.21 | 3.55 | 0.345 | 9.7 |
| | 60–69 | 1.96 | 2.14 | 0.165 | 7.7 |
| | 70+ | 0.90 | 0.96 | 0.057 | 5.9 |
| | All ages | 5.40 | 6.09 | 0.856 | 14.1 |
| EAR, $D + D^2$, age, years SE[f] | 0–9 | 6.38 | 7.26 | 1.196 | 16.5 |
| | 10–19 | 5.64 | 6.41 | 1.013 | 15.8 |
| | 20–29 | 4.82 | 5.46 | 0.809 | 14.8 |
| | 30–39 | 3.94 | 4.45 | 0.598 | 13.4 |
| | 40–49 | 3.02 | 3.39 | 0.396 | 11.7 |
| | 50–59 | 2.12 | 2.34 | 0.227 | 9.7 |
| | 60–69 | 1.30 | 1.41 | 0.109 | 7.7 |
| | 70+ | 0.59 | 0.63 | 0.037 | 5.9 |
| | All ages | 3.56 | 4.02 | 0.57 | 14.09 |

| *Model, modifying factors*[a] | *Age at exposure* | *Per cent excess cancer deaths ($Sv^{-1}$)* | *Per cent radiation-induced cancer deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/ radiation-induced cancer death (a)* |
|---|---|---|---|---|---|
| **Japan** | | | | | |
| ERR, *D*, sex, age, years SE[b] | 0–9 | 11.78 | 14.18 | 2.434 | 17.2 |
| | 10–19 | 9.86 | 11.84 | 1.898 | 16.0 |
| | 20–29 | 8.03 | 9.62 | 1.448 | 15.1 |
| | 30–39 | 6.23 | 7.43 | 1.029 | 13.8 |
| | 40–49 | 4.52 | 5.36 | 0.663 | 12.4 |
| | 50–59 | 2.99 | 3.50 | 0.373 | 10.7 |
| | 60–69 | 1.71 | 1.98 | 0.175 | 8.8 |
| | 70+ | 0.57 | 0.64 | 0.046 | 7.1 |
| | All ages | 5.59 | 6.67 | 0.988 | 14.8 |
| ERR, *D*, sex, age AE[c] | 0–9 | 30.02 | 35.61 | 4.942 | 13.9 |
| | 10–19 | 11.37 | 13.48 | 1.844 | 13.7 |
| | 20–29 | 8.23 | 9.75 | 1.325 | 13.6 |
| | 30–39 | 6.65 | 7.88 | 1.048 | 13.3 |
| | 40–49 | 5.60 | 6.62 | 0.833 | 12.6 |
| | 50–59 | 4.70 | 5.53 | 0.624 | 11.3 |
| | 60–69 | 3.72 | 4.31 | 0.406 | 9.4 |
| | 70+ | 1.96 | 2.21 | 0.162 | 7.3 |
| | All ages | 8.88 | 10.49 | 1.372 | 13.1 |
| ERR, $D + D^2$, sex, age, years SE[d] | 0–9 | 8.39 | 10.09 | 1.737 | 17.2 |
| | 10–19 | 7.02 | 8.42 | 1.354 | 16.1 |
| | 20–29 | 5.72 | 6.84 | 1.034 | 15.1 |
| | 30–39 | 4.44 | 5.29 | 0.734 | 13.9 |
| | 40–49 | 3.22 | 3.82 | 0.473 | 12.4 |
| | 50–59 | 2.13 | 2.50 | 0.266 | 10.7 |
| | 60–69 | 1.23 | 1.41 | 0.125 | 8.9 |
| | 70+ | 0.41 | 0.46 | 0.033 | 7.2 |
| | All ages | 3.98 | 4.75 | 0.705 | 14.8 |
| EAR, *D*, age, years SE[e] | 0–9 | 11.59 | 13.91 | 2.424 | 17.4 |
| | 10–19 | 10.31 | 12.36 | 2.074 | 16.8 |
| | 20–29 | 8.93 | 10.67 | 1.690 | 15.8 |
| | 30–39 | 7.44 | 8.85 | 1.286 | 14.5 |
| | 40–49 | 5.87 | 6.94 | 0.893 | 12.9 |
| | 50–59 | 4.31 | 5.03 | 0.550 | 11.0 |
| | 60–69 | 2.84 | 3.27 | 0.292 | 8.9 |
| | 70+ | 1.32 | 1.48 | 0.103 | 6.9 |
| | All ages | 6.44 | 7.65 | 1.140 | 14.9 |
| EAR, $D + D^2$, age, years SE[f] | 0–9 | 7.65 | 9.19 | 1.605 | 17.5 |
| | 10–19 | 6.81 | 8.16 | 1.373 | 16.8 |
| | 20–29 | 5.90 | 7.05 | 1.118 | 15.9 |
| | 30–39 | 4.91 | 5.84 | 0.850 | 14.6 |
| | 40–49 | 3.87 | 4.57 | 0.590 | 12.9 |
| | 50–59 | 2.84 | 3.31 | 0.363 | 11.0 |
| | 60–69 | 1.87 | 2.15 | 0.192 | 8.9 |
| | 70+ | 0.87 | 0.97 | 0.068 | 6.9 |
| | All ages | 4.25 | 5.05 | 0.754 | 14.9 |

| *Model, modifying factors*[a] | *Age at exposure* | *Per cent excess cancer deaths ($Sv^{-1}$)* | *Per cent radiation-induced cancer deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/ radiation-induced cancer death (a)* |
|---|---|---|---|---|---|
| **Puerto Rico** | | | | | |
| ERR, *D*, sex, age, years SE[b] | 0–9 | 8.81 | 10.18 | 1.767 | 17.4 |
| | 10–19 | 7.28 | 8.40 | 1.339 | 15.9 |
| | 20–29 | 5.90 | 6.80 | 1.007 | 14.8 |
| | 30–39 | 4.60 | 5.30 | 0.714 | 13.5 |
| | 40–49 | 3.37 | 3.87 | 0.460 | 11.9 |
| | 50–59 | 2.23 | 2.55 | 0.258 | 10.1 |
| | 60–69 | 1.30 | 1.48 | 0.122 | 8.2 |
| | 70+ | 0.47 | 0.53 | 0.035 | 6.5 |
| | All ages | 4.35 | 5.01 | 0.737 | 14.7 |
| ERR, *D*, sex, age AE[c] | 0–9 | 21.70 | 24.89 | 3.388 | 13.6 |
| | 10–19 | 8.19 | 9.38 | 1.259 | 13.4 |
| | 20–29 | 5.96 | 6.83 | 0.908 | 13.3 |
| | 30–39 | 4.90 | 5.62 | 0.726 | 12.9 |
| | 40–49 | 4.21 | 4.82 | 0.584 | 12.1 |
| | 50–59 | 3.56 | 4.07 | 0.436 | 10.7 |
| | 60–69 | 2.84 | 3.23 | 0.284 | 8.8 |
| | 70+ | 1.63 | 1.83 | 0.122 | 6.7 |
| | All ages | 6.80 | 7.79 | 0.994 | 12.8 |
| ERR, $D + D^2$, sex, age, years SE[d] | 0–9 | 6.29 | 7.26 | 1.265 | 17.4 |
| | 10–19 | 5.20 | 6.00 | 0.959 | 16.0 |
| | 20–29 | 4.21 | 4.85 | 0.721 | 14.9 |
| | 30–39 | 3.29 | 3.78 | 0.510 | 13.5 |
| | 40–49 | 2.41 | 2.76 | 0.329 | 11.9 |
| | 50–59 | 1.60 | 1.82 | 0.184 | 10.1 |
| | 60–69 | 0.93 | 1.06 | 0.087 | 8.2 |
| | 70+ | 0.34 | 0.38 | 0.025 | 6.5 |
| | All ages | 3.11 | 3.58 | 0.527 | 14.7 |
| EAR, *D*, age, years SE[e] | 0–9 | 10.00 | 11.55 | 1.960 | 17.0 |
| | 10–19 | 8.86 | 10.24 | 1.671 | 16.3 |
| | 20–29 | 7.67 | 8.85 | 1.360 | 15.4 |
| | 30–39 | 6.44 | 7.42 | 1.043 | 14.1 |
| | 40–49 | 5.13 | 5.88 | 0.730 | 12.4 |
| | 50–59 | 3.75 | 4.28 | 0.449 | 10.5 |
| | 60–69 | 2.46 | 2.79 | 0.236 | 8.5 |
| | 70+ | 1.14 | 1.27 | 0.082 | 6.4 |
| | All ages | 5.78 | 6.65 | 0.967 | 14.5 |
| EAR, $D + D^2$, age, years SE[f] | 0–9 | 6.61 | 7.63 | 1.298 | 17.0 |
| | 10–19 | 5.85 | 6.76 | 1.106 | 16.4 |
| | 20–29 | 5.07 | 5.84 | 0.900 | 15.4 |
| | 30–39 | 4.25 | 4.90 | 0.689 | 14.1 |
| | 40–49 | 3.38 | 3.88 | 0.482 | 12.4 |
| | 50–59 | 2.47 | 2.82 | 0.296 | 10.5 |
| | 60–69 | 1.62 | 1.84 | 0.156 | 8.5 |
| | 70+ | 0.75 | 0.84 | 0.054 | 6.4 |
| | All ages | 3.82 | 4.39 | 0.640 | 14.6 |

| *Model, modifying factors*[a] | *Age at exposure* | *Per cent excess cancer deaths ($Sv^{-1}$)* | *Per cent radiation-induced cancer deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/ radiation-induced cancer death (a)* |
|---|---|---|---|---|---|
| **United States** | | | | | |
| ERR, *D*, sex, age, years SE[b] | 0–9 | 11.94 | 14.23 | 2.480 | 17.4 |
| | 10–19 | 9.92 | 11.80 | 1.917 | 16.2 |
| | 20–29 | 8.04 | 9.53 | 1.458 | 15.3 |
| | 30–39 | 6.20 | 7.32 | 1.035 | 14.1 |
| | 40–49 | 4.43 | 5.20 | 0.659 | 12.7 |
| | 50–59 | 2.85 | 3.30 | 0.357 | 10.8 |
| | 60–69 | 1.57 | 1.79 | 0.158 | 8.8 |
| | 70+ | 0.51 | 0.58 | 0.039 | 6.8 |
| | All ages | 5.73 | 6.78 | 1.026 | 15.1 |
| ERR, *D*, sex, age AE[c] | 0–9 | 29.20 | 34.34 | 4.888 | 14.2 |
| | 10–19 | 11.08 | 13.01 | 1.826 | 14.0 |
| | 20–29 | 8.04 | 9.44 | 1.315 | 13.9 |
| | 30–39 | 6.53 | 7.67 | 1.046 | 13.6 |
| | 40–49 | 5.52 | 6.47 | 0.837 | 12.9 |
| | 50–59 | 4.60 | 5.35 | 0.616 | 11.5 |
| | 60–69 | 3.52 | 4.04 | 0.380 | 9.4 |
| | 70+ | 1.79 | 2.01 | 0.141 | 7.0 |
| | All ages | 8.87 | 10.40 | 1.398 | 13.4 |
| ERR, $D + D^2$, sex, age, years SE[d] | 0–9 | 8.54 | 10.17 | 1.776 | 17.5 |
| | 10–19 | 7.09 | 8.43 | 1.373 | 16.3 |
| | 20–29 | 5.75 | 6.81 | 1.045 | 15.3 |
| | 30–39 | 4.43 | 5.23 | 0.741 | 14.2 |
| | 40–49 | 3.17 | 3.72 | 0.472 | 12.7 |
| | 50–59 | 2.04 | 2.36 | 0.256 | 10.8 |
| | 60–69 | 1.12 | 1.28 | 0.113 | 8.8 |
| | 70+ | 0.37 | 0.41 | 0.028 | 6.9 |
| | All ages | 4.10 | 4.84 | 0.735 | 15.2 |
| EAR, *D*, age, years SE[e] | 0–9 | 10.32 | 12.29 | 2.095 | 17.0 |
| | 10–19 | 9.16 | 10.89 | 1.786 | 16.4 |
| | 20–29 | 7.91 | 9.38 | 1.449 | 15.4 |
| | 30–39 | 6.57 | 7.76 | 1.096 | 14.1 |
| | 40–49 | 5.16 | 6.05 | 0.754 | 12.5 |
| | 50–59 | 3.75 | 4.35 | 0.459 | 10.6 |
| | 60–69 | 2.48 | 2.83 | 0.242 | 8.6 |
| | 70+ | 1.18 | 1.31 | 0.087 | 6.6 |
| | All ages | 5.84 | 6.89 | 1.006 | 14.6 |
| EAR, $D + D^2$, age, years SE[f] | 0–9 | 6.82 | 8.12 | 1.387 | 17.1 |
| | 10–19 | 6.05 | 7.19 | 1.182 | 16.4 |
| | 20–29 | 5.23 | 6.20 | 0.959 | 15.5 |
| | 30–39 | 4.34 | 5.12 | 0.724 | 14.1 |
| | 40–49 | 3.40 | 3.99 | 0.498 | 12.5 |
| | 50–59 | 2.47 | 2.87 | 0.303 | 10.6 |
| | 60–69 | 1.63 | 1.86 | 0.160 | 8.6 |
| | 70+ | 0.78 | 0.86 | 0.057 | 6.6 |
| | All ages | 3.86 | 4.55 | 0.665 | 14.6 |

| *Model, modifying factors*[a] | *Age at exposure* | *Per cent excess cancer deaths ($Sv^{-1}$)* | *Per cent radiation-induced cancer deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/ radiation-induced cancer death (a)* |
|---|---|---|---|---|---|
| **United Kingdom** | | | | | |
| ERR, *D*, sex, age, years SE[b] | 0–9 | 12.77 | 15.49 | 2.510 | 16.2 |
| | 10–19 | 10.64 | 12.86 | 1.914 | 14.9 |
| | 20–29 | 8.65 | 10.44 | 1.455 | 13.9 |
| | 30–39 | 6.73 | 8.08 | 1.037 | 12.8 |
| | 40–49 | 4.87 | 5.81 | 0.663 | 11.4 |
| | 50–59 | 3.18 | 3.75 | 0.362 | 9.6 |
| | 60–69 | 1.78 | 2.06 | 0.158 | 7.7 |
| | 70+ | 0.56 | 0.63 | 0.034 | 5.5 |
| | All ages | 6.12 | 7.36 | 1.015 | 13.8 |
| ERR, *D*, sex, age AE[c] | 0–9 | 32.06 | 38.33 | 4.942 | 12.9 |
| | 10–19 | 12.18 | 14.54 | 1.841 | 12.7 |
| | 20–29 | 8.81 | 10.52 | 1.320 | 12.6 |
| | 30–39 | 7.14 | 8.52 | 1.048 | 12.3 |
| | 40–49 | 6.03 | 7.18 | 0.837 | 11.7 |
| | 50–59 | 5.06 | 5.98 | 0.618 | 10.3 |
| | 60–69 | 3.96 | 4.61 | 0.384 | 8.3 |
| | 70+ | 1.97 | 2.23 | 0.127 | 5.7 |
| | All ages | 9.63 | 11.46 | 1.387 | 12.1 |
| ERR, $D + D^2$, sex, age, years SE[d] | 0–9 | 9.13 | 11.07 | 1.798 | 16.3 |
| | 10–19 | 7.60 | 9.19 | 1.371 | 14.9 |
| | 20–29 | 6.19 | 7.45 | 1.042 | 14.0 |
| | 30–39 | 4.81 | 5.77 | 0.742 | 12.9 |
| | 40–49 | 3.48 | 4.15 | 0.475 | 11.4 |
| | 50–59 | 2.27 | 2.68 | 0.259 | 9.7 |
| | 60–69 | 1.27 | 1.48 | 0.113 | 7.7 |
| | 70+ | 0.40 | 0.45 | 0.025 | 5.5 |
| | All ages | 4.38 | 5.26 | 0.727 | 13.8 |
| EAR, *D*, age, years SE[e] | 0–9 | 10.35 | 12.65 | 2.132 | 16.9 |
| | 10–19 | 9.17 | 11.18 | 1.812 | 16.2 |
| | 20–29 | 7.89 | 9.60 | 1.460 | 15.2 |
| | 30–39 | 6.52 | 7.88 | 1.092 | 13.8 |
| | 40–49 | 5.07 | 6.08 | 0.736 | 12.1 |
| | 50–59 | 3.62 | 4.29 | 0.431 | 10.0 |
| | 60–69 | 2.28 | 2.65 | 0.207 | 7.8 |
| | 70+ | 0.89 | 1.01 | 0.054 | 5.4 |
| | All ages | 5.69 | 6.88 | 0.987 | 14.4 |

| *Model, modifying factors*[a] | *Age at exposure* | *Per cent excess cancer deaths ($Sv^{-1}$)* | *Per cent radiation-induced cancer deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/ radiation-induced cancer death (a)* |
|---|---|---|---|---|---|
| EAR, $D + D^2$, age, years SE[f] | 0–9 | 6.84 | 8.36 | 1.412 | 16.9 |
| | 10–19 | 6.06 | 7.39 | 1.199 | 16.2 |
| | 20–29 | 5.21 | 6.34 | 0.966 | 15.2 |
| | 30–39 | 4.30 | 5.20 | 0.722 | 13.9 |
| | 40–49 | 3.34 | 4.01 | 0.486 | 12.1 |
| | 50–59 | 2.38 | 2.83 | 0.284 | 10.1 |
| | 60–69 | 1.50 | 1.75 | 0.136 | 7.8 |
| | 70+ | 0.59 | 0.66 | 0.036 | 5.4 |
| | All ages | 3.76 | 4.54 | 0.653 | 14.4 |

[a] ERR = generalized excess relative risk, EAR = generalized excess absolute risk, years SE = years since exposure, age AE = age at exposure.
[b] ERR = $\alpha_s D [a - e]^{\kappa} a^{\tau}$, as per model (14) with quadratic coefficient in dose, $\beta$, set to 0 ($a$ = attained age, $e$ = age at exposure, $s$ = sex).
[c] ERR = $\alpha_s D e^{\kappa}$, as per model (15) with quadratic coefficient in dose, $\beta$, set to 0 ($e$ = age at exposure, $s$ = sex).
[d] ERR = $\alpha_s [D+\beta D^2] [a - e]^{\kappa} a^{\tau}$, as per model (14) ($a$ = attained age, $e$ = age at exposure, $s$ = sex).
[e] EAR = $\alpha D [a - e]^{\kappa} a^{\tau}$, as per model (16) with quadratic coefficient in dose, $\beta$, set to 0 ($a$ = attained age, $e$ = age at exposure).
[f] EAR = $\alpha [D+\beta D^2] [a - e]^{\kappa} a^{\tau}$, as per model (16) ($a$ = attained age, $e$ = age at exposure).

**Table 62 Risk estimates for solid cancer mortality in United Kingdom populations, assuming a test dose, $D_t$, of 0.1 Sv, using linear generalized ERR models (models described in table 45 and analogues) fitted using DS86 and DS02 dose estimates, and using follow-up over the periods 1950–1990 and 1950–2000**

Risk estimates are calculated for a population in equilibrium (underlying mortality rates and population structure of current United Kingdom population) from linear ERR models fitted to LSS mortality data [P10], assuming 35% GSD errors

| *Period of fit* | *Dose estimates used* | *Model, modifying terms*[a] | *Per cent excess cancer deaths ($Sv^{-1}$)* | *Per cent radiation-induced cancer deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/ radiation-induced cancer death (a)* |
|---|---|---|---|---|---|---|
| 1950–1990 | DS86 | ERR, $D$, sex, age, years SE[b] | 7.07 | 8.48 | 1.128 | 13.3 |
| | | ERR, $D$, sex, age AE[c] | 11.48 | 13.66 | 1.659 | 12.1 |
| | DS02 | ERR, $D$, sex, age, years SE[b] | 6.34 | 7.60 | 1.010 | 13.3 |
| | | ERR, $D$, sex, age AE[c] | 10.35 | 12.31 | 1.496 | 12.2 |
| 1950–2000 | DS86 | ERR, $D$, sex, age, years SE[b] | 6.85 | 8.25 | 1.137 | 13.8 |
| | | ERR, $D$, sex, age AE[c] | 10.69 | 12.73 | 1.539 | 12.1 |
| | DS02 | ERR, $D$, sex, age, years SE[b] | 6.12 | 7.36 | 1.015 | 13.8 |
| | | ERR, $D$, sex, age AE[c] | 9.63 | 11.46 | 1.387 | 12.1 |

[a] ERR = generalized excess relative risk, years SE = years since exposure, age AE = age at exposure.
[b] ERR = $\alpha_s D [a - e]^{\kappa} a^{\tau}$, as per model (14) with quadratic coefficient in dose, $\beta$, set to 0 ($a$ = attained age, $e$ = age at exposure, $s$ = sex).
[c] ERR = $\alpha_s D e^{\kappa}$, as per model (15) with quadratic coefficient in dose, $\beta$, set to 0 ($e$ = age at exposure, s = *sex).*

**Table 63 Distribution of solid cancer mortality risk estimates for various current populations, using generalized linear–quadratic–exponential ERR models fitted by Bayesian MCMC (models described in appendix E)**

Risk estimates are calculated for a population in equilibrium (underlying mortality rates and population structure of current Chinese, Japanese, Puerto Rican, United States and United Kingdom populations) from various models fitted to LSS mortality data [P10], assuming 35% GSD errors

| *Test dose, $D_t$ (Sv)* | *Mean/centile* | *Per cent excess cancer deaths ($Sv^{-1}$)* | *Per cent radiation-induced cancer deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/radiation-induced cancer death (a)* |
|---|---|---|---|---|---|
| **China** | | | | | |
| 0.01 | Mean | 1.70 | 1.94 | 0.297 | 15.4 |
| | 2.5% centile | –2.26 | –2.57 | –0.394 | 13.8 |
| | 5% centile | –1.59 | –1.80 | –0.279 | 14.0 |
| | 50% centile | 1.78 | 2.03 | 0.312 | 15.3 |
| | 95% centile | 4.68 | 5.32 | 0.816 | 17.1 |
| | 97.5% centile | 5.15 | 5.86 | 0.892 | 17.5 |
| 0.1 | Mean | 2.25 | 2.56 | 0.394 | 15.4 |
| | 2.5% centile | –0.91 | –1.04 | –0.161 | 13.8 |
| | 5% centile | –0.41 | –0.46 | –0.071 | 14.0 |
| | 50% centile | 2.28 | 2.60 | 0.400 | 15.3 |
| | 95% centile | 4.78 | 5.44 | 0.833 | 17.1 |
| | 97.5% centile | 5.22 | 5.93 | 0.906 | 17.5 |
| 1 | Mean | 4.94 | 5.63 | 0.882 | 15.7 |
| | 2.5% centile | 3.79 | 4.32 | 0.690 | 14.1 |
| | 5% centile | 3.96 | 4.51 | 0.719 | 14.3 |
| | 50% centile | 4.93 | 5.62 | 0.879 | 15.6 |
| | 95% centile | 5.96 | 6.79 | 1.054 | 17.4 |
| | 97.5% centile | 6.16 | 7.02 | 1.089 | 17.8 |
| **Japan** | | | | | |
| 0.01 | Mean | 1.90 | 2.27 | 0.339 | 15.0 |
| | 2.5% centile | –2.51 | –3.00 | –0.450 | 13.6 |
| | 5% centile | –1.76 | –2.10 | –0.317 | 13.8 |
| | 50% centile | 1.98 | 2.36 | 0.356 | 15.0 |
| | 95% centile | 5.24 | 6.26 | 0.927 | 16.6 |
| | 97.5% centile | 5.77 | 6.89 | 1.017 | 17.0 |
| 0.1 | Mean | 2.51 | 3.00 | 0.449 | 15.1 |
| | 2.5% centile | –1.02 | –1.22 | –0.182 | 13.6 |
| | 5% centile | –0.45 | –0.53 | –0.080 | 13.8 |
| | 50% centile | 2.53 | 3.03 | 0.456 | 15.0 |
| | 95% centile | 5.34 | 6.39 | 0.945 | 16.6 |
| | 97.5% centile | 5.84 | 6.99 | 1.031 | 17.0 |
| 1 | Mean | 5.43 | 6.51 | 0.997 | 15.4 |
| | 2.5% centile | 4.06 | 4.87 | 0.780 | 13.9 |
| | 5% centile | 4.27 | 5.12 | 0.814 | 14.1 |
| | 50% centile | 5.42 | 6.49 | 0.995 | 15.3 |
| | 95% centile | 6.68 | 7.99 | 1.188 | 16.9 |
| | 97.5% centile | 6.92 | 8.28 | 1.225 | 17.3 |

| *Test dose, $D_t$ (Sv)* | *Mean/centile* | *Per cent excess cancer deaths ($Sv^{-1}$)* | *Per cent radiation-induced cancer deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/radiation-induced cancer death (a)* |
|---|---|---|---|---|---|
| **Puerto Rico** | | | | | |
| 0.01 | Mean | 1.48 | 1.70 | 0.253 | 15.0 |
| | 2.5% centile | –1.95 | –2.25 | –0.337 | 13.3 |
| | 5% centile | –1.37 | –1.58 | –0.237 | 13.5 |
| | 50% centile | 1.54 | 1.78 | 0.266 | 14.9 |
| | 95% centile | 4.06 | 4.68 | 0.692 | 16.8 |
| | 97.5% centile | 4.47 | 5.15 | 0.757 | 17.3 |
| 0.1 | Mean | 1.95 | 2.25 | 0.336 | 15.0 |
| | 2.5% centile | –0.79 | –0.91 | –0.136 | 13.3 |
| | 5% centile | –0.35 | –0.40 | –0.060 | 13.5 |
| | 50% centile | 1.98 | 2.28 | 0.341 | 14.9 |
| | 95% centile | 4.14 | 4.78 | 0.706 | 16.8 |
| | 97.5% centile | 4.53 | 5.23 | 0.768 | 17.3 |
| 1 | Mean | 4.29 | 4.95 | 0.753 | 15.3 |
| | 2.5% centile | 3.25 | 3.75 | 0.592 | 13.6 |
| | 5% centile | 3.40 | 3.92 | 0.617 | 13.8 |
| | 50% centile | 4.27 | 4.93 | 0.751 | 15.2 |
| | 95% centile | 5.23 | 6.03 | 0.894 | 17.1 |
| | 97.5% centile | 5.41 | 6.24 | 0.922 | 17.6 |
| **United States** | | | | | |
| 0.01 | Mean | 1.94 | 2.30 | 0.352 | 15.4 |
| | 2.5% centile | –2.57 | –3.05 | –0.467 | 13.9 |
| | 5% centile | –1.81 | –2.14 | –0.330 | 14.1 |
| | 50% centile | 2.04 | 2.41 | 0.370 | 15.3 |
| | 95% centile | 5.35 | 6.33 | 0.962 | 16.9 |
| | 97.5% centile | 5.89 | 6.97 | 1.050 | 17.3 |
| 0.1 | Mean | 2.57 | 3.04 | 0.466 | 15.4 |
| | 2.5% centile | –1.04 | –1.24 | –0.190 | 13.9 |
| | 5% centile | –0.46 | –0.54 | –0.084 | 14.1 |
| | 50% centile | 2.60 | 3.08 | 0.474 | 15.3 |
| | 95% centile | 5.45 | 6.45 | 0.980 | 16.9 |
| | 97.5% centile | 5.96 | 7.05 | 1.066 | 17.3 |
| 1 | Mean | 5.56 | 6.59 | 1.033 | 15.7 |
| | 2.5% centile | 4.22 | 5.02 | 0.814 | 14.3 |
| | 5% centile | 4.43 | 5.26 | 0.847 | 14.5 |
| | 50% centile | 5.54 | 6.58 | 1.031 | 15.6 |
| | 95% centile | 6.75 | 8.00 | 1.224 | 17.3 |
| | 97.5% centile | 6.98 | 8.27 | 1.261 | 17.6 |
| **United Kingdom** | | | | | |
| 0.01 | Mean | 2.07 | 2.50 | 0.348 | 14.0 |
| | 2.5% centile | –2.74 | –3.31 | –0.462 | 12.5 |
| | 5% centile | –1.92 | –2.32 | –0.327 | 12.8 |
| | 50% centile | 2.17 | 2.61 | 0.366 | 14.0 |
| | 95% centile | 5.70 | 6.87 | 0.952 | 15.7 |
| | 97.5% centile | 6.29 | 7.57 | 1.039 | 16.1 |

| *Test dose, $D_t$ (Sv)* | *Mean/centile* | *Per cent excess cancer deaths ($Sv^{-1}$)* | *Per cent radiation-induced cancer deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/radiation-induced cancer death (a)* |
|---|---|---|---|---|---|
| 0.1 | Mean | 2.74 | 3.30 | 0.461 | 14.1 |
| | 2.5% centile | –1.11 | –1.34 | –0.187 | 12.6 |
| | 5% centile | –0.49 | –0.59 | –0.083 | 12.8 |
| | 50% centile | 2.77 | 3.34 | 0.470 | 14.0 |
| | 95% centile | 5.82 | 7.01 | 0.970 | 15.7 |
| | 97.5% centile | 6.37 | 7.66 | 1.055 | 16.1 |
| 1 | Mean | 5.90 | 7.12 | 1.022 | 14.4 |
| | 2.5% centile | 4.45 | 5.38 | 0.805 | 13.0 |
| | 5% centile | 4.67 | 5.65 | 0.839 | 13.2 |
| | 50% centile | 5.88 | 7.10 | 1.020 | 14.3 |
| | 95% centile | 7.19 | 8.67 | 1.212 | 16.0 |
| | 97.5% centile | 7.45 | 8.97 | 1.248 | 16.5 |

**Table 64 Distribution of solid cancer mortality risk estimates for various current populations, using generalized linear–quadratic ERR models fitted by Bayesian MCMC (models described in appendix E)**

Risk estimates are calculated for a population in equilibrium (underlying mortality rates and population structure of current Chinese, Japanese, Puerto Rican, United States and United Kingdom populations) from various models fitted to LSS mortality data [P10], assuming 35% GSD errors

| *Test dose, $D_t$ (Sv)* | *Mean/centile* | *Per cent excess cancer deaths ($Sv^{-1}$)* | *Per cent radiation-induced cancer deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/radiation-induced cancer death (a)* |
|---|---|---|---|---|---|
| **China** | | | | | |
| 0.01 | Mean | 3.60 | 4.09 | 0.624 | 15.3 |
| | 2.5% centile | 1.60 | 1.82 | 0.280 | 13.7 |
| | 5% centile | 1.90 | 2.15 | 0.332 | 14.0 |
| | 50% centile | 3.57 | 4.06 | 0.620 | 15.2 |
| | 95% centile | 5.41 | 6.16 | 0.929 | 16.9 |
| | 97.5% centile | 5.76 | 6.55 | 0.986 | 17.3 |
| 0.1 | Mean | 3.70 | 4.21 | 0.642 | 15.3 |
| | 2.5% centile | 1.82 | 2.07 | 0.318 | 13.8 |
| | 5% centile | 2.10 | 2.38 | 0.367 | 14.0 |
| | 50% centile | 3.67 | 4.17 | 0.638 | 15.2 |
| | 95% centile | 5.41 | 6.14 | 0.929 | 16.9 |
| | 97.5% centile | 5.74 | 6.52 | 0.982 | 17.3 |
| 1 | Mean | 4.59 | 5.23 | 0.812 | 15.6 |
| | 2.5% centile | 3.52 | 4.00 | 0.634 | 14.0 |
| | 5% centile | 3.69 | 4.20 | 0.662 | 14.2 |
| | 50% centile | 4.58 | 5.22 | 0.811 | 15.5 |
| | 95% centile | 5.54 | 6.30 | 0.966 | 17.2 |
| | 97.5% centile | 5.72 | 6.51 | 0.996 | 17.6 |

| *Test dose, $D_t$ (Sv)* | *Mean/centile* | *Per cent excess cancer deaths ($Sv^{-1}$)* | *Per cent radiation-induced cancer deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/radiation-induced cancer death (a)* |
|---|---|---|---|---|---|
| **Japan** | | | | | |
| 0.01 | Mean | 4.03 | 4.81 | 0.715 | 14.9 |
| | 2.5% centile | 1.78 | 2.12 | 0.322 | 13.5 |
| | 5% centile | 2.09 | 2.50 | 0.381 | 13.7 |
| | 50% centile | 3.98 | 4.75 | 0.710 | 14.9 |
| | 95% centile | 6.12 | 7.31 | 1.064 | 16.5 |
| | 97.5% centile | 6.53 | 7.80 | 1.131 | 16.8 |
| 0.1 | Mean | 4.14 | 4.94 | 0.736 | 15.0 |
| | 2.5% centile | 2.01 | 2.41 | 0.365 | 13.5 |
| | 5% centile | 2.31 | 2.75 | 0.420 | 13.7 |
| | 50% centile | 4.09 | 4.89 | 0.731 | 14.9 |
| | 95% centile | 6.10 | 7.29 | 1.064 | 16.5 |
| | 97.5% centile | 6.50 | 7.76 | 1.125 | 16.9 |
| 1 | Mean | 5.08 | 6.08 | 0.924 | 15.3 |
| | 2.5% centile | 3.80 | 4.55 | 0.723 | 13.8 |
| | 5% centile | 4.00 | 4.79 | 0.755 | 14.0 |
| | 50% centile | 5.06 | 6.06 | 0.923 | 15.2 |
| | 95% centile | 6.23 | 7.45 | 1.098 | 16.8 |
| | 97.5% centile | 6.46 | 7.73 | 1.132 | 17.1 |
| **Puerto Rico** | | | | | |
| 0.01 | Mean | 3.14 | 3.61 | 0.534 | 14.9 |
| | 2.5% centile | 1.39 | 1.60 | 0.241 | 13.2 |
| | 5% centile | 1.64 | 1.89 | 0.286 | 13.5 |
| | 50% centile | 3.10 | 3.57 | 0.531 | 14.8 |
| | 95% centile | 4.73 | 5.45 | 0.792 | 16.6 |
| | 97.5% centile | 5.04 | 5.81 | 0.839 | 17.0 |
| 0.1 | Mean | 3.22 | 3.71 | 0.550 | 14.9 |
| | 2.5% centile | 1.58 | 1.82 | 0.274 | 13.3 |
| | 5% centile | 1.81 | 2.09 | 0.316 | 13.5 |
| | 50% centile | 3.19 | 3.68 | 0.546 | 14.8 |
| | 95% centile | 4.72 | 5.45 | 0.792 | 16.6 |
| | 97.5% centile | 5.03 | 5.79 | 0.836 | 17.0 |
| 1 | Mean | 4.01 | 4.62 | 0.696 | 15.1 |
| | 2.5% centile | 3.04 | 3.50 | 0.548 | 13.5 |
| | 5% centile | 3.19 | 3.67 | 0.571 | 13.8 |
| | 50% centile | 3.99 | 4.60 | 0.696 | 15.0 |
| | 95% centile | 4.87 | 5.62 | 0.824 | 16.8 |
| | 97.5% centile | 5.05 | 5.82 | 0.848 | 17.3 |
| **United States** | | | | | |
| 0.01 | Mean | 4.14 | 4.89 | 0.744 | 15.3 |
| | 2.5% centile | 1.84 | 2.17 | 0.337 | 13.8 |
| | 5% centile | 2.17 | 2.56 | 0.398 | 14.0 |
| | 50% centile | 4.09 | 4.84 | 0.739 | 15.2 |
| | 95% centile | 6.24 | 7.37 | 1.102 | 16.8 |
| | 97.5% centile | 6.64 | 7.85 | 1.168 | 17.1 |

| *Test dose, $D_t$ (Sv)* | *Mean/centile* | *Per cent excess cancer deaths ($Sv^{-1}$)* | *Per cent radiation-induced cancer deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/radiation-induced cancer death (a)* |
|---|---|---|---|---|---|
| 0.1 | Mean | 4.24 | 5.02 | 0.765 | 15.3 |
| | 2.5% centile | 2.09 | 2.47 | 0.382 | 13.9 |
| | 5% centile | 2.39 | 2.83 | 0.440 | 14.1 |
| | 50% centile | 4.20 | 4.97 | 0.760 | 15.2 |
| | 95% centile | 6.22 | 7.35 | 1.101 | 16.8 |
| | 97.5% centile | 6.60 | 7.80 | 1.162 | 17.1 |
| 1 | Mean | 5.20 | 6.16 | 0.957 | 15.6 |
| | 2.5% centile | 3.96 | 4.70 | 0.756 | 14.2 |
| | 5% centile | 4.15 | 4.92 | 0.787 | 14.4 |
| | 50% centile | 5.18 | 6.14 | 0.957 | 15.5 |
| | 95% centile | 6.30 | 7.46 | 1.131 | 17.1 |
| | 97.5% centile | 6.52 | 7.71 | 1.165 | 17.4 |
| **United Kingdom** | | | | | |
| 0.01 | Mean | 4.42 | 5.31 | 0.736 | 13.9 |
| | 2.5% centile | 1.96 | 2.35 | 0.334 | 12.5 |
| | 5% centile | 2.30 | 2.77 | 0.394 | 12.7 |
| | 50% centile | 4.36 | 5.25 | 0.731 | 13.9 |
| | 95% centile | 6.67 | 8.02 | 1.091 | 15.5 |
| | 97.5% centile | 7.11 | 8.54 | 1.156 | 15.9 |
| 0.1 | Mean | 4.53 | 5.45 | 0.757 | 14.0 |
| | 2.5% centile | 2.22 | 2.67 | 0.377 | 12.5 |
| | 5% centile | 2.54 | 3.06 | 0.436 | 12.7 |
| | 50% centile | 4.48 | 5.39 | 0.752 | 13.9 |
| | 95% centile | 6.65 | 7.99 | 1.090 | 15.5 |
| | 97.5% centile | 7.08 | 8.51 | 1.150 | 15.9 |
| 1 | Mean | 5.52 | 6.66 | 0.948 | 14.3 |
| | 2.5% centile | 4.18 | 5.04 | 0.749 | 12.9 |
| | 5% centile | 4.38 | 5.29 | 0.779 | 13.1 |
| | 50% centile | 5.50 | 6.64 | 0.947 | 14.2 |
| | 95% centile | 6.72 | 8.09 | 1.120 | 15.8 |
| | 97.5% centile | 6.96 | 8.38 | 1.153 | 16.2 |

**Table 65 Risk estimates for leukaemia mortality in various current populations, using generalized ERR and generalized EAR models (models described in table 46)**

Risk estimates are calculated for a population in equilibrium (underlying mortality rates and population structure of current Chinese, Japanese, Puerto Rican, United States and United Kingdom populations) from various models fitted to LSS mortality data [P10], assuming 35% GSD errors

| *Model, modifying factors*[a] | *Test dose, $D_t$ (Sv)* | *Per cent excess cancer deaths ($Sv^{-1}$)* | *Per cent radiation-induced leukaemia deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/ radiation-induced leukaemia death (a)* |
|---|---|---|---|---|---|
| **China** | | | | | |
| ERR, $D^2$, age[b] | 0.01 | 0.00 | 0.00 | 0.002 | 36.9 |
| | 0.1 | 0.04 | 0.04 | 0.016 | 36.9 |
| | 1.0 | 0.42 | 0.42 | 0.155 | 36.9 |
| ERR, $D + D^2$, age[c] | 0.01 | 0.27 | 0.27 | 0.104 | 38.8 |
| | 0.1 | 0.29 | 0.30 | 0.114 | 38.8 |
| | 1.0 | 0.57 | 0.57 | 0.222 | 38.8 |
| EAR, $D^2$, sex, years SE[d] | 0.01 | 0.01 | 0.01 | 0.002 | 30.8 |
| | 0.1 | 0.07 | 0.07 | 0.022 | 30.8 |
| | 1.0 | 0.70 | 0.70 | 0.217 | 30.8 |
| EAR, $D + D^2$, sex, years SE[e] | 0.01 | 0.42 | 0.42 | 0.128 | 30.5 |
| | 0.1 | 0.46 | 0.46 | 0.140 | 30.5 |
| | 1.0 | 0.84 | 0.84 | 0.257 | 30.5 |
| **Japan** | | | | | |
| ERR, $D^2$, age[b] | 0.01 | 0.01 | 0.01 | 0.001 | 27.0 |
| | 0.1 | 0.05 | 0.05 | 0.014 | 27.0 |
| | 1.0 | 0.53 | 0.53 | 0.143 | 27.0 |
| ERR, $D + D^2$, age[c] | 0.01 | 0.32 | 0.32 | 0.092 | 28.6 |
| | 0.1 | 0.36 | 0.36 | 0.102 | 28.6 |
| | 1.0 | 0.69 | 0.69 | 0.198 | 28.6 |
| EAR, $D^2$, sex, years SE[d] | 0.01 | 0.01 | 0.01 | 0.002 | 32.6 |
| | 0.1 | 0.07 | 0.07 | 0.024 | 32.6 |
| | 1.0 | 0.72 | 0.72 | 0.234 | 32.6 |
| EAR, $D + D^2$, sex, years SE[e] | 0.01 | 0.43 | 0.43 | 0.139 | 32.2 |
| | 0.1 | 0.47 | 0.47 | 0.151 | 32.2 |
| | 1.0 | 0.86 | 0.86 | 0.278 | 32.2 |
| **Puerto Rico** | | | | | |
| ERR, $D^2$, age[b] | 0.01 | 0.01 | 0.01 | 0.001 | 20.2 |
| | 0.1 | 0.06 | 0.06 | 0.012 | 20.2 |
| | 1.0 | 0.58 | 0.58 | 0.118 | 20.3 |
| ERR, $D + D^2$, age[c] | 0.01 | 0.35 | 0.35 | 0.075 | 21.6 |
| | 0.1 | 0.38 | 0.39 | 0.083 | 21.6 |
| | 1.0 | 0.74 | 0.75 | 0.161 | 21.6 |
| EAR, $D^2$, sex, years SE[d] | 0.01 | 0.01 | 0.01 | 0.002 | 31.3 |
| | 0.1 | 0.07 | 0.07 | 0.022 | 31.3 |
| | 1.0 | 0.69 | 0.69 | 0.217 | 31.3 |

| *Model, modifying factors*[a] | *Test dose, $D_t$ (Sv)* | *Per cent excess cancer deaths ($Sv^{-1}$)* | *Per cent radiation-induced leukaemia deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/ radiation-induced leukaemia death (a)* |
|---|---|---|---|---|---|
| EAR, $D + D^2$, sex, years SE[e] | 0.01 | 0.41 | 0.41 | 0.128 | 30.9 |
| | 0.1 | 0.45 | 0.45 | 0.140 | 30.9 |
| | 1.0 | 0.83 | 0.83 | 0.257 | 31.0 |
| **United States** | | | | | |
| ERR, $D^2$, age[b] | 0.01 | 0.01 | 0.01 | 0.001 | 18.8 |
| | 0.1 | 0.08 | 0.08 | 0.015 | 18.8 |
| | 1.0 | 0.78 | 0.79 | 0.149 | 18.9 |
| ERR, $D + D^2$, age[c] | 0.01 | 0.47 | 0.47 | 0.093 | 19.7 |
| | 0.1 | 0.52 | 0.52 | 0.102 | 19.7 |
| | 1.0 | 1.00 | 1.01 | 0.199 | 19.7 |
| EAR, $D^2$, sex, years SE[d] | 0.01 | 0.01 | 0.01 | 0.002 | 31.7 |
| | 0.1 | 0.07 | 0.07 | 0.023 | 31.7 |
| | 1.0 | 0.70 | 0.71 | 0.224 | 31.7 |
| EAR, $D + D^2$, sex, years SE[e] | 0.01 | 0.42 | 0.42 | 0.133 | 31.4 |
| | 0.1 | 0.46 | 0.46 | 0.145 | 31.4 |
| | 1.0 | 0.84 | 0.85 | 0.266 | 31.4 |
| **United Kingdom** | | | | | |
| ERR, $D^2$, age[b] | 0.01 | 0.01 | 0.01 | 0.001 | 18.8 |
| | 0.1 | 0.06 | 0.06 | 0.012 | 18.8 |
| | 1.0 | 0.64 | 0.64 | 0.120 | 18.8 |
| ERR, $D + D^2$, age[c] | 0.01 | 0.38 | 0.38 | 0.075 | 19.8 |
| | 0.1 | 0.42 | 0.42 | 0.083 | 19.8 |
| | 1.0 | 0.81 | 0.82 | 0.162 | 19.8 |
| EAR, $D^2$, sex, years SE[d] | 0.01 | 0.01 | 0.01 | 0.002 | 31.9 |
| | 0.1 | 0.07 | 0.07 | 0.023 | 31.9 |
| | 1.0 | 0.71 | 0.71 | 0.228 | 32.0 |
| EAR, $D + D^2$, sex, years SE[e] | 0.01 | 0.43 | 0.43 | 0.135 | 31.6 |
| | 0.1 | 0.46 | 0.47 | 0.147 | 31.6 |
| | 1.0 | 0.85 | 0.86 | 0.271 | 31.6 |

[a] ERR = generalized excess relative risk, EAR = generalized excess absolute risk, years SE = years since exposure.

[b] ERR = $\beta D^2 a^{\tau}$, as per model (17) with linear coefficient in dose, $\alpha$, set to 0 ($a$ = attained age).

[c] ERR = $\alpha[D+\beta D^2] a^{\tau}$, as per model (17) ($a$ = attained age).

[d] EAR = $\beta_s D^2 [a - e]^{\kappa}$, as per model (18) ($a$ = attained age, $e$ = age at exposure, $s$ = sex).

[e] EAR = $\alpha_s [D+\beta D^2] [a - e]^{\kappa}$, as per model (18) with linear coefficient in dose, $\alpha$, set to 0 ($a$ = attained age, $e$ = age at exposure).

**Table 66 Risk estimates for leukaemia mortality by sex for various current populations, assuming a test dose, $D_t$, of 0.1 Sv, using generalized ERR and generalized EAR models (models described in table 46)**

Risk estimates are calculated for a population in equilibrium (underlying mortality rates and population structure of current Chinese, Japanese, Puerto Rican, United States and United Kingdom populations) from various models fitted to LSS mortality data [P10], assuming 35% GSD errors

| *Model, modifying factors*[a] | *Sex* | *Per cent excess leukaemia deaths ($Sv^{-1}$)* | *Per cent radiation-induced leukaemia deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/ radiation-induced leukaemia death (a)* |
|---|---|---|---|---|---|
| **China** | | | | | |
| ERR, $D^2$, age[b] | Males | 0.05 | 0.05 | 0.017 | 35.5 |
| | Females | 0.04 | 0.04 | 0.014 | 38.9 |
| | Both | 0.04 | 0.04 | 0.016 | 36.9 |
| ERR, $D + D^2$, age[c] | Males | 0.34 | 0.34 | 0.126 | 37.3 |
| | Females | 0.25 | 0.25 | 0.102 | 40.8 |
| | Both | 0.29 | 0.30 | 0.114 | 38.8 |
| EAR, $D^2$, sex, years SE[d] | Males | 0.09 | 0.09 | 0.026 | 30.2 |
| | Females | 0.05 | 0.05 | 0.017 | 31.8 |
| | Both | 0.07 | 0.07 | 0.022 | 30.8 |
| EAR, $D + D^2$, sex, years SE[e] | Males | 0.57 | 0.57 | 0.170 | 29.9 |
| | Females | 0.35 | 0.35 | 0.109 | 31.5 |
| | Both | 0.46 | 0.46 | 0.140 | 30.5 |
| **Japan** | | | | | |
| ERR, $D^2$, age[b] | Males | 0.06 | 0.06 | 0.016 | 25.4 |
| | Females | 0.04 | 0.04 | 0.013 | 29.3 |
| | Both | 0.05 | 0.05 | 0.014 | 27.0 |
| ERR, $D + D^2$, age[c] | Males | 0.42 | 0.42 | 0.114 | 26.9 |
| | Females | 0.29 | 0.29 | 0.090 | 31.0 |
| | Both | 0.36 | 0.36 | 0.102 | 28.6 |
| EAR, $D^2$, sex, years SE[d] | Males | 0.09 | 0.09 | 0.028 | 31.6 |
| | Females | 0.06 | 0.06 | 0.019 | 34.2 |
| | Both | 0.07 | 0.07 | 0.024 | 32.6 |
| EAR, $D + D^2$, sex, years SE[e] | Males | 0.58 | 0.58 | 0.182 | 31.2 |
| | Females | 0.36 | 0.36 | 0.121 | 33.7 |
| | Both | 0.47 | 0.47 | 0.151 | 32.2 |
| **Puerto Rico** | | | | | |
| ERR, $D^2$, age[b] | Males | 0.51 | 0.07 | 20.227 | 0.0 |
| | Females | 0.34 | 0.06 | 20.261 | 0.0 |
| | Both | 0.06 | 0.06 | 0.012 | 20.2 |
| ERR, $D + D^2$, age[c] | Males | 0.51 | 0.45 | 21.656 | 0.0 |
| | Females | 0.34 | 0.39 | 21.415 | 0.0 |
| | Both | 0.38 | 0.39 | 0.083 | 21.6 |
| EAR, $D^2$, sex, years SE[d] | Males | 0.51 | 0.09 | 30.320 | 0.0 |
| | Females | 0.34 | 0.05 | 32.697 | 0.0 |
| | Both | 0.07 | 0.07 | 0.022 | 31.3 |
| EAR, $D + D^2$, sex, years SE[e] | Males | 0.51 | 0.56 | 29.991 | 0.0 |
| | Females | 0.34 | 0.35 | 32.316 | 0.0 |
| | Both | 0.45 | 0.45 | 0.140 | 30.9 |

| *Model, modifying factors*[a] | *Sex* | *Per cent excess leukaemia deaths ($Sv^{-1}$)* | *Per cent radiation-induced leukaemia deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/ radiation-induced leukaemia death (a)* |
|---|---|---|---|---|---|
| **United States** | | | | | |
| ERR, $D^2$, age[b] | Males | 0.09 | 0.09 | 0.017 | 18.2 |
| | Females | 0.07 | 0.07 | 0.013 | 19.7 |
| | Both | 0.08 | 0.08 | 0.015 | 18.8 |
| ERR, $D + D^2$, age[c] | Males | 0.59 | 0.60 | 0.114 | 19.0 |
| | Females | 0.44 | 0.44 | 0.091 | 20.6 |
| | Both | 0.52 | 0.52 | 0.102 | 19.7 |
| EAR, $D^2$, sex, years SE[d] | Males | 0.09 | 0.09 | 0.027 | 31.0 |
| | Females | 0.05 | 0.05 | 0.018 | 32.9 |
| | Both | 0.07 | 0.07 | 0.023 | 31.7 |
| EAR, $D + D^2$, sex, years SE[e] | Males | 0.57 | 0.57 | 0.176 | 30.7 |
| | Females | 0.35 | 0.35 | 0.114 | 32.5 |
| | Both | 0.46 | 0.46 | 0.145 | 31.4 |
| **United Kingdom** | | | | | |
| ERR, $D^2$, age[b] | Males | 0.08 | 0.08 | 0.014 | 18.4 |
| | Females | 0.05 | 0.05 | 0.010 | 19.4 |
| | Both | 0.06 | 0.06 | 0.012 | 18.8 |
| ERR, $D + D^2$, age[c] | Males | 0.50 | 0.50 | 0.097 | 19.3 |
| | Females | 0.34 | 0.34 | 0.069 | 20.4 |
| | Both | 0.42 | 0.42 | 0.083 | 19.8 |
| EAR, $D^2$, sex, years SE[d] | Males | 0.09 | 0.09 | 0.028 | 31.4 |
| | Females | 0.05 | 0.05 | 0.018 | 32.9 |
| | Both | 0.07 | 0.07 | 0.023 | 31.9 |
| EAR, $D + D^2$, sex, years SE[e] | Males | 0.58 | 0.58 | 0.180 | 31.0 |
| | Females | 0.35 | 0.35 | 0.115 | 32.5 |
| | Both | 0.46 | 0.47 | 0.147 | 31.6 |

[a] ERR = generalized excess relative risk, EAR = generalized excess absolute risk, years SE = years since exposure.

[b] ERR = $\beta D^2 a^{\tau}$, as per model (17) with linear coefficient in dose, $\alpha$, set to 0 ($a$ = attained age).

[c] ERR = $\alpha[D+\beta D^2] a^{\tau}$, as per model (17) ($a$ = attained age).

[d] EAR = $\beta_s D^2 [a - e]^{\kappa}$, as per model (18) ($a$ = attained age, $e$ = age at exposure, $s$ = sex).

[e] EAR = $\alpha_s [D+\beta D^2] [a - e]^{\kappa}$, as per model (18) with linear coefficient in dose, $\alpha$, set to 0 ($a$ = attained age, $e$ = age at exposure).

**Table 67 Risk estimates for leukaemia mortality by age-at-exposure group in various current populations, assuming a test dose, $D_t$, of 0.1 Sv, using generalized ERR and generalized EAR models (models described in table 46)**

Risk estimates are calculated for a population in equilibrium (underlying mortality rates and population structure of current Chinese, Japanese, Puerto Rican, United States and United Kingdom populations) from various models fitted to LSS mortality data [P10], assuming 35% GSD errors

| *Model, modifying factors*[a] | *Age at exposure* | *Per cent excess leukaemia deaths ($Sv^{-1}$)* | *Per cent radiation-induced leukaemia deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/ radiation-induced leukaemia death (a)* |
|---|---|---|---|---|---|
| **China** | | | | | |
| ERR, $D^2$, age[b] | 0–9 | 0.13 | 0.13 | 0.071 | 53.0 |
| | 10–19 | 0.06 | 0.06 | 0.024 | 37.5 |
| | 20–29 | 0.04 | 0.04 | 0.011 | 27.4 |
| | 30–39 | 0.03 | 0.03 | 0.007 | 21.2 |
| | 40–49 | 0.02 | 0.02 | 0.004 | 16.4 |
| | 50–59 | 0.02 | 0.02 | 0.002 | 12.4 |
| | 60–69 | 0.01 | 0.01 | 0.001 | 9.4 |
| | 70+ | 0.01 | 0.01 | 0.000 | 6.7 |
| | All ages | 0.04 | 0.04 | 0.016 | 36.9 |
| ERR, $D + D^2$, age[c] | 0–9 | 0.99 | 0.99 | 0.542 | 54.6 |
| | 10–19 | 0.43 | 0.43 | 0.166 | 38.4 |
| | 20–29 | 0.27 | 0.27 | 0.076 | 27.9 |
| | 30–39 | 0.20 | 0.20 | 0.043 | 21.5 |
| | 40–49 | 0.15 | 0.15 | 0.025 | 16.5 |
| | 50–59 | 0.11 | 0.11 | 0.014 | 12.4 |
| | 60–69 | 0.08 | 0.08 | 0.008 | 9.5 |
| | 70+ | 0.04 | 0.04 | 0.003 | 6.7 |
| | All ages | 0.29 | 0.30 | 0.114 | 38.8 |
| EAR, $D^2$, sex, years SE[d] | 0–9 | 0.10 | 0.10 | 0.049 | 47.1 |
| | 10–19 | 0.10 | 0.10 | 0.039 | 40.4 |
| | 20–29 | 0.09 | 0.09 | 0.030 | 33.9 |
| | 30–39 | 0.08 | 0.08 | 0.022 | 27.5 |
| | 40–49 | 0.07 | 0.07 | 0.015 | 21.5 |
| | 50–59 | 0.06 | 0.06 | 0.009 | 15.8 |
| | 60–69 | 0.04 | 0.04 | 0.005 | 11.0 |
| | 70+ | 0.02 | 0.02 | 0.002 | 7.0 |
| | All ages | 0.07 | 0.07 | 0.022 | 30.8 |
| EAR, $D + D^2$, sex, years SE[e] | 0–9 | 0.68 | 0.68 | 0.315 | 46.2 |
| | 10–19 | 0.63 | 0.63 | 0.251 | 39.7 |
| | 20–29 | 0.57 | 0.57 | 0.191 | 33.3 |
| | 30–39 | 0.51 | 0.51 | 0.138 | 27.1 |
| | 40–49 | 0.44 | 0.44 | 0.093 | 21.1 |
| | 50–59 | 0.36 | 0.36 | 0.056 | 15.6 |
| | 60–69 | 0.27 | 0.27 | 0.029 | 10.9 |
| | 70+ | 0.15 | 0.15 | 0.010 | 6.9 |
| | All ages | 0.46 | 0.46 | 0.140 | 30.5 |

| *Model, modifying factors*[a] | *Age at exposure* | *Per cent excess leukaemia deaths ($Sv^{-1}$)* | *Per cent radiation-induced leukaemia deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/ radiation-induced leukaemia death (a)* |
|---|---|---|---|---|---|
| **Japan** | | | | | |
| ERR, $D^2$, age[b] | 0–9 | 0.12 | 0.12 | 0.054 | 46.1 |
| | 10–19 | 0.07 | 0.07 | 0.022 | 30.1 |
| | 20–29 | 0.06 | 0.06 | 0.014 | 23.0 |
| | 30–39 | 0.05 | 0.05 | 0.010 | 19.2 |
| | 40–49 | 0.05 | 0.05 | 0.007 | 16.1 |
| | 50–59 | 0.04 | 0.04 | 0.005 | 13.5 |
| | 60–69 | 0.03 | 0.03 | 0.003 | 10.7 |
| | 70+ | 0.02 | 0.02 | 0.001 | 7.6 |
| | All ages | 0.05 | 0.05 | 0.014 | 27.0 |
| ERR, $D + D^2$, age[c] | 0–9 | 0.84 | 0.85 | 0.410 | 48.4 |
| | 10–19 | 0.48 | 0.49 | 0.151 | 31.0 |
| | 20–29 | 0.39 | 0.39 | 0.091 | 23.5 |
| | 30–39 | 0.34 | 0.34 | 0.066 | 19.5 |
| | 40–49 | 0.29 | 0.30 | 0.048 | 16.3 |
| | 50–59 | 0.25 | 0.25 | 0.034 | 13.6 |
| | 60–69 | 0.20 | 0.20 | 0.021 | 10.7 |
| | 70+ | 0.10 | 0.10 | 0.008 | 7.7 |
| | All ages | 0.36 | 0.36 | 0.102 | 28.6 |
| EAR, $D^2$, sex, years SE[d] | 0–9 | 0.11 | 0.11 | 0.053 | 50.2 |
| | 10–19 | 0.10 | 0.10 | 0.043 | 43.5 |
| | 20–29 | 0.09 | 0.09 | 0.034 | 36.8 |
| | 30–39 | 0.08 | 0.08 | 0.025 | 30.4 |
| | 40–49 | 0.07 | 0.07 | 0.018 | 24.2 |
| | 50–59 | 0.06 | 0.06 | 0.011 | 18.4 |
| | 60–69 | 0.05 | 0.05 | 0.006 | 13.2 |
| | 70+ | 0.03 | 0.03 | 0.002 | 8.2 |
| | All ages | 0.07 | 0.07 | 0.024 | 32.6 |
| EAR, $D + D^2$, sex, years SE[e] | 0–9 | 0.70 | 0.70 | 0.345 | 49.2 |
| | 10–19 | 0.65 | 0.65 | 0.278 | 42.6 |
| | 20–29 | 0.60 | 0.60 | 0.216 | 36.2 |
| | 30–39 | 0.54 | 0.54 | 0.160 | 29.8 |
| | 40–49 | 0.47 | 0.47 | 0.112 | 23.8 |
| | 50–59 | 0.39 | 0.39 | 0.071 | 18.1 |
| | 60–69 | 0.31 | 0.31 | 0.040 | 13.0 |
| | 70+ | 0.17 | 0.17 | 0.014 | 8.2 |
| | All ages | 0.47 | 0.47 | 0.151 | 32.2 |

| *Model, modifying factors*[a] | *Age at exposure* | *Per cent excess leukaemia deaths ($Sv^{-1}$)* | *Per cent radiation-induced leukaemia deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/ radiation-induced leukaemia death (a)* |
|---|---|---|---|---|---|
| **Puerto Rico** | | | | | |
| ERR, $D^2$, age[b] | 0–9 | 0.10 | 0.10 | 0.040 | 38.0 |
| | 10–19 | 0.07 | 0.07 | 0.015 | 22.3 |
| | 20–29 | 0.06 | 0.06 | 0.011 | 17.9 |
| | 30–39 | 0.05 | 0.06 | 0.008 | 15.0 |
| | 40–49 | 0.05 | 0.05 | 0.007 | 12.7 |
| | 50–59 | 0.05 | 0.05 | 0.005 | 11.1 |
| | 60–69 | 0.04 | 0.04 | 0.004 | 9.1 |
| | 70+ | 0.03 | 0.03 | 0.002 | 7.1 |
| | All ages | 0.06 | 0.06 | 0.012 | 20.2 |
| ERR, $D + D^2$, age[c] | 0–9 | 0.74 | 0.74 | 0.300 | 40.5 |
| | 10–19 | 0.44 | 0.44 | 0.101 | 23.0 |
| | 20–29 | 0.38 | 0.39 | 0.071 | 18.3 |
| | 30–39 | 0.36 | 0.36 | 0.054 | 15.2 |
| | 40–49 | 0.33 | 0.33 | 0.043 | 12.8 |
| | 50–59 | 0.31 | 0.31 | 0.035 | 11.1 |
| | 60–69 | 0.28 | 0.28 | 0.026 | 9.1 |
| | 70+ | 0.20 | 0.20 | 0.014 | 7.1 |
| | All ages | 0.38 | 0.39 | 0.083 | 21.6 |
| EAR, $D^2$, sex, years SE[d] | 0–9 | 0.10 | 0.10 | 0.047 | 47.0 |
| | 10–19 | 0.09 | 0.09 | 0.038 | 40.6 |
| | 20–29 | 0.08 | 0.09 | 0.029 | 34.4 |
| | 30–39 | 0.08 | 0.08 | 0.022 | 28.5 |
| | 40–49 | 0.07 | 0.07 | 0.015 | 22.8 |
| | 50–59 | 0.06 | 0.06 | 0.010 | 17.3 |
| | 60–69 | 0.04 | 0.04 | 0.006 | 12.6 |
| | 70+ | 0.03 | 0.03 | 0.002 | 7.9 |
| | All ages | 0.07 | 0.07 | 0.022 | 31.3 |
| EAR, $D + D^2$, sex, years SE[e] | 0–9 | 0.66 | 0.67 | 0.307 | 46.1 |
| | 10–19 | 0.61 | 0.61 | 0.245 | 39.8 |
| | 20–29 | 0.55 | 0.56 | 0.188 | 33.8 |
| | 30–39 | 0.50 | 0.50 | 0.140 | 28.0 |
| | 40–49 | 0.43 | 0.44 | 0.098 | 22.4 |
| | 50–59 | 0.36 | 0.36 | 0.062 | 17.1 |
| | 60–69 | 0.28 | 0.28 | 0.035 | 12.4 |
| | 70+ | 0.16 | 0.17 | 0.013 | 7.9 |
| | All ages | 0.45 | 0.45 | 0.140 | 30.9 |

| *Model, modifying factors*[a] | *Age at exposure* | *Per cent excess leukaemia deaths ($Sv^{-1}$)* | *Per cent radiation-induced leukaemia deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/ radiation-induced leukaemia death (a)* |
|---|---|---|---|---|---|
| **United States** | | | | | |
| ERR, $D^2$, age[b] | 0–9 | 0.12 | 0.12 | 0.040 | 32.3 |
| | 10–19 | 0.10 | 0.10 | 0.022 | 22.4 |
| | 20–29 | 0.09 | 0.09 | 0.016 | 18.1 |
| | 30–39 | 0.08 | 0.08 | 0.013 | 15.8 |
| | 40–49 | 0.08 | 0.08 | 0.011 | 13.9 |
| | 50–59 | 0.07 | 0.07 | 0.009 | 12.1 |
| | 60–69 | 0.06 | 0.06 | 0.006 | 10.0 |
| | 70+ | 0.04 | 0.04 | 0.003 | 7.4 |
| | All ages | 0.08 | 0.08 | 0.015 | 18.8 |
| ERR, $D + D^2$, age[c] | 0–9 | 0.85 | 0.85 | 0.293 | 34.4 |
| | 10–19 | 0.64 | 0.64 | 0.148 | 23.1 |
| | 20–29 | 0.56 | 0.57 | 0.105 | 18.4 |
| | 30–39 | 0.53 | 0.53 | 0.084 | 16.0 |
| | 40–49 | 0.49 | 0.49 | 0.069 | 14.0 |
| | 50–59 | 0.45 | 0.45 | 0.055 | 12.1 |
| | 60–69 | 0.39 | 0.39 | 0.039 | 10.0 |
| | 70+ | 0.23 | 0.23 | 0.017 | 7.4 |
| | All ages | 0.52 | 0.52 | 0.102 | 19.7 |
| EAR, $D^2$, sex, years SE[d] | 0–9 | 0.10 | 0.10 | 0.050 | 48.4 |
| | 10–19 | 0.10 | 0.10 | 0.040 | 41.7 |
| | 20–29 | 0.09 | 0.09 | 0.031 | 35.3 |
| | 30–39 | 0.08 | 0.08 | 0.023 | 29.0 |
| | 40–49 | 0.07 | 0.07 | 0.016 | 23.0 |
| | 50–59 | 0.06 | 0.06 | 0.010 | 17.4 |
| | 60–69 | 0.05 | 0.05 | 0.006 | 12.5 |
| | 70+ | 0.03 | 0.03 | 0.002 | 7.9 |
| | All ages | 0.07 | 0.07 | 0.023 | 31.7 |
| EAR, $D + D^2$, sex, years SE[e] | 0–9 | 0.68 | 0.68 | 0.324 | 47.4 |
| | 10–19 | 0.63 | 0.63 | 0.259 | 40.9 |
| | 20–29 | 0.57 | 0.58 | 0.200 | 34.6 |
| | 30–39 | 0.51 | 0.52 | 0.147 | 28.5 |
| | 40–49 | 0.45 | 0.45 | 0.101 | 22.6 |
| | 50–59 | 0.37 | 0.37 | 0.064 | 17.2 |
| | 60–69 | 0.29 | 0.29 | 0.036 | 12.4 |
| | 70+ | 0.17 | 0.17 | 0.013 | 7.9 |
| | All ages | 0.46 | 0.46 | 0.145 | 31.4 |

| *Model, modifying factors*[a] | *Age at exposure* | *Per cent excess leukaemia deaths ($Sv^{-1}$)* | *Per cent radiation-induced leukaemia deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/ radiation-induced leukaemia death (a)* |
|---|---|---|---|---|---|
| **United Kingdom** | | | | | |
| ERR, $D^2$, age[b] | 0–9 | 0.11 | 0.11 | 0.036 | 34.2 |
| | 10–19 | 0.08 | 0.08 | 0.017 | 21.9 |
| | 20–29 | 0.07 | 0.07 | 0.012 | 17.2 |
| | 30–39 | 0.07 | 0.07 | 0.010 | 15.0 |
| | 40–49 | 0.06 | 0.06 | 0.008 | 13.2 |
| | 50–59 | 0.06 | 0.06 | 0.007 | 11.4 |
| | 60–69 | 0.05 | 0.05 | 0.005 | 9.3 |
| | 70+ | 0.03 | 0.03 | 0.002 | 6.3 |
| | All ages | 0.06 | 0.06 | 0.012 | 18.8 |
| ERR, $D + D^2$, age[c] | 0–9 | 0.73 | 0.74 | 0.270 | 36.7 |
| | 10–19 | 0.52 | 0.52 | 0.118 | 22.7 |
| | 20–29 | 0.45 | 0.46 | 0.080 | 17.5 |
| | 30–39 | 0.43 | 0.43 | 0.065 | 15.2 |
| | 40–49 | 0.40 | 0.40 | 0.053 | 13.3 |
| | 50–59 | 0.37 | 0.37 | 0.042 | 11.5 |
| | 60–69 | 0.31 | 0.31 | 0.029 | 9.3 |
| | 70+ | 0.17 | 0.17 | 0.011 | 6.3 |
| | All ages | 0.42 | 0.42 | 0.083 | 19.8 |
| EAR, $D^2$, sex, years SE[d] | 0–9 | 0.10 | 0.10 | 0.052 | 49.2 |
| | 10–19 | 0.10 | 0.10 | 0.042 | 42.5 |
| | 20–29 | 0.09 | 0.09 | 0.032 | 35.9 |
| | 30–39 | 0.08 | 0.08 | 0.024 | 29.4 |
| | 40–49 | 0.07 | 0.07 | 0.017 | 23.2 |
| | 50–59 | 0.06 | 0.06 | 0.010 | 17.4 |
| | 60–69 | 0.05 | 0.05 | 0.006 | 12.1 |
| | 70+ | 0.03 | 0.03 | 0.002 | 7.1 |
| | All ages | 0.07 | 0.07 | 0.023 | 31.9 |
| EAR, $D + D^2$, sex, years SE[e] | 0–9 | 0.69 | 0.70 | 0.335 | 48.2 |
| | 10–19 | 0.64 | 0.65 | 0.269 | 41.6 |
| | 20–29 | 0.59 | 0.59 | 0.208 | 35.2 |
| | 30–39 | 0.53 | 0.53 | 0.153 | 28.9 |
| | 40–49 | 0.46 | 0.46 | 0.105 | 22.8 |
| | 50–59 | 0.38 | 0.38 | 0.065 | 17.1 |
| | 60–69 | 0.29 | 0.29 | 0.035 | 12.0 |
| | 70+ | 0.16 | 0.16 | 0.011 | 7.0 |
| | All ages | 0.46 | 0.47 | 0.147 | 31.6 |

[a] ERR = generalized excess relative risk, EAR = generalized excess absolute risk, years SE = years since exposure.

[b] ERR = $\beta D^2 a^{\tau}$, as per model (17) with linear coefficient in dose, $\alpha$, set to 0 ($a$ = attained age).

[c] ERR = $\alpha[D+\beta D^2] a^{\tau}$, as per model (17) ($a$ = attained age).

[d] EAR = $\beta_s D^2 [a - e]^{\kappa}$, as per model (18) ($a$ = attained age, $e$ = age at exposure, $s$ = sex).

[e] EAR = $\alpha_s [D+\beta D^2] [a - e]^{\kappa}$, as per model (18) with linear coefficient in dose, $\alpha$, set to 0 ($a$ = attained age, $e$ = age at exposure).

**Table 68 Distribution of leukaemia mortality risk estimates for various current populations, using generalized linear–quadratic–exponential ERR models fitted by Bayesian MCMC (models described in appendix E)**

Risk estimates are calculated for a population in equilibrium (underlying mortality rates and population structure of current Chinese, Japanese, Puerto Rican, United States and United Kingdom populations) from various models fitted to LSS mortality data [P10], assuming 35% GSD errors

| *Test dose, $D_t$ (Sv)* | *Mean/centile* | *Per cent excess leukaemia deaths ($Sv^{-1}$)* | *Per cent radiation-induced leukaemia deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/radiation-induced leukaemia death (a)* |
|---|---|---|---|---|---|
| **China** | | | | | |
| 0.01 | Mean | 0.01 | 0.01 | 0.014 | 38.7 |
| | 2.5% centile | –0.39 | –0.39 | –0.133 | 26.5 |
| | 5% centile | –0.34 | –0.34 | –0.119 | 27.8 |
| | 50% centile | –0.04 | –0.04 | –0.014 | 38.0 |
| | 95% centile | 0.53 | 0.53 | 0.226 | 52.3 |
| | 97.5% centile | 0.65 | 0.65 | 0.312 | 55.1 |
| 0.1 | Mean | 0.14 | 0.14 | 0.066 | 38.5 |
| | 2.5% centile | –0.20 | –0.20 | –0.058 | 26.4 |
| | 5% centile | –0.15 | –0.15 | –0.048 | 27.7 |
| | 50% centile | 0.09 | 0.09 | 0.034 | 37.5 |
| | 95% centile | 0.60 | 0.60 | 0.277 | 52.8 |
| | 97.5% centile | 0.74 | 0.74 | 0.373 | 55.7 |
| 1 | Mean | 0.88 | 0.88 | 0.360 | 38.8 |
| | 2.5% centile | 0.49 | 0.49 | 0.149 | 26.5 |
| | 5% centile | 0.53 | 0.53 | 0.164 | 27.8 |
| | 50% centile | 0.80 | 0.80 | 0.297 | 38.0 |
| | 95% centile | 1.48 | 1.48 | 0.767 | 52.7 |
| | 97.5% centile | 1.77 | 1.77 | 0.958 | 55.5 |
| **Japan** | | | | | |
| 0.01 | Mean | –0.01 | –0.01 | 0.008 | 29.4 |
| | 2.5% centile | –0.56 | –0.56 | –0.129 | 19.6 |
| | 5% centile | –0.47 | –0.47 | –0.113 | 20.4 |
| | 50% centile | –0.04 | –0.04 | –0.013 | 27.9 |
| | 95% centile | 0.59 | 0.59 | 0.188 | 44.0 |
| | 97.5% centile | 0.72 | 0.72 | 0.240 | 48.1 |
| 0.1 | Mean | 0.15 | 0.15 | 0.053 | 29.3 |
| | 2.5% centile | –0.29 | –0.29 | –0.063 | 19.5 |
| | 5% centile | –0.22 | –0.22 | –0.050 | 20.3 |
| | 50% centile | 0.11 | 0.11 | 0.032 | 27.6 |
| | 95% centile | 0.65 | 0.65 | 0.219 | 44.5 |
| | 97.5% centile | 0.77 | 0.77 | 0.281 | 48.9 |
| 1 | Mean | 1.03 | 1.03 | 0.312 | 29.6 |
| | 2.5% centile | 0.65 | 0.65 | 0.160 | 19.6 |
| | 5% centile | 0.70 | 0.70 | 0.174 | 20.5 |
| | 50% centile | 1.00 | 1.00 | 0.273 | 28.0 |
| | 95% centile | 1.44 | 1.44 | 0.577 | 44.6 |
| | 97.5% centile | 1.58 | 1.58 | 0.708 | 48.8 |

| *Test dose, $D_t$ (Sv)* | *Mean/centile* | *Per cent excess leukaemia deaths ($Sv^{-1}$)* | *Per cent radiation-induced leukaemia deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/radiation-induced leukaemia death (a)* |
|---|---|---|---|---|---|
| **Puerto Rico** | | | | | |
| 0.01 | Mean | –0.01 | –0.01 | 0.006 | 22.6 |
| | 2.5% centile | –0.64 | –0.64 | –0.109 | 14.5 |
| | 5% centile | –0.53 | –0.53 | –0.094 | 15.1 |
| | 50% centile | –0.05 | –0.05 | –0.011 | 21.0 |
| | 95% centile | 0.63 | 0.63 | 0.153 | 36.0 |
| | 97.5% centile | 0.76 | 0.76 | 0.195 | 40.2 |
| 0.1 | Mean | 0.16 | 0.16 | 0.043 | 22.5 |
| | 2.5% centile | –0.33 | –0.34 | –0.053 | 14.5 |
| | 5% centile | –0.25 | –0.25 | –0.041 | 15.1 |
| | 50% centile | 0.12 | 0.12 | 0.026 | 20.7 |
| | 95% centile | 0.69 | 0.69 | 0.178 | 36.5 |
| | 97.5% centile | 0.82 | 0.82 | 0.227 | 40.9 |
| 1 | Mean | 1.10 | 1.11 | 0.256 | 22.8 |
| | 2.5% centile | 0.70 | 0.70 | 0.136 | 14.6 |
| | 5% centile | 0.76 | 0.76 | 0.147 | 15.2 |
| | 50% centile | 1.08 | 1.09 | 0.225 | 21.1 |
| | 95% centile | 1.53 | 1.54 | 0.464 | 36.5 |
| | 97.5% centile | 1.64 | 1.65 | 0.569 | 40.6 |
| **United States** | | | | | |
| 0.01 | Mean | –0.03 | –0.03 | 0.002 | 20.5 |
| | 2.5% centile | –0.89 | –0.89 | –0.147 | 14.9 |
| | 5% centile | –0.73 | –0.73 | –0.124 | 15.3 |
| | 50% centile | –0.06 | –0.06 | –0.013 | 19.4 |
| | 95% centile | 0.81 | 0.82 | 0.176 | 29.8 |
| | 97.5% centile | 0.98 | 0.98 | 0.212 | 33.1 |
| 0.1 | Mean | 0.20 | 0.20 | 0.046 | 20.5 |
| | 2.5% centile | –0.47 | –0.47 | –0.075 | 14.9 |
| | 5% centile | –0.35 | –0.35 | –0.058 | 15.3 |
| | 50% centile | 0.16 | 0.16 | 0.032 | 19.2 |
| | 95% centile | 0.89 | 0.89 | 0.199 | 30.1 |
| | 97.5% centile | 1.05 | 1.06 | 0.235 | 33.7 |
| 1 | Mean | 1.46 | 1.46 | 0.301 | 20.7 |
| | 2.5% centile | 0.92 | 0.93 | 0.180 | 15.0 |
| | 5% centile | 0.99 | 1.00 | 0.194 | 15.4 |
| | 50% centile | 1.43 | 1.44 | 0.283 | 19.5 |
| | 95% centile | 2.01 | 2.02 | 0.461 | 30.3 |
| | 97.5% centile | 2.14 | 2.15 | 0.535 | 33.8 |

| *Test dose, $D_t$ (Sv)* | *Mean/centile* | *Per cent excess leukaemia deaths ($Sv^{-1}$)* | *Per cent radiation-induced leukaemia deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/radiation-induced leukaemia death (a)* |
|---|---|---|---|---|---|
| **United Kingdom** | | | | | |
| 0.01 | Mean | –0.02 | –0.02 | 0.003 | 20.8 |
| | 2.5% centile | –0.72 | –0.72 | –0.116 | 14.3 |
| | 5% centile | –0.59 | –0.59 | –0.098 | 14.8 |
| | 50% centile | –0.05 | –0.05 | –0.010 | 19.4 |
| | 95% centile | 0.66 | 0.67 | 0.148 | 31.8 |
| | 97.5% centile | 0.80 | 0.81 | 0.181 | 35.8 |
| 0.1 | Mean | 0.16 | 0.16 | 0.040 | 20.7 |
| | 2.5% centile | –0.38 | –0.38 | –0.058 | 14.3 |
| | 5% centile | –0.28 | –0.28 | –0.045 | 14.7 |
| | 50% centile | 0.13 | 0.13 | 0.026 | 19.2 |
| | 95% centile | 0.73 | 0.73 | 0.168 | 32.3 |
| | 97.5% centile | 0.87 | 0.87 | 0.203 | 36.7 |
| 1 | Mean | 1.19 | 1.20 | 0.250 | 21.0 |
| | 2.5% centile | 0.76 | 0.76 | 0.144 | 14.3 |
| | 5% centile | 0.81 | 0.82 | 0.155 | 14.8 |
| | 50% centile | 1.17 | 1.17 | 0.229 | 19.5 |
| | 95% centile | 1.64 | 1.65 | 0.410 | 32.5 |
| | 97.5% centile | 1.75 | 1.76 | 0.492 | 36.8 |

**Table 69 Distribution of leukaemia mortality risk estimates for various current populations, using generalized linear–quadratic ERR models fitted by Bayesian MCMC (models described in appendix E)**

Risk estimates are calculated for a population in equilibrium (underlying mortality rates and population structure of current Chinese, Japanese, Puerto Rican, United States and United Kingdom populations) from various models fitted to LSS mortality data [P10], assuming 35% GSD errors

| *Test dose, $D_t$ (Sv)* | *Mean/centile* | *Per cent excess leukaemia deaths ($Sv^{-1}$)* | *Per cent radiation-induced leukaemia deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/radiation-induced leukaemia death (a)* |
|---|---|---|---|---|---|
| **China** | | | | | |
| 0.01 | Mean | 0.37 | 0.37 | 0.167 | 40.8 |
| | 2.5% centile | –0.01 | –0.01 | –0.004 | 27.4 |
| | 5% centile | 0.03 | 0.03 | 0.011 | 28.9 |
| | 50% centile | 0.31 | 0.31 | 0.122 | 40.0 |
| | 95% centile | 0.87 | 0.87 | 0.453 | 55.3 |
| | 97.5% centile | 1.11 | 1.11 | 0.612 | 58.2 |
| 0.1 | Mean | 0.41 | 0.42 | 0.185 | 40.7 |
| | 2.5% centile | 0.04 | 0.04 | 0.014 | 27.4 |
| | 5% centile | 0.08 | 0.08 | 0.027 | 28.9 |
| | 50% centile | 0.35 | 0.35 | 0.137 | 40.0 |
| | 95% centile | 0.92 | 0.92 | 0.481 | 55.3 |
| | 97.5% centile | 1.16 | 1.17 | 0.649 | 58.2 |

| *Test dose, $D_t$ (Sv)* | *Mean/centile* | *Per cent excess leukaemia deaths ($Sv^{-1}$)* | *Per cent radiation-induced leukaemia deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/radiation-induced leukaemia death (a)* |
|---|---|---|---|---|---|
| 1 | Mean | 0.81 | 0.82 | 0.354 | 40.7 |
| | 2.5% centile | 0.43 | 0.43 | 0.132 | 27.4 |
| | 5% centile | 0.47 | 0.47 | 0.147 | 28.9 |
| | 50% centile | 0.72 | 0.72 | 0.285 | 40.0 |
| | 95% centile | 1.47 | 1.47 | 0.789 | 54.9 |
| | 97.5% centile | 1.79 | 1.79 | 1.019 | 57.7 |
| **Japan** | | | | | |
| 0.01 | Mean | 0.40 | 0.41 | 0.137 | 31.5 |
| | 2.5% centile | –0.01 | –0.01 | –0.004 | 20.1 |
| | 5% centile | 0.04 | 0.04 | 0.010 | 21.1 |
| | 50% centile | 0.37 | 0.37 | 0.109 | 29.7 |
| | 95% centile | 0.86 | 0.86 | 0.337 | 48.3 |
| | 97.5% centile | 0.99 | 0.99 | 0.440 | 52.9 |
| 0.1 | Mean | 0.45 | 0.45 | 0.151 | 31.5 |
| | 2.5% centile | 0.05 | 0.05 | 0.014 | 20.1 |
| | 5% centile | 0.10 | 0.10 | 0.027 | 21.1 |
| | 50% centile | 0.41 | 0.41 | 0.123 | 29.7 |
| | 95% centile | 0.89 | 0.89 | 0.356 | 48.3 |
| | 97.5% centile | 1.02 | 1.02 | 0.469 | 52.9 |
| 1 | Mean | 0.90 | 0.91 | 0.296 | 31.5 |
| | 2.5% centile | 0.56 | 0.57 | 0.141 | 20.2 |
| | 5% centile | 0.60 | 0.60 | 0.153 | 21.1 |
| | 50% centile | 0.86 | 0.86 | 0.251 | 29.7 |
| | 95% centile | 1.31 | 1.31 | 0.584 | 47.9 |
| | 97.5% centile | 1.49 | 1.49 | 0.740 | 52.4 |
| **Puerto Rico** | | | | | |
| 0.01 | Mean | 0.43 | 0.43 | 0.111 | 24.5 |
| | 2.5% centile | –0.01 | –0.01 | –0.003 | 14.9 |
| | 5% centile | 0.04 | 0.04 | 0.009 | 15.6 |
| | 50% centile | 0.39 | 0.39 | 0.090 | 22.6 |
| | 95% centile | 0.89 | 0.90 | 0.272 | 40.2 |
| | 97.5% centile | 1.02 | 1.02 | 0.357 | 45.0 |
| 0.1 | Mean | 0.48 | 0.48 | 0.124 | 24.5 |
| | 2.5% centile | 0.05 | 0.05 | 0.011 | 14.9 |
| | 5% centile | 0.11 | 0.11 | 0.022 | 15.6 |
| | 50% centile | 0.44 | 0.44 | 0.101 | 22.6 |
| | 95% centile | 0.92 | 0.93 | 0.288 | 40.2 |
| | 97.5% centile | 1.05 | 1.05 | 0.380 | 45.0 |
| 1 | Mean | 0.96 | 0.96 | 0.241 | 24.4 |
| | 2.5% centile | 0.61 | 0.61 | 0.119 | 14.9 |
| | 5% centile | 0.65 | 0.65 | 0.129 | 15.7 |
| | 50% centile | 0.92 | 0.93 | 0.205 | 22.6 |
| | 95% centile | 1.35 | 1.35 | 0.470 | 39.7 |
| | 97.5% centile | 1.49 | 1.50 | 0.594 | 44.3 |

| *Test dose, $D_t$ (Sv)* | *Mean/centile* | *Per cent excess leukaemia deaths ($Sv^{-1}$)* | *Per cent radiation-induced leukaemia deaths ($Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost/radiation-induced leukaemia death (a)* |
|---|---|---|---|---|---|
| **United States** | | | | | |
| 0.01 | Mean | 0.55 | 0.55 | 0.122 | 21.8 |
| | 2.5% centile | –0.02 | –0.02 | –0.004 | 15.2 |
| | 5% centile | 0.05 | 0.05 | 0.011 | 15.7 |
| | 50% centile | 0.51 | 0.51 | 0.107 | 20.4 |
| | 95% centile | 1.13 | 1.14 | 0.271 | 33.1 |
| | 97.5% centile | 1.27 | 1.28 | 0.325 | 37.4 |
| 0.1 | Mean | 0.61 | 0.61 | 0.136 | 21.8 |
| | 2.5% centile | 0.07 | 0.07 | 0.014 | 15.2 |
| | 5% centile | 0.14 | 0.14 | 0.028 | 15.7 |
| | 50% centile | 0.58 | 0.58 | 0.121 | 20.4 |
| | 95% centile | 1.17 | 1.18 | 0.282 | 33.1 |
| | 97.5% centile | 1.31 | 1.32 | 0.341 | 37.4 |
| 1 | Mean | 1.24 | 1.24 | 0.273 | 21.9 |
| | 2.5% centile | 0.79 | 0.80 | 0.157 | 15.2 |
| | 5% centile | 0.85 | 0.85 | 0.169 | 15.8 |
| | 50% centile | 1.21 | 1.22 | 0.250 | 20.4 |
| | 95% centile | 1.72 | 1.72 | 0.444 | 33.0 |
| | 97.5% centile | 1.83 | 1.84 | 0.535 | 37.3 |
| **United Kingdom** | | | | | |
| 0.01 | Mean | 0.45 | 0.45 | 0.105 | 22.4 |
| | 2.5% centile | –0.02 | –0.02 | –0.003 | 14.6 |
| | 5% centile | 0.04 | 0.04 | 0.009 | 15.2 |
| | 50% centile | 0.42 | 0.42 | 0.089 | 20.6 |
| | 95% centile | 0.93 | 0.93 | 0.238 | 35.9 |
| | 97.5% centile | 1.05 | 1.05 | 0.301 | 41.0 |
| 0.1 | Mean | 0.50 | 0.50 | 0.116 | 22.4 |
| | 2.5% centile | 0.06 | 0.06 | 0.012 | 14.6 |
| | 5% centile | 0.11 | 0.11 | 0.023 | 15.2 |
| | 50% centile | 0.47 | 0.47 | 0.100 | 20.6 |
| | 95% centile | 0.97 | 0.97 | 0.251 | 36.0 |
| | 97.5% centile | 1.08 | 1.09 | 0.317 | 41.0 |
| 1 | Mean | 1.02 | 1.02 | 0.231 | 22.4 |
| | 2.5% centile | 0.65 | 0.65 | 0.126 | 14.6 |
| | 5% centile | 0.70 | 0.70 | 0.135 | 15.2 |
| | 50% centile | 0.99 | 1.00 | 0.205 | 20.6 |
| | 95% centile | 1.41 | 1.42 | 0.406 | 35.8 |
| | 97.5% centile | 1.52 | 1.53 | 0.505 | 40.7 |

**Table 70 Risk estimates for solid cancer incidence (per cent exposure-induced cancer incidence (REIC)) for various current populations, using generalized ERR and generalized EAR models (models described in tables 47–58)**

Risk estimates are calculated for a population in equilibrium (underlying cancer incidence and mortality rates, and population structure of current Chinese, Japanese, Puerto Rican, United States and United Kingdom populations) from various models fitted to LSS incidence data [P48]. Risks are given as per cent per sievert and are assumed to result from acute exposure

| *Model type* | *Test dose (Sv)* | *Oesophagus* | *Stomach* | *Colon* | *Liver* | *Lung* | *Bone* | *NMSC* | *Female breast* | *Bladder* | *Brain and CNS* | *Thyroid* | *All other solid* | *Solid total* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **China** | | | | | | | | | | | | | | |
| ERR | 0.01 | 0.47 | 0.93 | 0.87 | 0.68 | 2.63 | 0.01 | 0.00 | 1.42 | 0.49 | 0.34 | 0.40 | 1.22 | 9.46 |
| | 0.1 | 0.46 | 0.93 | 0.87 | 0.68 | 2.61 | 0.13 | 0.02 | 1.41 | 0.49 | 0.34 | 0.40 | 1.21 | 9.56 |
| | 1.0 | 0.44 | 0.88 | 0.83 | 0.64 | 2.43 | 1.19 | 0.17 | 1.35 | 0.46 | 0.30 | 0.39 | 1.13 | 10.21 |
| EAR | 0.01 | 0.05 | 2.25 | 1.36 | 0.62 | 1.73 | 0.00 | 0.01 | 1.38 | 0.65 | 0.17 | 0.82 | 1.67 | 10.72 |
| | 0.1 | 0.05 | 2.23 | 1.34 | 0.62 | 1.71 | 0.00 | 0.07 | 1.36 | 0.64 | 0.17 | 0.82 | 1.65 | 10.66 |
| | 1.0 | 0.05 | 2.05 | 1.13 | 0.56 | 1.53 | 0.03 | 0.46 | 1.20 | 0.57 | 0.16 | 0.76 | 1.44 | 9.94 |
| **Japan** | | | | | | | | | | | | | | |
| ERR | 0.01 | 0.44 | 1.71 | 1.37 | 1.51 | 3.22 | 0.01 | 0.00 | 1.51 | 0.84 | 0.18 | 0.39 | 1.82 | 13.01 |
| | 0.1 | 0.44 | 1.70 | 1.37 | 1.50 | 3.19 | 0.13 | 0.03 | 1.50 | 0.84 | 0.18 | 0.38 | 1.81 | 13.08 |
| | 1.0 | 0.41 | 1.61 | 1.30 | 1.42 | 2.95 | 1.17 | 0.23 | 1.44 | 0.78 | 0.16 | 0.36 | 1.66 | 13.49 |
| EAR | 0.01 | 0.05 | 2.60 | 1.71 | 0.79 | 2.36 | 0.00 | 0.01 | 1.64 | 0.96 | 0.18 | 0.88 | 1.96 | 13.16 |
| | 0.1 | 0.05 | 2.58 | 1.67 | 0.78 | 2.33 | 0.00 | 0.08 | 1.62 | 0.94 | 0.18 | 0.87 | 1.93 | 13.05 |
| | 1.0 | 0.05 | 2.34 | 1.36 | 0.70 | 2.02 | 0.03 | 0.55 | 1.39 | 0.82 | 0.17 | 0.80 | 1.65 | 11.88 |
| **Puerto Rico** | | | | | | | | | | | | | | |
| ERR | 0.01 | 0.38 | 0.38 | 1.12 | 0.23 | 1.09 | 0.01 | 0.00 | 2.79 | 0.88 | 0.23 | 0.54 | 2.76 | 10.40 |
| | 0.1 | 0.37 | 0.38 | 1.11 | 0.23 | 1.08 | 0.13 | 0.01 | 2.77 | 0.88 | 0.23 | 0.54 | 2.74 | 10.47 |
| | 1.0 | 0.36 | 0.36 | 1.07 | 0.22 | 1.03 | 1.19 | 0.04 | 2.62 | 0.83 | 0.21 | 0.52 | 2.51 | 10.98 |
| EAR | 0.01 | 0.05 | 2.40 | 1.49 | 0.70 | 2.04 | 0.00 | 0.01 | 1.51 | 0.78 | 0.17 | 0.86 | 1.68 | 11.69 |
| | 0.1 | 0.05 | 2.38 | 1.46 | 0.69 | 2.01 | 0.00 | 0.07 | 1.49 | 0.77 | 0.17 | 0.86 | 1.66 | 11.61 |
| | 1.0 | 0.05 | 2.17 | 1.21 | 0.62 | 1.77 | 0.03 | 0.49 | 1.30 | 0.67 | 0.16 | 0.79 | 1.43 | 10.69 |
| **United States** | | | | | | | | | | | | | | |
| ERR | 0.01 | 0.23 | 0.20 | 1.74 | 0.18 | 4.41 | 0.02 | 0.36 | 6.38 | 1.84 | 0.32 | 1.18 | 4.08 | 20.95 |
| | 0.1 | 0.23 | 0.20 | 1.73 | 0.18 | 4.36 | 0.21 | 3.49 | 6.30 | 1.83 | 0.31 | 1.17 | 4.04 | 24.06 |
| | 1.0 | 0.21 | 0.19 | 1.64 | 0.17 | 3.94 | 1.80 | 16.75 | 5.59 | 1.68 | 0.28 | 1.11 | 3.62 | 37.00 |

| *Model type* | *Test dose (Sv)* | *Oesophagus* | *Stomach* | *Colon* | *Liver* | *Lung* | *Bone* | *NMSC* | *Female breast* | *Bladder* | *Brain and CNS* | *Thyroid* | *All other solid* | *Solid total* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EAR | 0.01 | 0.05 | 2.49 | 1.52 | 0.73 | 2.02 | 0.00 | 0.01 | 1.41 | 0.81 | 0.17 | 0.86 | 1.65 | 11.71 |
| | 0.1 | 0.05 | 2.47 | 1.49 | 0.72 | 2.00 | 0.00 | 0.06 | 1.39 | 0.79 | 0.17 | 0.85 | 1.63 | 11.62 |
| | 1.0 | 0.05 | 2.25 | 1.24 | 0.65 | 1.76 | 0.03 | 0.41 | 1.21 | 0.69 | 0.16 | 0.78 | 1.41 | 10.64 |
| **United Kingdom** | | | | | | | | | | | | | | |
| ERR | 0.01 | 0.54 | 0.33 | 1.33 | 0.14 | 3.49 | 0.02 | 0.13 | 4.48 | 1.42 | 0.35 | 0.30 | 3.17 | 15.68 |
| | 0.1 | 0.53 | 0.32 | 1.32 | 0.14 | 3.46 | 0.16 | 1.26 | 4.44 | 1.41 | 0.35 | 0.30 | 3.14 | 16.83 |
| | 1.0 | 0.50 | 0.30 | 1.25 | 0.13 | 3.15 | 1.44 | 7.65 | 4.01 | 1.30 | 0.30 | 0.28 | 2.81 | 23.12 |
| EAR | 0.01 | 0.05 | 2.50 | 1.53 | 0.72 | 1.99 | 0.00 | 0.01 | 1.43 | 0.76 | 0.18 | 0.86 | 1.74 | 11.77 |
| | 0.1 | 0.05 | 2.48 | 1.50 | 0.71 | 1.96 | 0.00 | 0.07 | 1.41 | 0.75 | 0.18 | 0.85 | 1.72 | 11.70 |
| | 1.0 | 0.05 | 2.27 | 1.26 | 0.65 | 1.75 | 0.03 | 0.48 | 1.24 | 0.67 | 0.17 | 0.78 | 1.49 | 10.85 |

**Table 71 Risk estimates for solid cancer incidence (per cent exposure-induced cancer incidence (REIC)) by sex for various current populations, assuming a test dose, $D_t$, of 0.1 Sv, using generalized ERR and generalized EAR models (models described in tables 47–58)**

Risk estimates are calculated for a population in equilibrium (underlying mortality rates and population structure of current Chinese, Japanese, Puerto Rican, United States and United Kingdom populations) from various models fitted to LSS mortality data [P48]. Risks are given as per cent per sievert and are assumed to result from acute exposure

| *Model type* | *Sex* | *Oesophagus* | *Stomach* | *Colon* | *Liver* | *Lung* | *Bone* | *NMSC* | *Female breast* | *Bladder* | *Brain and CNS* | *Thyroid* | *All other solid* | *Solid total* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **China** | | | | | | | | | | | | | | |
| ERR | Males | 0.55 | 1.13 | 0.84 | 0.83 | 1.63 | 0.19 | 0.02 | 0.00 | 0.69 | 0.30 | 0.18 | 1.14 | 7.50 |
| | Females | 0.37 | 0.71 | 0.90 | 0.52 | 3.62 | 0.08 | 0.03 | 2.88 | 0.29 | 0.37 | 0.64 | 1.29 | 11.70 |
| | Both | 0.46 | 0.93 | 0.87 | 0.68 | 2.61 | 0.13 | 0.02 | 1.41 | 0.49 | 0.34 | 0.40 | 1.21 | 9.56 |
| EAR | Males | 0.05 | 2.07 | 1.21 | 0.55 | 1.16 | 0.00 | 0.06 | 0.00 | 0.54 | 0.16 | 0.33 | 1.54 | 7.66 |
| | Females | 0.05 | 2.40 | 1.47 | 0.69 | 2.28 | 0.00 | 0.07 | 2.78 | 0.75 | 0.17 | 1.33 | 1.77 | 13.78 |
| | Both | 0.05 | 2.23 | 1.34 | 0.62 | 1.71 | 0.00 | 0.07 | 1.36 | 0.64 | 0.17 | 0.82 | 1.65 | 10.66 |

| *Model type* | *Sex* | *Oesophagus* | *Stomach* | *Colon* | *Liver* | *Lung* | *Bone* | *NMSC* | *Female breast* | *Bladder* | *Brain and CNS* | *Thyroid* | *All other solid* | *Solid total* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Japan** | | | | | | | | | | | | | | |
| ERR | Males | 0.70 | 2.30 | 1.57 | 2.13 | 2.30 | 0.15 | 0.03 | 0.00 | 1.27 | 0.18 | 0.18 | 2.04 | 12.85 |
| | Females | 0.18 | 1.13 | 1.17 | 0.89 | 4.06 | 0.11 | 0.03 | 2.96 | 0.42 | 0.18 | 0.58 | 1.59 | 13.29 |
| | Both | 0.44 | 1.70 | 1.37 | 1.50 | 3.19 | 0.13 | 0.03 | 1.50 | 0.84 | 0.18 | 0.38 | 1.81 | 13.08 |
| EAR | Males | 0.05 | 2.27 | 1.42 | 0.64 | 1.42 | 0.00 | 0.07 | 0.00 | 0.71 | 0.17 | 0.34 | 1.71 | 8.82 |
| | Females | 0.06 | 2.87 | 1.91 | 0.92 | 3.21 | 0.00 | 0.10 | 3.19 | 1.17 | 0.19 | 1.39 | 2.15 | 17.15 |
| | Both | 0.05 | 2.58 | 1.67 | 0.78 | 2.33 | 0.00 | 0.08 | 1.62 | 0.94 | 0.18 | 0.87 | 1.93 | 13.05 |
| **Puerto Rico** | | | | | | | | | | | | | | |
| ERR | Males | 0.56 | 0.49 | 1.13 | 0.27 | 0.71 | 0.19 | 0.01 | 0.00 | 1.27 | 0.24 | 0.21 | 3.98 | 9.06 |
| | Females | 0.20 | 0.27 | 1.10 | 0.19 | 1.43 | 0.08 | 0.00 | 5.33 | 0.51 | 0.22 | 0.84 | 1.59 | 11.76 |
| | Both | 0.37 | 0.38 | 1.11 | 0.23 | 1.08 | 0.13 | 0.01 | 2.77 | 0.88 | 0.23 | 0.54 | 2.74 | 10.47 |
| EAR | Males | 0.05 | 2.14 | 1.27 | 0.60 | 1.31 | 0.00 | 0.06 | 0.00 | 0.63 | 0.16 | 0.33 | 1.40 | 7.96 |
| | Females | 0.05 | 2.61 | 1.63 | 0.78 | 2.65 | 0.00 | 0.08 | 2.87 | 0.89 | 0.18 | 1.35 | 1.90 | 14.99 |
| | Both | 0.05 | 2.38 | 1.46 | 0.69 | 2.01 | 0.00 | 0.07 | 1.49 | 0.77 | 0.17 | 0.86 | 1.66 | 11.61 |
| **United States** | | | | | | | | | | | | | | |
| ERR | Males | 0.35 | 0.26 | 1.82 | 0.25 | 2.02 | 0.24 | 4.19 | 0.00 | 2.75 | 0.37 | 0.57 | 5.31 | 18.12 |
| | Females | 0.11 | 0.15 | 1.65 | 0.12 | 6.65 | 0.18 | 2.81 | 12.42 | 0.93 | 0.26 | 1.76 | 2.81 | 29.84 |
| | Both | 0.23 | 0.20 | 1.73 | 0.18 | 4.36 | 0.21 | 3.49 | 6.30 | 1.83 | 0.31 | 1.17 | 4.04 | 24.06 |
| EAR | Males | 0.05 | 2.27 | 1.33 | 0.63 | 1.34 | 0.00 | 0.05 | 0.00 | 0.65 | 0.17 | 0.33 | 1.41 | 8.25 |
| | Females | 0.05 | 2.66 | 1.65 | 0.80 | 2.64 | 0.00 | 0.07 | 2.74 | 0.93 | 0.18 | 1.35 | 1.83 | 14.90 |
| | Both | 0.05 | 2.47 | 1.49 | 0.72 | 2.00 | 0.00 | 0.06 | 1.39 | 0.79 | 0.17 | 0.85 | 1.63 | 11.62 |
| **United Kingdom** | | | | | | | | | | | | | | |
| ERR | Males | 0.68 | 0.44 | 1.44 | 0.16 | 2.00 | 0.19 | 1.43 | 0.00 | 2.08 | 0.41 | 0.16 | 3.87 | 12.85 |
| | Females | 0.39 | 0.21 | 1.21 | 0.11 | 4.93 | 0.14 | 1.09 | 8.88 | 0.73 | 0.29 | 0.44 | 2.40 | 20.80 |
| | Both | 0.53 | 0.32 | 1.32 | 0.14 | 3.46 | 0.16 | 1.26 | 4.44 | 1.41 | 0.35 | 0.30 | 3.14 | 16.83 |
| EAR | Males | 0.05 | 2.33 | 1.38 | 0.65 | 1.36 | 0.00 | 0.07 | 0.00 | 0.65 | 0.17 | 0.34 | 1.57 | 8.56 |
| | Females | 0.05 | 2.64 | 1.63 | 0.78 | 2.57 | 0.00 | 0.08 | 2.83 | 0.86 | 0.18 | 1.36 | 1.86 | 14.84 |
| | Both | 0.05 | 2.48 | 1.50 | 0.71 | 1.96 | 0.00 | 0.07 | 1.41 | 0.75 | 0.18 | 0.85 | 1.72 | 11.70 |

**Table 72 Comparison of risk estimates for mortality due to solid cancers and to leukaemia derived in this report with those from various other studies**

| *Cancer type* | *Reference* | *Population* | *Test dose, $D_t$ (Sv)* | *Excess cancer mortality (% $Sv^{-1}$)* | *Radiation-induced cancer mortality (% $Sv^{-1}$)* | *Years life lost (a $Sv^{-1}$)* | *Years life lost per radiation-induced cancer death (a)* |
|---|---|---|---|---|---|---|---|
| Solid | Present report | Japan | 0.01 | 3.90[a,b], 4.12[c,b] | 4.65[a,b], 4.90[c,b] | 0.69[a,b], 0.73[c,b] | 14.8[a,b], 14.9[c,b] |
| | | | 0.1 | 3.98[a,b], 4.25[c,b]<br>2.51 (–0.45, 5.34)[d,f]<br>4.14 (2.31, 6.10)[f,p] | 4.75[a,b], 5.05[c,b]<br>3.00 (–0.53, 6.39)[d,f]<br>4.94 (2.75, 7.29)[f,p] | 0.71[a,b], 0.75[c,b]<br>0.45 (–0.08, 0.94)[d,f]<br>0.74 (0.42, 1.06)[f,p] | 14.8[a,b], 14.9[c,b]<br>15.1 (13.8, 16.6)[d,f]<br>15.0 (13.7, 16.5)[f,p] |
| | | | 1.0 | 4.73[a,b], 5.38[c,b] | 5.65[a,b], 6.40[c,b] | 0.85[a,b], 0.98[c,b] | 15.1[a,b], 15.2[c,b] |
| | | United States | 0.01 | 4.01[a,b], 3.74[c,b] | 4.74[a,b], 4.41[c,b] | 0.72[a,b], 0.64[c,b] | 15.2[a,b], 14.6[c,b] |
| | | | 0.1 | 4.10[a,b], 3.86[c,b]<br>2.57 (–0.46, 5.45)[d,f]<br>4.24 (2.39, 6.22)[f,p] | 4.84[a,b], 4.55[c,b]<br>3.04 (–0.54, 6.45)[d,f]<br>5.02 (2.83, 7.35)[f,p] | 0.74[a,b], 0.67[c,b]<br>0.47 (–0.08, 0.98)[d,f]<br>0.76 (0.44, 1.10)[f,p] | 15.2[a,b], 14.6[c,b]<br>15.4 (14.1, 16.9)[d,f]<br>15.3 (14.1, 16.8)[f,p] |
| | | | 1.0 | 4.86[a,b], 4.91[c,b] | 5.75[a,b], 5.80[c,b] | 0.89[a,b], 0.86[c,b] | 15.4[a,b], 14.9[c,b] |
| | | United Kingdom | 0.01 | 4.29[a,b], 3.64[c,b] | 5.15[a,b], 4.40[c,b] | 0.71[a,b], 0.63[c,b] | 13.8[a,b], 14.4[c,b] |
| | | | 0.1 | 4.38[a,b], 3.76[c,b]<br>2.74 (–0.49, 5.82)[d,f]<br>4.53 (2.54, 6.65)[f,p] | 5.26[a,b], 4.54[c,b]<br>3.30 (–0.59, 7.01)[d,f]<br>5.45 (3.06, 7.99)[f,p] | 0.73[a,b], 0.65[c,b]<br>0.46 (–0.08, 0.97)[d,f]<br>0.76 (0.44, 1.09)[f,p] | 13.8[a,b], 14.4[c,b]<br>14.1 (12.8, 15.7)[d,f]<br>14.0 (12.7, 15.5)[f,p] |
| | | | 1.0 | 5.16[a,b], 4.80[c,b] | 6.21[a,b], 5.81[c,b] | 0.88[a,b], 0.85[c,b] | 14.1[a,b], 14.7[c,b] |
| | [L17][a] | United Kingdom | 0.001 | 10.18 (7.99, 12.65)[e] | 12.10 (9.46, 15.05)[e] | 1.53 (1.20, 1.91)[e] | 12.6 (12.2, 13.0)[e] |
| | | | 1.0 | 8.67 (7.06, 10.36)[e] | 10.36 (8.41, 12.42)[e] | 1.38 (1.11, 1.68)[e] | 13.3 (12.8, 13.9)[e] |
| | [C35] | United States | 0.1 | 6.95 (5.45, 9.34)[f] | – | – | – |
| | [C37] | United States | 0.1 | – | 7.4 (3.7, 15.0)[e,n] | – | – |
| | [I11] | United Kingdom | 1.0 | – | 8.95[g], 12.07[h] | – | – |
| | [U4] | Japan | 0.2 | – | 12.0[i], 8.0[j] | 1.34[i], 1.09[j] | 11.2[i], 13.6[j] |
| | | | 1.0 | – | 10.9[i], 7.5[j] | 1.26[i], 1.00[j] | 11.6[i], 13.3[j] |
| | [U2] | Japan | 1.0 | 7.6[k,l], 4.9[k,m] | 11.2[l], 7.4[m] | 1.05[k,l], 0.79[k,m] | 11.1[k,l], 12.8[k,m] |
| | | United States | 1.0 | – | 12.5[l,a], 9.9[l,c], 9.3[m,a], 6.5[m,c] | – | – |
| | | United Kingdom | 1.0 | – | 14.4[l,a], 12.6[l,c], 10.1[m,a], 7.9[m,c] | – | – |
| | [L50] | European Union/ United States | 1.0 | – | 9.29 | – | – |
| | [L16] | United Kingdom | 0.001 | – | 6.93, 13.79[o] | 1.04, 1.71[o] | 12.4, 15.0[o] |

| *Cancer type* | *Reference* | *Population* | *Test dose, $D_t$ (Sv)* | *Excess cancer mortality (% Sv$^{-1}$)* | *Radiation-induced cancer mortality (% Sv$^{-1}$)* | *Years life lost (a Sv$^{-1}$)* | *Years life lost per radiation-induced cancer death (a)* |
|---|---|---|---|---|---|---|---|
| Leukaemia | Present report | Japan | 0.01 | 0.32[a,b], 0.43[c,b] | 0.32[a,b], 0.43[c,b] | 0.09[a,b], 0.14[c,b] | 28.6[a,b], 32.2[c,b] |
| | | | 0.1 | 0.36[a,b], 0.47[c,b]<br>0.15 (–0.22, 0.65)[d,f]<br>0.45 (0.10, 0.89)[f,p] | 0.36[a,b], 0.47[c,b]<br>0.15 (–0.22, 0.65)[d,f]<br>0.45 (0.10, 0.89)[f,p] | 0.10[a,b], 0.15[c,b]<br>0.05 (–0.05, 0.22)[d,f]<br>0.15 (0.03, 0.36)[f,p] | 28.6[a,b], 32.2[c,b]<br>29.3 (20.3, 44.5)[d,f]<br>31.5 (21.1, 48.3)[f,p] |
| | | | 1.0 | 0.69[a,b], 0.86[c,b] | 0.69[a,b], 0.86[c,b] | 0.20[a,b], 0.28[c,b] | 28.6[a,b], 32.2[c,b] |
| | | United States | 0.01 | 0.47[a,b], 0.42[c,b] | 0.47[a,b], 0.42[c,b] | 0.09[a,b], 0.13[c,b] | 19.7[a,b], 31.4[c,b] |
| | | | 0.1 | 0.52[a,b], 0.46[c,b]<br>0.20 (–0.35, 0.89)[d,f]<br>0.61 (0.14, 1.17)[f,p] | 0.52[a,b], 0.46[c,b]<br>0.20 (–0.35, 0.89)[d,f]<br>0.61 (0.14, 1.18)[f,p] | 0.10[a,b], 0.14[c,b]<br>0.05 (–0.06, 0.20)[d,f]<br>0.14 (0.03, 0.28)[f,p] | 19.7[a,b], 31.4[c,b]<br>20.5 (15.3, 30.1)[d,f]<br>21.8 (15.7, 33.1)[f,p] |
| | | | 1.0 | 1.00[a,b], 0.84[c,b] | 1.01[a,b], 0.85[c,b] | 0.20[a,b], 0.27[c,b] | 19.7[a,b], 31.4[c,b] |
| | | United Kingdom | 0.01 | 0.38[a,b], 0.43[c,b] | 0.38[a,b], 0.43[c,b] | 0.08[a,b], 0.13[c,b] | 19.8[a,b], 31.6[c,b] |
| | | | 0.1 | 0.42[a,b], 0.46[c,b]<br>0.16 (–0.28, 0.73)[d,f]<br>0.50 (0.11, 0.97)[f,p] | 0.42[a,b], 0.47[c,b]<br>0.16 (–0.28, 0.73)[d,f]<br>0.50 (0.11, 0.97)[f,p] | 0.08[a,b], 0.15[c,b]<br>0.04 (–0.05, 0.17)[d,f]<br>0.12 (0.02, 0.25)[f,p] | 19.8[a,b], 31.6[c,b]<br>20.7 (14.7, 32.3)[d,f]<br>22.4 (15.2, 36.0)[f,p] |
| | | | 1.0 | 0.81[a,b], 0.85[c,b] | 0.82[a,b], 0.86[c,b] | 0.16[a,b], 0.27[c,b] | 19.8[a,b], 31.6[c,b] |
| | [L17][a] | United Kingdom | 0.001 | 0.84 (0.02, 2.04)[e] | 0.84 (0.02, 2.04)[e] | 0.19 (0.00, 0.53)[e] | 22.3 (16.4, 32.2)[e] |
| | | | 1.0 | 1.93 (1.14, 3.37)[e] | 1.93 (1.14, 3.38)[e] | 0.44 (0.22, 0.94)[e] | 22.5 (16.5, 32.7)[e] |
| | [C35] | United States | 0.1 | 0.95 (0.56, 1.96)[f] | – | – | – |
| | [C37] | United States | 0.1 | – | 0.61 | – | – |
| | [I11] | United Kingdom | 1.0 | – | 0.75[g], 0.83[h] | – | – |
| | [U4] | Japan | 0.2 | – | 0.70 | 0.22 | 31 |
| | | | 1.0 | – | 1.1 | 0.34 | 31 |
| | [U2] | Japan | 1.0 | 1.0[k] | 0.92 | 0.3[k] | 30.6[k] |
| | | United States | 1.0 | – | 1.19 | – | – |
| | | United Kingdom | 1.0 | – | 0.95 | – | – |
| | [L50] | European Union/ United States | 1.0 | – | 0.91 (0.03, 2.33)[f] | – | – |

[a] Model with multiplicative transport of risk, as described in section IV.B.1 of annex I of the UNSCEAR 2000 Report [U2].
[b] Model with linear–quadratic dose response, fitted to full dose range in reference [P10].
[c] Model with additive transport of risk, as described in section IV.B.1 of annex I of the UNSCEAR 2000 Report [U2].
[d] Based on Bayesian MCMC fit (linear–quadratic–exponential fit) (see appendix E for details).
[e] 95% CI.

*f* 90% CI.
*g* NIH projection model.
*h* Multiplicative projection model.
*i* Constant relative risk.
*j* Constant relative risk for first 45 years after exposure, risk declining to 0 at attained age 90.
*k* Males only.
*l* Model with ERR declining as an exponential function of age at exposure, as described in section IV.B.1 of annex I of the UNSCEAR 2000 Report [U2].
*m* Model with ERR declining as an exponential function of attained age, as described in section IV.B.1 of annex I of the UNSCEAR 2000 Report [U2].
*n* Combined 95% subjective uncertainty interval based on weighted EAR and ERR model, taking account of DDREF.
*o* Range of risks for models with: (a) power adjustment to ERR for age and time since exposure; (b) exponential adjustment to ERR for age; (c) exponential adjustment to ERR for age at exposure, and for years since exposure for those with age at exposure <15; and (d) exponential adjustment to ERR for age at exposure.
*p* Based on Bayesian MCMC fit (linear–quadratic fit) (see appendix E for details).

**Table 73 Comparison of risk estimates for solid cancer incidence (per cent exposure-induced cancer incidence (REIC)) derived in this report with those from various other studies**

Risks are given as per cent per sievert and are assumed to result from acute exposure

| *Population* | *Publication* | *Model type* | *Test dose (Sv)* | *Oesophagus* | *Stomach* | *Colon* | *Liver* | *Lung* | *Female breast* | *Bladder* | *Thyroid* | *Solid total* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Japan | Present report | ERR | 0.01 | 0.44 | 1.71 | 1.37 | 1.51 | 3.22 | 1.51 | 0.84 | 0.39 | 13.01 |
| | | | 1.0 | 0.41 | 1.61 | 1.30 | 1.42 | 2.95 | 1.44 | 0.78 | 0.36 | 13.49 |
| | | EAR | 0.01 | 0.05 | 2.60 | 1.71 | 0.79 | 2.36 | 1.64 | 0.96 | 0.88 | 13.16 |
| | | | 1.0 | 0.05 | 2.34 | 1.36 | 0.70 | 2.02 | 1.39 | 0.82 | 0.80 | 11.88 |
| | [U2] | ERR | 1.0 | 0.4 | 1.9 | 1.7 | 1.7 | 3.7 | 2.7 | 0.6 | 0.8 | 15.7 |
| United States | Present report | ERR | 0.01 | 0.23 | 0.20 | 1.74 | 0.18 | 4.41 | 6.38 | 1.84 | 1.18 | 20.95 |
| | | | 1.0 | 0.21 | 0.19 | 1.64 | 0.17 | 3.94 | 5.59 | 1.68 | 1.11 | 37.00 |
| | | EAR | 0.01 | 0.05 | 2.49 | 1.52 | 0.73 | 2.02 | 1.41 | 0.81 | 0.86 | 11.71 |
| | | | 1.0 | 0.05 | 2.25 | 1.24 | 0.65 | 1.76 | 1.21 | 0.69 | 0.78 | 10.64 |
| | [C37] | ERR | 0.1 | – | 0.3 | 2.1 | 0.2 | 5.0 | 2.6 | 1.6 | 1.0 | 18.6 |
| | | EAR | 0.1 | – | 3.1 | 1.5 | 1.2 | 2.8 | 2.3 | 1.1 | – | 16.9 |
| United Kingdom | Present report | ERR | 0.01 | 0.54 | 0.33 | 1.33 | 0.14 | 3.49 | 4.48 | 1.42 | 0.30 | 15.68 |
| | | | 1.0 | 0.50 | 0.30 | 1.25 | 0.13 | 3.15 | 4.01 | 1.30 | 0.28 | 23.12 |
| | | EAR | 0.01 | 0.05 | 2.50 | 1.53 | 0.72 | 1.99 | 1.43 | 0.76 | 0.86 | 11.77 |
| | | | 1.0 | 0.05 | 2.27 | 1.26 | 0.65 | 1.75 | 1.24 | 0.67 | 0.78 | 10.85 |
| | [L16] | ERR | 0.001 | 0.42–0.91[a,b] | | – | – | 3.41–5.01[b] | 2.58–3.98[b] | – | 0.12–0.19[b] | 12.13–21.98[b] |
| | [U2] | ERR | 1.0 | 0.5 | 0.5 | 1.6 | 0.2 | 6.2 | 6.2 | 0.2 | 0.5 | 19.3 |
| | | EAR | 1.0 | 0.4 | 2.1 | 1.9 | 1.9 | 4.3 | 2.7 | 0.8 | 0.7 | 17.0 |

*a* Combined risk for oesophagus and stomach.
*b* Range of risks for models with: (a) power adjustment to ERR for age and time since exposure; (b) exponential adjustment to ERR for age; (c) exponential adjustment to ERR for age at exposure, and for years since exposure for those with age at exposure <15; and (d) exponential adjustment to ERR for age at exposure.

## Appendix A. Score tests and statistical power

A1. The score test [C43] is a commonly used method for assessing trends of risk with dose. In particular, it has been used in this way to assess trends of cancer risk with dose in various occupational studies [K27, M12]. This appendix outlines its use for this purpose, and describes how it can be used to assess statistical power. The score is the derivative of the log likelihood with respect to the dose trend parameter. In particular, if a relative risk model is assumed in which the cancer risk (whether for incidence or mortality) in cell $j$ of stratum $i$ is given by $p_{ij} \cdot [1 + \theta \cdot D_{ij}]$, then the log (binomial) likelihood is given by:

$$L = C + \sum_{i=1}^{S} \left\{ \sum_{j=1}^{K_i} m_{ij} \cdot \ln\left[ M_i \cdot p_{ij} \cdot \left(1+\theta_i \cdot D_{ij}\right)\right] - M_i \cdot \ln\left[ \sum_{j=1}^{K_i} M_i \cdot p_{ij} \cdot \left(1+\theta_i \cdot D_{ij}\right)\right]\right\}$$

where $M_i$ is the total number of cancer cases or deaths in stratum $i$, $m_{ij}$ is the observed number of cancer cases or deaths in cell $j$ of stratum $i$ (so that $\sum_{j=1}^{K_i} m_{ij} = M_i$), $p_{ij}$ is the proportion of the population (e.g. proportion of person-years of observation) of cell $j$ making up stratum $i$ (so that $\sum_{j=1}^{K_i} p_{ij} = 1$). (This is the likelihood obtained by conditioning on the total number, $M_i$, of cases in each stratum $i$.)

A2. If we assume that $\theta_i \equiv \theta$, then:

$$\frac{dL}{d\theta} = \sum_{i=1}^{S} \left\{ \sum_{j=1}^{K_i} \frac{m_{ij} \cdot D_{ij}}{1+\theta \cdot D_{ij}} - M_i \cdot \frac{\sum_{j=1}^{K_i} p_{ij} \cdot D_{ij}}{\sum_{j=1}^{K_i} p_{ij} \cdot \left(1+\theta \cdot D_{ij}\right)} \right\}$$

so that at $\theta = 0$; this reduces to:

$$\left.\frac{dL}{d\theta}\right|_{\theta=0} = \sum_{i=1}^{S} \left\{ \sum_{j=1}^{K_i} m_{ij} \cdot D_{ij} - M_i \cdot \sum_{j=1}^{K_i} p_{ij} \cdot D_{ij} \right\}$$

Therefore:

$$E_\theta\left[\left.\frac{dL}{d\theta}\right|_{\theta=0}\right] = \sum_{i=1}^{S} M_i \cdot \left\{ \frac{\sum_{j=1}^{K_i} p_{ij} \cdot \left(1+\theta \cdot D_{ij}\right) \cdot D_{ij}}{\sum_{j=1}^{K_i} p_{ij} \cdot \left(1+\theta \cdot D_{ij}\right)} - \sum_{j=1}^{K_i} p_{ij} \cdot D_{ij} \right\}$$

$$= \theta \cdot \sum_{i=1}^{S} M_i \cdot \left\{ \frac{\sum_{j=1}^{K_i} p_{ij} \cdot {D_{ij}}^2 - \left[\sum_{j=1}^{K_i} p_{ij} \cdot D_{ij}\right]^2}{1+\theta \cdot \sum_{j=1}^{K_i} p_{ij} \cdot D_{ij}} \right\}$$

$$\mathrm{var}_\theta\left[\left.\frac{dL}{d\theta}\right|_{\theta=0}\right]=\mathrm{var}_\theta\left[\sum_{i=1}^{S}\sum_{j=1}^{K_i}m_{ij}\cdot D_{ij}\right]=\sum_{i=1}^{S}\mathrm{var}_\theta\left[\sum_{j=1}^{K_i}m_{ij}\cdot D_{ij}\right]$$

$$=\sum_{i=1}^{S}M_i\cdot\left[\frac{\sum_{j=1}^{K_i}{D_{ij}}^2\cdot p_{ij}\cdot\left(1+\theta\cdot D_{ij}\right)}{\sum_{j=1}^{K_i}p_{ij}\cdot\left(1+\theta\cdot D_{ij}\right)}-\left\{\frac{\sum_{j=1}^{K_i}D_{ij}\cdot p_{ij}\cdot\left(1+\theta\cdot D_{ij}\right)}{\sum_{j=1}^{K_i}p_{ij}\cdot\left(1+\theta\cdot D_{ij}\right)}\right\}^2\right]$$

$$=\sum_{i=1}^{S}M_i\cdot\left[\frac{\left(\sum_{j=1}^{K_i}{D_{ij}}^2\cdot p_{ij}+\theta\cdot\sum_{j=1}^{K_i}{D_{ij}}^3\cdot p_{ij}\right)\cdot\left(1+\theta\cdot\sum_{j=1}^{K_i}p_{ij}\cdot D_{ij}\right)-\left(\sum_{j=1}^{K_i}D_{ij}\cdot p_{ij}+\theta\cdot\sum_{j=1}^{K_i}{D_{ij}}^2\cdot p_{ij}\right)^2}{\left(1+\theta\cdot\sum_{j=1}^{K_i}p_{ij}\cdot D_{ij}\right)^2}\right]$$

(It should be noted that this last expression is not the same as $\mathrm{var}_{\theta=0}\left[\left.\frac{dL}{d\theta}\right|_{\theta=0}\right]=E_{\theta=0}\left[-\left.\frac{d^2L}{d\theta^2}\right|_{\theta=0}\right]$.)

A3. Therefore the normalized score, given by $Z=\left.\frac{dL}{d\theta}\right|_{\theta=0}\Big/\mathrm{var}_\theta\left[\left.\frac{dL}{d\theta}\right|_{\theta=0}\right]^{0.5}$, has expectation given by:

$$Z_0=E_\theta\left[\left.\frac{dL}{d\theta}\right|_{\theta=0}\right]\Big/\mathrm{var}_\theta\left[\left.\frac{dL}{d\theta}\right|_{\theta=0}\right]^{0.5}$$

$$=\frac{\theta\cdot\sum_{i=1}^{S}M_i\cdot\left\{\frac{\sum_{j=1}^{K_i}p_{ij}\cdot{D_{ij}}^2-\left[\sum_{j=1}^{K_i}p_{ij}\cdot D_{ij}\right]^2}{1+\theta\cdot\sum_{j=1}^{K_i}p_{ij}\cdot D_{ij}}\right\}}{\left[\sum_{i=1}^{S}M_i\cdot\frac{\left(\sum_{j=1}^{K_i}{D_{ij}}^2\cdot p_{ij}+\theta\cdot\sum_{j=1}^{K_i}{D_{ij}}^3\cdot p_{ij}\right)\cdot\left(1+\theta\cdot\sum_{j=1}^{K_i}p_{ij}\cdot D_{ij}\right)-\left(\sum_{j=1}^{K_i}D_{ij}\cdot p_{ij}+\theta\cdot\sum_{j=1}^{K_i}{D_{ij}}^2\cdot p_{ij}\right)^2}{\left(1+\theta\cdot\sum_{j=1}^{K_i}p_{ij}\cdot D_{ij}\right)^2}\right]^{0.5}} \quad (A.1)$$

and has variance 1. It is assumed that the normalized score, Z, is approximately normally distributed, $Z\sim N(Z_0,1)$. Therefore, if the $100\cdot p$-centile of the standard normal distribution is $N_p$, so that $p = P[\mathrm{N}(0,1)\le N_p)$, then:

$$P[Z>N_{1-\alpha}]=P[Z-Z_0>N_{1-\alpha}-Z_0]=P[N(0,1)>N_{1-\alpha}-Z_0]$$

If this is to equal $p$, then:

$$1-p=P[N(0,1)\le N_{1-\alpha}-Z_0]=P[N(0,1)\le N_{1-p}]$$

A4. Therefore it must be that $N_{1-\alpha}-Z_0=N_{1-p}$, or equivalently that:

$$Z_0=N_{1-\alpha}-N_{1-p} \quad (A.2)$$

Considering a single stratum, with $M_1 = M$, $K_1 = K$, etc., then by (A.1) and (A.2), in order for the cohort to have power $p$ it must be that:

$$M = \frac{\left(\left(\sum_{j=1}^{K} D_j^{\,2} \cdot p_j + \theta \cdot \sum_{j=1}^{K} D_j^{\,3} \cdot p_j\right) \cdot \left(1 + \theta \cdot \sum_{j=1}^{K} p_j \cdot D_j\right) - \left(\sum_{j=1}^{K} D_j \cdot p_j + \theta \cdot \sum_{j=1}^{K} D_j^{\,2} \cdot p_j\right)^2\right) \cdot \left(N_{1-\alpha} - N_{1-p}\right)^2}{\theta^2 \cdot \left(\sum_{j=1}^{K} p_j \cdot D_j^{\,2} - \left[\sum_{j=1}^{K} p_j \cdot D_j\right]^2\right)^2} \tag{A.3}$$

For small $\theta$ and $D_i$ this varies approximately as the inverse of the square of the average dose, and as the inverse of the square of the expected ERR per unit dose, $\theta$.

A5. Figures I and II in the main text illustrate these formulae with calculations of power for a cohort having the dose distribution from the latest mortality data set on the survivors of the atomic bombings in Japan [P10], for both bone marrow dose and colon dose. Table A1 gives the dose distribution assumed.

**Table A1 Colon and bone marrow person-year-weighted dose distribution in the atomic bombing survivor mortality data, taken from data set used for reference** [P10]

| *Colon dose group (Sv)* | *Average colon dose (Sv)* | *Average bone marrow dose (Sv)* | *Proportion of person-years follow-up in group* |
|---|---|---|---|
| 0–0.005 | 0.001 06 | 0.001 20 | 0.446 10 |
| 0.005–0.02 | 0.011 04 | 0.012 22 | 0.169 46 |
| 0.02–0.04 | 0.030 65 | 0.034 52 | 0.073 60 |
| 0.04–0.06 | 0.051 71 | 0.058 46 | 0.049 80 |
| 0.06–0.08 | 0.072 55 | 0.082 21 | 0.031 38 |
| 0.08–0.10 | 0.094 01 | 0.106 85 | 0.023 99 |
| 0.10–0.125 | 0.116 32 | 0.132 08 | 0.022 57 |
| 0.125–0.15 | 0.141 46 | 0.161 31 | 0.017 47 |
| 0.15–0.175 | 0.166 44 | 0.189 78 | 0.017 21 |
| 0.175–0.20 | 0.190 97 | 0.218 28 | 0.011 65 |
| 0.20–0.25 | 0.228 00 | 0.260 21 | 0.018 09 |
| 0.25–0.30 | 0.278 14 | 0.318 08 | 0.016 31 |
| 0.30–0.50 | 0.388 96 | 0.447 99 | 0.038 83 |
| 0.50–0.75 | 0.618 25 | 0.712 94 | 0.024 91 |
| 0.75–1.00 | 0.876 56 | 1.012 81 | 0.014 55 |
| 1.00–1.25 | 1.147 07 | 1.331 69 | 0.008 76 |
| 1.25–1.50 | 1.421 71 | 1.663 34 | 0.006 06 |
| 1.50–1.75 | 1.689 03 | 1.993 72 | 0.003 39 |
| 1.75–2.00 | 1.959 92 | 2.303 23 | 0.002 17 |
| 2.00–2.50 | 2.326 39 | 2.734 08 | 0.003 18 |
| 2.50–3.00 | 2.827 22 | 3.163 34 | 0.000 52 |

# Appendix B. Measures of radiation risk, including lifetime risk

B1. Fundamental to the calculation of measures of population risk is the estimation of the instantaneous cancer mortality rate, $\mu_c(s,t \mid a,D)$, expressed as cancer deaths per year, that will result for a given cancer type *c* at age *t* for persons of sex *s* following some instantaneously administered radiation dose *D* given at age *a*. This is typically evaluated by fitting a model for radiation risk to data corresponding to some exposed cohort. For example, the generalized relative risk model assumes that the mortality rate for cancer type *c* at age *t, y* years after instantaneous exposure to a radiation dose *D* administered at age *a* (so that $t = a + y$) is given by $\mu_c(s,t \mid a,D) = \mu_c(s,t) \cdot [1 + ERR_c(s,a,y,D)]$. Similar models can also be fitted to cancer incidence data. Typically one can multiplicatively separate the radiation dose–response term from the temporal modifiers in this expression, as for example $\mu_c(s,t \mid a,D) = \mu_c(s,t) \cdot [1 + F_c(D) \cdot \phi_c(s,a,y)]$. For instance, one might use as the form of dose response the linear–quadratic–exponential expression $F_c(D) = [a \cdot D + \beta \cdot D^2] \cdot \exp[\gamma \cdot D]$ (a model suggested by much radiobiological data [U5]) (see also section I.K), and as the temporal modifier term some empirical exponential function, $\phi_c(s,a,y) = \exp[\kappa_0 + \kappa_1 \cdot s + \kappa_2 \cdot a + \kappa_3 \cdot y]$.

B2. Once a model for radiation risk has been developed, it is in principle straightforward to use it to estimate the burden of cancer in some hypothetically exposed population. Fundamental to assessment of risk in such a population, one must assume "background" or "underlying" mortality rates, $\mu_c(s,t)$, that this population will experience in the absence of radiation exposure, both overall and for each cancer type. Moreover, to calculate cancer risks for cancer incidence, cancer incidence rates must also be specified. These background rates are generally estimated from national morbidity and mortality rates. It is usual to calculate the consequence of an instantaneous exposure to a "test" dose $D_t$ that is assumed administered at some age *a*. However, other more general patterns of exposure are possible, and may be derived by obvious generalizations of the calculations below. There are six commonly used measures of population cancer risk, extensively reviewed elsewhere [B18, L17, T18]. The first measure is excess cancer deaths (ECD) per unit dose:

$$ECD_c(s,a,D_t) = \frac{\int_a^{y_T} \mu_c(s,t \mid a,D_t) \cdot S_c(s,t \mid a,D_t)dt - \int_a^{y_T} \mu_c(s,t) \cdot S(s,t \mid a)dt}{D_t}$$

where $\mu_c(s,t \mid a,D_t)$ is the instantaneous cancer mortality rate (cancers/year) for cancer type *c* at age *t* for persons of sex *s* following the assumed dose $D_t$ given at age *a*. As above, this is evaluated by some model fitted to data. $S_c(s,t \mid a,D_t)$ is the fraction of the population of sex *s* alive at age *a* who remain alive at age *t* (>*a*), and can be estimated by

$S_c(s,t \mid a,D_t) = \exp\left[-\int_a^t \mu(s,w \mid a,D_t)dw\right]$, where $\mu(s,t \mid a,D_t) = \mu_c(s,t \mid a,D_t) + \sum_{l \neq c} \mu_l(s,t)$ is the all-cause mortality rate, a summation over the specific cancer type of interest, and all other cancer and non-cancer causes of death. $S(s,t) = S_c(s,t \mid a,0)$ is the analogous survival probability at 0 radiation dose. If a generalized relative risk model were to be fitted, in which for cancer type *c* the mortality rate at age *t, y* years after exposure to a dose $D_t$ administered at age *a* (so that $t = a + y$) is given by $\mu_c(s,t \mid a,D_t) = \mu_c(s,t) \cdot [1 + ERR_c(s,a,y,D_t)]$, then this risk can be written:

$$ECD_c(s,a,D_t) = \frac{\left\{\begin{array}{l}\int_a^{y_T} \mu_c(s,t) \cdot [1 + ERR_c(s,a,t-a,D_t)] \cdot S(s,t) \cdot \exp\left[-\int_a^t \mu_c(s,w) \cdot ERR_c(s,a,w-a,D_t)dw\right]dt \\ -\int_a^{y_T} \mu_c(s,t) \cdot S(s,t)dt\end{array}\right\}}{D_t}$$

Persons are assumed capable of surviving in principle up to the age of $y_T$, at which point they are assumed to die instantaneously (i.e. the population is truncated at that age). The particular $y_T$ used does not much matter as long as it is

sufficiently large. Little et al. [L17] used a value of 121 years, as did Bennett et al. [B18]. This measure has been used in the BEIR V report [C35] and elsewhere [L15, L16, L17]. A very similar measure, excess cancer incidence (ECI) per unit dose, can also be calculated.

B3. A population risk measure closely related to ECD is the risk of exposure-induced death (REID) per unit dose:

$$REID_c(s,a,D_t) = \frac{\int_a^{y_T} [\mu_c(s,t \mid a,D_t) - \mu_c(s,t)] \cdot S_c(s,t \mid a,D_t) dt}{D_t}$$

As above, when a generalized relative risk model,

$\mu_c(s,t \mid a,D_t) = \mu_c(s,t) \cdot [1 + ERR_c(s,a,y,D_t)]$, is assumed, this reduces to:

$$REID_c(s,a,D_t) = \frac{\int_a^{y_T} \mu_c(s,t) \cdot ERR_c(s,a,t-a,D_t) \cdot S(t,a) \cdot \exp\left[-\int_a^t \mu_c(s,w) \cdot ERR_c(s,a,w-a,D_t) dw\right] dt}{D_t}$$

This risk measure has been employed by many scientific committees [I11, U2, U4] and others [L15, L16, L17], and is arguably the most commonly used such summary risk measure. The ECD measure, which is calculated by taking the difference between the numbers of cancers that would occur in an irradiated population and in an otherwise equivalent unirradiated population, in general gives a somewhat lower value than the REID measure. This is because the former quantity does not include that fraction (about 20% for the general population in equilibrium) of the people developing a fatal radiation-induced cancer who would have died from some sort of cancer anyway. The analogous quantity calculated for cancer incidence, risk of exposure-induced cancer incidence (REIC) per unit dose, can also be defined, and has been used by some [B18].

B4. The measure of years of life lost (YLL) per unit dose is given by:

$$YLL_c(s,a,D_t) = \frac{\int_a^{y_T} S(s,t \mid a) dt - \int_a^{y_T} S_c(s,t \mid a,D_t) dt}{D_t}$$

As above, when a relative risk model, $\mu_c(s,t \mid a,D_t) = \mu_c(s,t) \cdot [1 + ERR_c(s,a,y,D_t)]$, is assumed, this reduces to:

$$YLL_c(s,a,D_t) = \frac{\int_a^{y_T} \exp\left[-\int_a^t \mu(s,w) dw\right] dt - \int_a^{y_T} \exp\left[-\int_a^t \mu(s,w) + \mu_c(s,w) \cdot RR_c(s,a,w-a,D_t) dw\right] dt}{D_t}$$

This measure has been used by many scientific committees [C35, I11, U2, U4] and others [L15, L16, L17]. A related measure, years of life lost per radiation-induced cancer (YLLRIC), which is given by:

$$YLLRIC_c(s,a,D_t) = \frac{YLL_c(s,a,D_t)}{REID_c(s,a,D_t)}$$

has also been employed by some [C35, I11, L17, U2].

B5. The non-constancy of all six measures of risk as a function of the test dose $D_t$ should be noted, even when the excess relative risk $ERR(s,a,t,D_t)$ is linear in $D_t$; this is a consequence of the non-linearity (in $D_t$) of the numerators of the above expressions.

B6. In calculation of an overall population risk, suitable averages of all of the above measures have to be taken, averaged over the age at exposure distribution in the hypothetical exposed population. Most scientific committees [C35, I11, U2, U4] and others [B18, L15, L16, L17] use the equilibrium population distribution in the absence of radiation exposure,

$$S_c(s,a) = \exp\left[-\int_0^a \mu(s,w)dw\right]$$

and weight across sexes by the relative birth rates of each sex (in most populations approximately equal). Using the equilibrium distribution has the advantage that the time distribution of the administered pattern of dose does not matter. Assuming linearity of the excess relative risk $ERR(s,a,t,D)$ in dose $D$, all risk measures are approximately (asymptotically in the low-dose limit) invariant to arbitrary fractionation of a given test dose, $D_t$, over time. In principle, other age/sex distributions could be used to derive aggregate risks, for example the actual population distribution by age and sex at a given time for some country. However, population risk measures for a population that is not in equilibrium when the radiation dose is given will not be (asymptotically in the low-dose limit) invariant to the pattern of test dose distribution.

# Appendix C. Modelling of dosimetric error for the data on the atomic bombing survivors

C1. This appendix details the methods used to model dosimetric error, in the data set on the atomic bombing survivor LSS cohort, for the purpose of fitting the risk models used for calculations of population cancer risk. The methods for adjusting for dosimetric error are reasonably similar to those employed by Pierce et al. [P2, P11, P16], Neriishi et al. [N7], and Little and colleagues [L29, L32, L33, L34, L35, L37]. In general, the true dose $D$ is not known; the only observable dosimetric quantity in any stratum is the nominal (or estimated) (DS02) dose $d$. Approximately unbiased parameter estimates are obtained by replacing $ERR(i,D)$ (or $EAR(i,D)$) by $E[ERR(i,D) \mid d]$ (or by $E[EAR(i,D) \mid d]$) in the model fitting, in which this last expression represents the average of the excess relative risk $ERR(i,D)$ (or the excess absolute risk $EAR(i,D)$) over the stratum with average nominal (DS02) dose $d$. This approach to measurement error correction is an example of "regression calibration" [C12].

C2. When random errors are assumed to be present in the dose estimates, the true dose $D$ in any stratum is not known; the only observable dosimetric quantity in any stratum is the nominal (or estimated) dose $d$. Jablon [J3] investigated the errors in the Japanese atomic bombing dosimetry and found that these errors were most likely to be distributed log-normally, with a GSD of about 30%. Therefore it is assumed here that the distribution of the nominal dose $d$ conditional on the true dose $D$ is given by the standard log-normal density function:

$$f(d \mid D) = \frac{1}{\sigma \cdot d\sqrt{2\pi}} \exp\left[-\frac{(\ln[d] - \ln[D])^2}{2 \cdot \sigma^2}\right] \tag{C.1}$$

C3. Pierce et al. [P2, P11, P16] found that a Weibull distribution provided an adequate description of the true dose distribution in the two cities, apart from a low-dose group, which they did not model. Following their example, the probability density of the distribution of the true dose $D$ in each sex ($s$ = male, female) and city ($c$ = Hiroshima, Nagasaki) is modelled here by the superposition of an extended Weibull density function (similar to that used previously by Little [L32, L49]), with an additional uniform density on the true dose interval [0.0, 0.01] given by:

$$w_{sc}(D) = \omega_{1sc} \cdot \left[\omega_{2sc} \cdot \omega_{3sc} \cdot D^{\omega_{3sc}-1} + \omega_{4sc}\right] \cdot \exp\left[-\omega_{2sc} \cdot D^{\omega_{3sc}} - \omega_{4sc} \cdot D\right] + [1 - \omega_{1sc}] \cdot 100 \cdot 1_{D<0.01} \tag{C.2}$$

C4. In general, the canonical Weibull distribution (with $\omega_{4sc} = 0$) did not adequately fit the current LSS mortality data [P10], and neither did the density function without the uniform density in the range [0.0, 0.01] (with $\omega_{1sc} = 1$), but this extended Weibull density function fitted the data very well over the full dose range (including the low-dose group excluded by Pierce et al. [P2, P11, P16]).

C5. The joint distribution of true dose $D$ and nominal dose $d$ is then given by the density function:

$$p_{sc}(d,D) = f(d \mid D) \cdot w_{sc}(D) \tag{C.3}$$

from which one can numerically integrate to obtain:

$$\Pr_{sc}(d \le d_0) = \int_0^{d_0} dq \int_0^{D_{\max}} p_{sc}(q,D)dD = \int_0^{d_0} dq \int_0^{D_{\max}} f(q \mid D) \cdot w_{sc}(D)dD \tag{C.4}$$

where $D_{\max}$ is the maximum assumed true dose, taken to be 6 Sv for the colon and bone marrow. The fitting of the modified Weibull distribution parameters ($\omega_{1sc}$, $\omega_{2sc}$, $\omega_{3sc}$, $\omega_{4sc}$,) for each sex (male, female) and city (Hiroshima, Nagasaki) separately, is achieved by maximizing the multinomial likelihood of the joint distribution of persons by nominal colon or bone marrow dose (using as dose groups 0.0–0.005, 0.005–0.02, 0.02–0.04, 0.04–0.06, 0.06–0.08, 0.08–0.10, 0.10–0.125, 0.125–0.15, 0.15–0.175, 0.175–0.20, 0.20–0.25, 0.25–0.30, 0.30–0.50, 0.50–0.75, 0.75–1.00, 1.00–1.25, 1.25–1.50, 1.50–1.75, 1.75–2.00, 2.00–2.50, 2.50–3.00, >3.00 Sv). In all fits of the extended Weibull distributions the DS02 colon and bone marrow dose estimates are used, unadjusted for dosimetric error and without the truncation of dose estimates at 4 Sv that have been used in some of the most recent analyses [P10]. However, as noted above, it is implicitly assumed in the integrations involved in Eq. (C.4) that the true dose (colon, bone marrow) cannot exceed 6 Sv.

C6. It can be shown [C12] that approximately unbiased estimates of the parameters in ERR or EAR models expressed by Eqs (12) and (13) in the main text (particular cases of which are given by expressions (14)–(20)) are obtained by replacing $ERR(i,D)$ or $EAR(i,D)$ in the model fitting by $E[ERR(i,D) \mid d]$ and $E[EAR(i,D) \mid d]$, respectively. These last expressions represent the conditional expectation of the excess relative risk $ERR(i,D)$ or excess absolute risk $EAR(i,D)$ at the true dose $D$, given the average nominal DS02 dose $d$; in other words, $E[ERR(i,D) \mid d]$ is the average of the excess relative risk $ERR(i,D)$ at the true dose $D$ over the stratum with (person-) averaged nominal dose $d$, and similarly for the excess absolute risk. $E[ERR(i,D) \mid d]$ and $E[EAR(i,D) \mid d]$ are calculated by numerical integration of the product of the excess relative risk $ERR(i,D)$ and excess absolute risk $EAR(i,D)$, for example as given by expressions (12)–(20), and the density function, Eq. (C.3), over the true dose range (0–6 Sv). Numerical integrations are performed using a Rosenbrock-type stiff integration routine (employing the Shampine parameter set) [P22].

## Appendix D. Risk models fitted to the atomic bombing survivor data by classical, likelihood-based methods

D1. This appendix presents the models used to fit the current LSS cancer mortality [P10] and cancer incidence data [P48] by classical, likelihood-based methods. The models fitted are of the general form described in section IV of the main text, namely generalized ERR and generalized EAR models. Generalized ERR models were fitted in which the expected cancer mortality or incidence rate at age $a$, for sex $s$ and city $c$, following exposure at age $e$ to a dose $D$ of radiation is given by:

$$h_0(a,e,c,s) \cdot [1 + F(D) \cdot \phi(a,e,c,s)] = h_0(a,e,c,s) \cdot [1 + ERR(D,a,e,c,s)] \tag{D.1}$$

Likewise, generalized EAR models were fitted in which the expected cancer rate (for mortality or incidence) is given by:

$$h_0(a,e,c,s) + F(D) \cdot \psi(a,e,c,s) = h_0(a,e,c,s) + EAR(D,a,e,c,s) \tag{D.2}$$

D2. Poisson disease models were used for all fitting to the LSS data. The models that are used here are fundamentally functions of the (unobserved) "true" organ dose $D$ received by a survivor. In general, the true dose $D$ is not known; the only observable dosimetric quantity in any stratum $i$ is the nominal (or estimated) (DS02) dose $d$. As discussed in appendix C, approximately unbiased parameter estimates are obtained by replacing $ERR(D,a,e,c,s)$ (or $EAR(D,a,e,c,s)$) by $E_i[ERR(D,a,e,c,s)|d]$ (or by $E_i[EAR(D,a,e,c,s)|d]$) in the model fitting, in which this last expression represents the average of the excess relative risk $ERR(D,a,e,c,s)$ (or the excess absolute risk $EAR(D,a,e,c,s)$) over the stratum $i$ with average nominal (DS02) dose $d$. Since the adjustment functions $\phi(a,e,c,s)$ and $\psi(a,e,c,s)$ do not involve dose, this is equivalent to replacing the dose–response function $F(D)$ by $E_i[F(D)|d]$. This approach to measurement error correction is an example of "regression calibration" [C12].

D3. For all the model fitting carried out, two basic forms of dose response *F(D)* were implemented, namely:

$$F(D) = (\alpha \cdot D + \beta \cdot D^2) \cdot \exp(\gamma \cdot D) \tag{D.3}$$

and

$$F(D) = \alpha \cdot D^k \tag{D.4}$$

D4. For the LSS mortality data, the regression calibration approach was implemented exactly as described in appendix C, assuming 35% GSD errors. For computational simplicity, in the LSS mortality data $E_i[D \mid d]$ and $E_i[D^2 \mid d]$ were evaluated, and substituted into *F(D)*. Therefore Eq. (D.3) was replaced by:

$$F(D) = (\alpha \cdot E_i[D \mid d] + \beta \cdot E_i[D^2 \mid d]) \cdot \exp(\gamma \cdot E_i[D \mid d]) \tag{D.5}$$

and Eq. (D.4) was replaced by:

$$F(D) = \alpha \cdot E_i[D \mid d]^k \tag{D.6}$$

As can be seen, at least for linear–quadratic forms of dose response ($\gamma$ = 0, $k$ = 1,2), these are equivalent to the exact regression calibration substitution estimate. Even when departures from pure linear–quadratic forms of dose response are used, these approximations work well. Over the typical range of parameters $\gamma$, $k$ fitted, these approximations to $E_i[F(D)|d]$ were found to be accurate to at least 5%, and often better than that, paralleling previous such calculations [L33].

D5. The latest LSS incidence data set did not contain unadjusted doses that would allow us to employ the method of appendix C. The incidence data file contained measurement-error-adjusted, truncated organ doses, evaluated using the methodology previously employed by Pierce et al. [P2, P11, P16] for the LSS11 mortality data. It should be noted that this procedure is based on estimation of ratios of $E_i[D \mid d] / d$ derived for the DS86 dosimetry [P2], assuming 35% GSD errors. These ratios may possibly not be valid for the updated DS02 dosimetry. The estimated values of $E_i[D \mid d]$ were used in this data file and were substituted for $D$ in the various forms of *F(D)*, as above.

D6. The adjustment factors used in both generalized ERR and EAR models are of the same form, namely:

$$\begin{aligned}\phi(a,e,c,s) &= \exp\left[\kappa_1 \cdot 1_{s=female} + \kappa_2 \cdot 1_{c=Nagasaki} + \kappa_3 \cdot \ln[a] + \kappa_4 \cdot \ln[e] + \kappa_5 \cdot \ln[a-e]\right] \\ &= \exp\left[\kappa_1 \cdot 1_{s=female} + \kappa_2 \cdot 1_{c=Nagasaki}\right] \cdot a^{\kappa_3} \cdot e^{\kappa_4} \cdot [a-e]^{\kappa_5}\end{aligned} \tag{D.7}$$

Similar forms of adjustment factors have been employed by many others in analysis of these data [L15, L16, L21, L53, L90, P46, P47], and fit well. A general motivation for use of this form of adjustment factors as a function of age and age at exposure is provided by the Armitage–Doll multistage model, as discussed in references [L15, L21]. In particular, the special case of this model in which $\kappa_3 = -1$, so that:

$$\phi(a,e,c,s) = \exp\left[\kappa_1 \cdot 1_{s=female} + \kappa_2 \cdot 1_{c=Nagasaki} - \ln[a]\right] = (1/a) \cdot \exp\left[\kappa_1 \cdot 1_{s=female} + \kappa_2 \cdot 1_{c=Nagasaki}\right] \tag{D.8}$$

has been advocated by Pierce and colleagues [P46, P47]. Other analyses [L5, L16, L53, L90, P4, T1] have employed exponential, rather than power, adjustments to ERR or EAR, of the form:

$$\phi(a,e,c,s) = \exp\left[\kappa_1 \cdot 1_{s=female} + \kappa_2 \cdot 1_{c=Nagasaki} + \kappa_3 \cdot a + \kappa_4 \cdot e\right] \tag{D.9}$$

or composites of the two [P9, P10]. These provide almost the same fit as the power adjustment factors (D.7) to the LSS data and to data for various other radiation-exposed groups [L16, L53, L90].

D7. In fits to the LSS mortality data, bone marrow dose was used for assessing risks of leukaemia, and colon dose for risks of all solid cancers. For the incidence data, generally the relevant organ-specific dose was used, except where indicated otherwise in the tables. In all cases a neutron RBE of 10 was used, as recommended by the ICRP [I11]. Those survivors not in (either) city (>10 km from either hypocentre) were excluded from the LSS incidence data, and survivors

with shielded kerma dose of >4 Gy were excluded from the mortality data [P10]. Tables D1–D4 provide details of the model fits to the mortality data, and tables D5–D16 to the incidence data.

D8. The form of the background mortality or incidence rate, $h_0(a,e,c,s)$, was determined by a forward stepwise process, whereby terms were successively added until no further statistically significant improvement in fit was obtained [M21]. Table D17 details the optimal background model for each mortality and cancer incidence end point considered in tables D1–D16. Likewise, a forward stepwise process was used to assess the significance of terms modifying the dose response. A backward stepwise process [M21] was then used to check that the indicated dose-modifying factors were still statistically significant.

D9. The recently published BEIR VII report [C37] employed somewhat unusual adjustment functions to the ERR and EAR for solid cancers, of the form:

$$\phi(a,e,c,s) = \exp\left[\kappa_1 \cdot 1_{s=female} + \kappa_2 \cdot \ln[a] + \kappa_3 \cdot \min[e-30,0]\right] \tag{D.10}$$

The principal novelty in this is that the adjustment for age at exposure, provided by the $\kappa_3 \cdot \min[e - 30,0]$ term, only varies under the age of 30. The current study fitted and tested this by use of a slightly more general form of model in which

$$\phi(a,e,c,s) = \exp\left[\kappa_1 \cdot 1_{s=female} + \kappa_2 \cdot \ln[a] + \kappa_3 \cdot \min[e-30,0] + \kappa_4 \cdot \max[e-30,0]\right] \tag{D.11}$$

In particular, by constraining $\kappa_3 = \kappa_4$ in the model fits, it is feasible to test for possible changes in the modifying effect of age at exposure on ERR or EAR at the age of 30. Table D2 details the fit of this model. As can be seen from the table, this model yields no better fit than the optimal models given in table D1. There is also no evidence for changes in the modifying effect of age at exposure on ERR or EAR at the age of 30.

D10. The BEIR VII report [C37] also employed somewhat unusual adjustment functions to the ERR and EAR for leukaemia, of the form:

$$\phi(a,e,c,s) = \exp\begin{bmatrix}\kappa_1 \cdot 1_{s=female} + \kappa_2 \cdot \ln[a-e] + \kappa_3 \cdot \min[e-30,0] \\ +\kappa_4 \cdot \ln[a-e] \cdot \min[e-30,0]\end{bmatrix} \tag{D.12}$$

Again, the principal novelty in this is that the adjustments for age at exposure (both as main effect and as interaction with the effect of time since exposure), provided by the $\kappa_3 \cdot \min[e - 30,0]$ and $\kappa_4 \cdot \ln[a - e] \cdot \min[e - 30,0]$ terms, only varies under the age of 30. In fits of the generalized EAR model, the constraint $\kappa_2 = 0$ appears to have been imposed [C37]. Again, this has been fitted and tested by use of a slightly more general form of model in which:

$$\phi(a,e,c,s) = \exp\begin{bmatrix}\kappa_1 \cdot 1_{s=female} + \kappa_2 \cdot \ln[a-e] + \kappa_3 \cdot \min[e-30,0] \\ +\kappa_4 \cdot \max[e-30,0] + \kappa_5 \cdot \ln[a-e] \cdot \min[e-30,0] \\ +\kappa_6 \cdot \ln[a-e] \cdot \max[e-30,0]\end{bmatrix} \tag{D.13}$$

Again, by constraining $\kappa_3 = \kappa_4$ in the model fits, it is feasible to test for possible changes in the modifying effect of age at exposure on ERR or EAR at the age of 30. Table D4 details the fit of this model. (The constraint $\kappa_2 = 0$ is not imposed in fits of the model with either interaction term. It is generally unwise to have interaction terms in a model without both associated main effect terms.) As can be seen from table D4, this model yields no better fit than the optimal leukaemia models given in table D3. There is also no evidence for changes in the modifying effect of age at exposure on ERR or EAR at the age of 30, although there is some evidence for interaction between the adjustments for time since exposure, $\ln[a - e]$, and either of the $\min[e - 30,0]$ or $\max[e - 30,0]$ terms.

**Table D1 Fits of generalized ERR and EAR models to LSS solid cancer mortality data**

Data set used for reference [P10]; models assume 35% GSD errors in colon dose; dose errors corrected using methods of appendix C.
The optimal models are shown in boldface

| | *Dose response* | *Modifier*[a] | *Deviance* | *df* | | *Dose response* | *Modifier*[a] | *Deviance* | *df* |
|---|---|---|---|---|---|---|---|---|---|
| Background | – | – | 13 553.081 | 31 399 | | | | | |
| Relative risk | $\alpha D$ | – | 13 423.324 | 31 398 | Additive risk | $\alpha D$ | – | 13 492.779 | 31 398 |
| | $\alpha D + \beta D^2$ | – | 13 420.980 | 31 397 | | $\alpha D + \beta D^2$ | – | 13 472.872 | 31 397 |
| | $\alpha D$ | Sex | 13 411.768 | 31 397 | | $\alpha D$ | Sex | 13 484.146 | 31 397 |
| | $\alpha D$ | City | 13 422.062 | 31 397 | | $\alpha D$ | City | 13 492.710 | 31 397 |
| | $\alpha D$ | Sex, ln[*y*] | 13 410.450 | 31 396 | | $\alpha D$ | Sex, ln[*y*] | 13 407.974 | 31 396 |
| | $\alpha D$ | Sex, ln[*e*] | 13 383.743 | 31 396 | | $\alpha D$ | Sex, ln[*e*] | 13 474.836 | 31 396 |
| | $\alpha D$ | Sex, ln[*a*] | 13 393.958 | 31 396 | | $\alpha D$ | Sex, ln[*a*] | 13 391.765 | 31 396 |
| | $\alpha D$ | Sex, ln[*y*], ln[*e*] | 13 382.864 | 31 395 | | $\alpha D$ | Sex, ln[*y*], ln[*e*] | 13 391.749 | 31 395 |
| | $\alpha D$ | Sex, ln[*y*], ln[*a*] | 13 379.354 | 31 395 | | $\alpha D$ | Sex, ln[*y*], ln[*a*] | 13 384.375 | 31 395 |
| | $\alpha D$ | Sex, ln[*e*], ln[*a*] | 13 379.611 | 31 395 | | $\alpha D$ | Sex, ln[*e*], ln[*a*] | 13 384.792 | 31 395 |
| | $\alpha D$ | Sex, ln[*y*], ln[*e*], ln[*a*] | 13 378.191 | 31 394 | | $\alpha D$ | Sex, ln[*y*], ln[*e*], ln[*a*] | 13 383.952 | 31 394 |
| | **$\alpha D$** | **Sex, ln[*y*], ln[*a*]** | **13 379.354** | **31 395** | | **$\alpha D$** | **ln[*y*], ln[*a*]** | **13 384.596** | **31 396** |
| | $\beta D^2$ | Sex, ln[*y*], ln[*a*] | 13 389.278 | 31 395 | | $\beta D^2$ | ln[*y*], ln[*a*] | 13 390.499 | 31 396 |
| | **$\alpha D + \beta D^2$** | **Sex, ln[*y*], ln[*a*]** | **13 376.676** | **31 394** | | **$\alpha D + \beta D^2$** | **ln[*y*], ln[*a*]** | **13 380.658** | **31 395** |
| | $(\alpha D + \beta D^2) \exp[\gamma D]$ | Sex, ln[*y*], ln[*a*] | 13 375.654 | 31 393 | | $(\alpha D + \beta D^2) \exp[\gamma D]$ | ln[*y*], ln[*a*] | 13 378.904 | 31 394 |
| | $\alpha D^k$ | Sex, ln[*y*], ln[*a*] | 13 376.600 | 31 394 | | $\alpha D^k$ | ln[*y*], ln[*a*] | 13 380.299 | 31 395 |
| | $\alpha D \exp[\gamma D]$ | Sex, ln[*y*], ln[*a*] | 13 377.047 | 31 394 | | $\alpha D \exp[\gamma D]$ | ln[*y*], ln[*a*] | 13 381.330 | 31 395 |

[a] $D$ = RBE 10 colon dose (Sv), $a$ = attained age, $e$ = age at exposure, $y$ = years since exposure ($= a - e$).

**Table D2 Comparison of fits of BEIR VII [C37] models with those of generalized ERR and EAR models to LSS solid cancer mortality data from table D1**
Data set used for reference [P10]; models assume 35% GSD errors in colon dose; dose errors corrected using methods of appendix C.
The optimal models are shown in boldface

| | *Dose response* | *Modifier*[a] | *Deviance* | *df* | | *Dose response* | *Modifier*[a] | *Deviance* | *df* |
|---|---|---|---|---|---|---|---|---|---|
| Background | – | – | 13 553.081 | 31 399 | | | | | |
| Relative risk | $\alpha D$ | – | 13 423.324 | 31 398 | Additive risk | $\alpha D$ | – | 13 492.779 | 31 398 |
| | **$\alpha D$** | **Sex, ln[*y*], ln[*a*]** | **13 379.354** | **31 395** | | **$\alpha D$** | **Sex, ln[*y*], ln[*a*]** | **13 384.596** | **31 396** |
| | $\alpha D$ | Sex, ln[*a*], min(*e* – 30, 0) | 13 378.098 | 31 395 | | $\alpha D$ | Sex, ln[*a*], min(*e* – 30, 0) | 13 384.145 | 31 396 |
| | $\alpha D$ | Sex, ln[*a*], max(*e* – 30, 0) | 13 388.418 | 31 395 | | $\alpha D$ | Sex, ln[*a*], max(*e* – 30, 0) | 13 389.128 | 31 396 |
| | $\alpha D$ | Sex, ln[*a*], min(*e* – 30, 0), max(*e* – 30, 0) | 13 377.914 | 31 394 | | $\alpha D$ | Sex, ln[*a*], min(*e* – 30, 0), max(*e* – 30, 0) | 13 383.834 | 31 395 |
| | $\alpha D$ | Sex, ln[*a*], min(*e* – 30, 0) = max(*e* – 30, 0)[b] | 13 379.616 | 31 395 | | $\alpha D$ | Sex, ln[*a*], min(*e* – 30, 0) = max(*e* – 30, 0)[b] | 13 384.522 | 31 396 |

[a] $D$ = RBE 10 colon dose (Sv), $a$ = attained age, $e$ = age at exposure, $y$ = years since exposure (= $a - e$).
[b] Coefficient of min($e$ – 30, 0) is constrained = coefficient of max($e$ – 30, 0), equivalent to a regression with adjustment for age at exposure $e$.

**Table D3 Fits of generalized ERR and EAR models to LSS leukaemia mortality data, assuming 35% GSD errors in red bone marrow dose**
Data set used for reference [P10], with dose errors corrected using methods of appendix C. The optimal models are shown in boldface

| | *Dose response* | *Modifier*[a] | *Deviance* | *df* | | *Dose response* | *Modifier*[a] | *Deviance* | *df* |
|---|---|---|---|---|---|---|---|---|---|
| Background | – | – | 2 304.986 | 31 415 | | – | | | |
| Relative risk | $\alpha D$ | – | 2 166.805 | 31 414 | Additive risk | $\alpha D$ | – | 2 163.391 | 31 414 |
| | $\beta D^2$ | – | 2 159.394 | 31 414 | | $\beta D^2$ | – | 2 159.996 | 31 414 |
| | $\alpha D + \beta D^2$ | – | 2 157.419 | 31 413 | | $\alpha D + \beta D^2$ | – | 2 156.286 | 31 413 |
| | $\alpha D + \beta D^2$ | Sex | 2 157.382 | 31 412 | | $\alpha D + \beta D^2$ | Sex | 2 152.052 | 31 412 |
| | $\alpha D + \beta D^2$ | City | 2 156.728 | 31 412 | | $\alpha D + \beta D^2$ | Sex, city | 2 147.281 | 31 411 |
| | $\alpha D + \beta D^2$ | ln[*y*] | 2 145.980 | 31 412 | | $\alpha D + \beta D^2$ | Sex, ln[*y*] | 2 143.252 | 31 411 |
| | $\alpha D + \beta D^2$ | ln[*e*] | 2 150.151 | 31 412 | | $\alpha D + \beta D^2$ | Sex, ln[*e*] | 2 151.746 | 31 411 |
| | $\alpha D + \beta D^2$ | ln[*a*] | 2 136.589 | 31 412 | | $\alpha D + \beta D^2$ | Sex, ln[*a*] | 2 147.385 | 31 411 |
| | $\alpha D + \beta D^2$ | ln[*y*], ln[*e*] | 2 137.715 | 31 411 | | $\alpha D + \beta D^2$ | Sex, ln[*y*], ln[*e*] | 2 143.171 | 31 410 |
| | $\alpha D + \beta D^2$ | ln[*y*], ln[*a*] | 2 135.696 | 31 411 | | $\alpha D + \beta D^2$ | Sex, ln[*y*], ln[*a*] | 2 142.753 | 31 410 |
| | $\alpha D + \beta D^2$ | ln[*e*], ln[*a*] | 2 136.196 | 31 411 | | $\alpha D + \beta D^2$ | Sex, ln[*e*], ln[*a*] | 2 142.412 | 31 410 |
| | $\alpha D + \beta D^2$ | ln[*y*], ln[*e*], ln[*a*] | 2 135.673 | 31 410 | | $\alpha D + \beta D^2$ | Sex, ln[*y*], ln[*e*], ln[*a*] | 2 142.113 | 31 409 |
| | $\alpha D$ | ln[*a*] | 2 145.119 | 31 413 | | $\alpha D$ | Sex, ln[*y*] | 2 150.796 | 31 412 |
| | **$\beta D^2$** | **ln[*a*]** | **2 139.632** | **31 413** | | **$\beta D^2$** | **Sex, ln[*y*]** | **2 146.742** | **31 412** |
| | **$\alpha D + \beta D^2$** | **ln[*a*]** | **2 136.589** | **31 412** | | **$\alpha D + \beta D^2$** | **Sex, ln[*y*]** | **2 143.252** | **31 411** |
| | $(\alpha D + \beta D^2) \exp[\gamma D]$ | ln[*a*] | 2 133.537 | 31 411 | | $(\alpha D + \beta D^2) \exp[\gamma D]$ | Sex, ln[*y*] | 2 141.538 | 31 410 |
| | $\alpha D^k$ | ln[*a*] | 2 134.859 | 31 412 | | $\alpha D^k$ | Sex, ln[*y*] | 2 142.082 | 31 411 |
| | $\alpha D \exp[\gamma D]$ | ln[*a*] | 2 138.449 | 31 412 | | $\alpha D \exp[\gamma D]$ | Sex, ln[*y*] | 2 144.620 | 31 411 |

[a] $D$ = RBE 10 bone marrow dose (Sv), $a$ = attained age, $e$ = age at exposure, $y$ = years since exposure ($= a - e$).

**Table D4 Comparison of fits of BEIR VII [C37] models with those of generalized ERR and EAR models to LSS leukaemia mortality data from table D3**
Data set used for reference [P10]; generalized models assume 35% GSD errors in colon dose; dose errors corrected using methods of appendix C.
The optimal models are shown in boldface

| | *Dose response* | *Modifier*[a] | *Deviance* | *df* | | *Dose response* | *Modifier*[a] | *Deviance* | *df* |
|---|---|---|---|---|---|---|---|---|---|
| Background | – | – | 2 304.986 | 31 415 | | | | | |
| Relative risk | $\alpha D + \beta D^2$ | – | 2 157.419 | 31 413 | Additive risk | $\alpha D + \beta D^2$ | – | 2 156.286 | 31 413 |
| | **$\alpha D + \beta D^2$** | **ln[*a*]** | **2 136.589** | **31 412** | | **$\alpha D + \beta D^2$** | **Sex, ln[*y*]** | **2 143.252** | **31 411** |
| | $\alpha D + \beta D^2$ | ln[*y*], min(*e* – 30, 0) | 2 137.205 | 31 411 | | $\alpha D + \beta D^2$ | Sex, ln[*y*], min(*e* – 30, 0) | 2 143.251 | 31 410 |
| | $\alpha D + \beta D^2$ | ln[*y*], max(*e* – 30, 0) | 2 144.070 | 31 411 | | $\alpha D + \beta D^2$ | Sex, ln[*y*], max(*e* – 30, 0) | 2 142.444 | 31 410 |
| | $\alpha D + \beta D^2$ | ln[*y*], min(*e* – 30, 0), max(*e* – 30, 0) | 2 137.041 | 31 410 | | $\alpha D + \beta D^2$ | Sex, ln[*y*], min(*e* – 30, 0), max(*e* – 30, 0) | 2 142.015 | 31 409 |
| | $\alpha D + \beta D^2$ | ln[*y*], min(*e* – 30, 0) = max(*e* – 30, 0)[b] | 2 139.570 | 31 411 | | $\alpha D + \beta D^2$ | Sex, ln[*y*], min(*e* – 30, 0) = max(*e* – 30, 0)[b] | 2 143.063 | 31 410 |
| | $\alpha D + \beta D^2$ | Sex, ln[*y*], min(*e* – 30, 0) = max(*e* – 30, 0) | 2 139.224 | 31 410 | | $\alpha D + \beta D^2$ | | | |
| | $\alpha D + \beta D^2$ | ln[*y*], min(*e* – 30, 0), max(*e* – 30, 0), ln[*y*] × min(*e* – 30, 0) | 2 134.669 | 31 409 | | $\alpha D + \beta D^2$ | Sex, ln[*y*], min(*e* – 30, 0), max(*e* – 30, 0), ln[*y*] × min(*e* – 30, 0) | 2 133.293 | 31 408 |
| | $\alpha D + \beta D^2$ | ln[*y*], min(*e* – 30, 0), max(*e* – 30, 0), ln[*y*] × max(*e* – 30, 0) | 2 133.060 | 31 409 | | $\alpha D + \beta D^2$ | Sex, ln[*y*], min(*e* – 30, 0), max(*e* – 30, 0), ln[*y*] × max(*e* – 30, 0) | 2 134.876 | 31 408 |
| | $\alpha D + \beta D^2$ | ln[*y*], min(*e* – 30, 0), max(*e* – 30, 0), ln[*y*] × min(*e* – 30, 0), ln[*y*] × max(*e* – 30, 0) | 2 132.813 | 31 408 | | $\alpha D + \beta D^2$ | Sex, ln[*y*], min(*e* – 30, 0), max(*e* – 30, 0), ln[*y*] × min(*e* – 30, 0), ln[*y*] × max(*e* – 30, 0) | 2 132.206 | 31 407 |

[a] $D$ = RBE 10 bone marrow dose (Sv), $a$ = attained age, $e$ = age at exposure, $y$ = years since exposure (= $a - e$).
[b] Coefficient of min($e$ – 30, 0) is constrained = coefficient of max($e$ – 30, 0), equivalent to a regression with adjustment for age at exposure $e$.

**Table D5 Fits of generalized ERR and EAR models to LSS oesophageal cancer incidence data**

Using DS02 stomach dose, adjusted for 35% GSD dose errors, truncated, using adjustment factors derived from DS86 [P2]

The optimal models are shown in boldface

| | *Dose response* | *Modifier*[a] | *Deviance* | *df* | | *Dose response* | *Modifier*[a] | *Deviance* | *df* |
|---|---|---|---|---|---|---|---|---|---|
| Background | – | – | 1 925.653 | 42 703 | | – | | | |
| Relative risk | $\alpha D$ | – | 1 919.240 | 42 702 | Additive risk | $\alpha D$ | – | 1 923.515 | 42 702 |
| | $\alpha D + \beta D^2$ | – | 1 917.113 | 42 701 | | $\alpha D + \beta D^2$ | – | 1 923.469 | 42 701 |
| | $\alpha D$ | Sex | 1 919.168 | 42 701 | | $\alpha D$ | Sex | 1 922.152 | 42 701 |
| | $\alpha D$ | City | 1 917.732 | 42 701 | | $\alpha D$ | City | 1 921.910 | 42 701 |
| | $\alpha D$ | ln[*y*] | 1 919.147 | 42 701 | | $\alpha D$ | ln[*y*] | 1 923.489 | 42 701 |
| | $\alpha D$ | ln[*e*] | 1 918.583 | 42 701 | | $\alpha D$ | ln[*e*] | 1 920.812 | 42 701 |
| | $\alpha D$ | ln[*a*] | 1 918.271 | 42 701 | | $\alpha D$ | ln[*a*] | 1 922.293 | 42 701 |
| | $\alpha D$ | ln[*y*], ln[*e*] | 1 918.147 | 42 700 | | $\alpha D$ | ln[*y*], ln[*e*] | 1 918.536 | 42 700 |
| | $\alpha D$ | ln[*y*], ln[*a*] | 1 918.247 | 42 700 | | $\alpha D$ | ln[*y*], ln[*a*] | 1 918.429 | 42 700 |
| | $\alpha D$ | ln[e], ln[*a*] | 1 918.239 | 42 700 | | $\alpha D$ | ln[e], ln[*a*] | 1 917.996 | 42 700 |
| | $\alpha D$ | ln[*y*], ln[*e*], ln[*a*] | 1 918.078 | 42 699 | | $\alpha D$ | ln[*y*], ln[*e*], ln[*a*] | 1 913.974 | 42 699[b] |
| | **$\alpha D$** | – | **1 919.240** | **42 702** | | **$\alpha D$** | – | **1 923.515** | **42 702** |
| | $\beta D^2$ | – | 1 917.256 | 42 702 | | $\beta D^2$ | – | 1 923.522 | 42 702 |
| | $\alpha D + \beta D^2$ | – | 1 917.113 | 42 701 | | $\alpha D + \beta D^2$ | – | 1 923.469 | 42 701 |
| | $(\alpha D + \beta D^2) \exp[\gamma D]$ | – | 1 917.086 | 42 700 | | $(\alpha D + \beta D^2) \exp[\gamma D]$ | – | 1 923.383 | 42 700 |
| | $\alpha D^k$ | – | 1 917.176 | 42 701 | | $\alpha D^k$ | – | 1 923.339 | 42 701 |
| | $\alpha D \exp[\gamma D]$ | – | 1 917.601 | 42 701 | | $\alpha D \exp[\gamma D]$ | – | 1 923.501 | 42 701 |

[a] $D$ = RBE 10 stomach dose (Sv), $a$ = attained age, $e$ = age at exposure, $y$ = years since exposure (= $a - e$).

[b] Parameters did not converge.

**Table D6 Fits of generalized ERR and EAR models to LSS stomach cancer incidence data**

Using DS02 stomach dose, adjusted for 35% GSD dose errors, truncated, using adjustment factors derived from DS86 [P2]

The optimal models are shown in boldface

| | *Dose response* | *Modifier*[a] | *Deviance* | *df* | | *Dose response* | *Modifier*[a] | *Deviance* | *df* |
|---|---|---|---|---|---|---|---|---|---|
| Background | – | – | 11 304.964 | 42 693 | | | | | |
| Relative risk | $\alpha D$ | – | 11 265.131 | 42 692 | Additive risk | $\alpha D$ | – | 11 262.194 | 42 692 |
| | $\alpha D + \beta D^2$ | – | 11 263.584 | 42 691 | | $\alpha D + \beta D^2$ | – | 11 259.493 | 42 691 |
| | $\alpha D$ | Sex | 11 261.969 | 42 691 | | $\alpha D$ | Sex | 11 260.766 | 42 691 |
| | $\alpha D$ | City | 11 264.458 | 42 691 | | $\alpha D$ | City | 11 259.838 | 42 691 |
| | $\alpha D$ | ln[*y*] | 11 264.971 | 42 691 | | $\alpha D$ | ln[*y*] | 11 257.131 | 42 691 |
| | $\alpha D$ | ln[*e*] | 11 263.019 | 42 691 | | $\alpha D$ | ln[*e*] | 11 252.494 | 42 691 |
| | $\alpha D$ | ln[*a*] | 11 255.425 | 42 691 | | $\alpha D$ | ln[*a*] | 11 248.148 | 42 691 |
| | $\alpha D$ | ln[*y*], ln[*e*] | 11 261.395 | 42 690 | | $\alpha D$ | ln[*y*], ln[*e*] | 11 247.269 | 42 690 |
| | $\alpha D$ | ln[*y*], ln[*a*] | 11 255.275 | 42 690 | | $\alpha D$ | ln[*y*], ln[*a*] | 11 248.126 | 42 690 |
| | $\alpha D$ | ln[e], ln[*a*] | 11 255.214 | 42 690 | | $\alpha D$ | ln[e], ln[*a*] | 11 247.804 | 42 690 |
| | $\alpha D$ | ln[*y*], ln[*e*], ln[*a*] | 11 252.828 | 42 689 | | $\alpha D$ | ln[*y*], ln[*e*], ln[*a*] | 11 247.254 | 42 689 |
| | **$\alpha D$** | **ln[*a*]** | **11 255.425** | **42 691** | | **$\alpha D$** | **ln[*a*]** | **11 248.148** | **42 691** |
| | $\beta D^2$ | ln[*a*] | 11 259.144 | 42 691 | | $\beta D^2$ | ln[*a*] | 11 250.575 | 42 691 |
| | $\alpha D + \beta D^2$ | ln[*a*] | 11 254.760 | 42 690 | | $\alpha D + \beta D^2$ | ln[*a*] | 11 246.779 | 42 690 |
| | $(\alpha D + \beta D^2) \exp[\gamma D]$ | ln[*a*] | 11 253.979 | 42 689 | | $(\alpha D + \beta D^2) \exp[\gamma D]$ | ln[*a*] | 11 245.876 | 42 689 |
| | $\alpha D^k$ | ln[*a*] | 11 254.323 | 42 690 | | $\alpha D^k$ | ln[*a*] | 11 246.237 | 42 690 |
| | $\alpha D \exp[\gamma D]$ | ln[*a*] | 11 254.819 | 42 690 | | $\alpha D \exp[\gamma D]$ | ln[*a*] | 11 246.917 | 42 690 |

[a] $D$ = RBE 10 stomach dose (Sv), $a$ = attained age, $e$ = age at exposure, $y$ = years since exposure ($= a - e$).

**Table D7 Fits of generalized ERR and EAR models to LSS colon cancer incidence data**

Using DS02 colon dose, adjusted for 35% GSD dose errors, truncated, using adjustment factors derived from DS86 [P2]

The optimal models are shown in boldface

| | *Dose response* | *Modifier*[a] | *Deviance* | *df* | | *Dose response* | *Modifier*[a] | *Deviance* | *df* |
|---|---|---|---|---|---|---|---|---|---|
| Background | – | – | 5 301.539 | 42 696 | | – | | | |
| Relative risk | $\alpha D$ | – | 5 271.708 | 42 695 | Additive risk | $\alpha D$ | – | 5 287.660 | 42 695 |
| | $\alpha D + \beta D^2$ | – | 5 270.855 | 42 694 | | $\alpha D + \beta D^2$ | – | 5 287.224 | 42 694 |
| | $\alpha D$ | Sex | 5 268.430 | 42 694 | | $\alpha D$ | Sex | 5 287.584 | 42 694 |
| | $\alpha D$ | City | 5 269.805 | 42 694 | | $\alpha D$ | City | 5 286.036 | 42 693 |
| | $\alpha D$ | ln[*y*] | 5 270.891 | 42 694 | | $\alpha D$ | ln[*y*] | 5 277.458 | 42 694 |
| | $\alpha D$ | ln[*e*] | 5 266.835 | 42 694 | | $\alpha D$ | ln[*e*] | 5 286.425 | 42 694 |
| | $\alpha D$ | ln[*a*] | 5 262.573 | 42 694 | | $\alpha D$ | ln[*a*] | 5 280.065 | 42 694 |
| | $\alpha D$ | ln[*y*], ln[*e*] | 5 263.827 | 42 693 | | $\alpha D$ | ln[*y*], ln[*e*] | 5 277.171 | 42 693 |
| | $\alpha D$ | ln[*y*], ln[*a*] | 5 262.570 | 42 693 | | $\alpha D$ | ln[*y*], ln[*a*] | 5 276.497 | 42 693 |
| | $\alpha D$ | ln[e], ln[*a*] | 5 262.412 | 42 693 | | $\alpha D$ | ln[e], ln[*a*] | 5 276.193 | 42 693 |
| | $\alpha D$ | ln[*y*], ln[*e*], ln[*a*] | 5 262.255 | 42 692 | | $\alpha D$ | ln[*y*], ln[*e*], ln[*a*] | 5 275.759 | 42 692 |
| | **$\alpha D$** | **ln[*a*]** | **5 262.573** | **42 694** | | **$\alpha D$** | ln[*y*] | **5 277.458** | **42 694** |
| | $\beta D^2$ | ln[*a*] | 5 265.940 | 42 694 | | $\beta D^2$ | ln[*y*] | 5 275.931 | 42 694 |
| | $\alpha D + \beta D^2$ | ln[*a*] | 5 262.020 | 42 693 | | $\alpha D + \beta D^2$ | ln[*y*] | 5 275.434 | 42 693 |
| | $(\alpha D + \beta D^2) \exp[\gamma D]$ | ln[*a*] | 5 261.896 | 42 692 | | $(\alpha D + \beta D^2) \exp[\gamma D]$ | ln[*y*] | 5 275.344 | 42 692 |
| | $\alpha D^k$ | ln[*a*] | 5 262.344 | 42 693 | | $\alpha D^k$ | ln[*y*] | 5 275.624 | 42 693 |
| | $\alpha D \exp[\gamma D]$ | ln[*a*] | 5 261.896 | 42 693 | | $\alpha D \exp[\gamma D]$ | ln[*y*] | 5 275.344 | 42 693 |

[a] $D$ = RBE 10 colon dose (Sv), $a$ = attained age, $e$ = age at exposure, $y$ = years since exposure ($= a - e$).

**Table D8 Fits of generalized ERR and EAR models to LSS liver cancer incidence data**

Using DS02 liver dose, adjusted for 35% GSD dose errors, truncated, using adjustment factors derived from DS86 [P2]

The optimal models are shown in boldface

| | *Dose response* | *Modifier*[a] | *Deviance* | *df* | | *Dose response* | *Modifier*[a] | *Deviance* | *df* |
|---|---|---|---|---|---|---|---|---|---|
| Background | – | – | 5 385.654 | 42 691 | | | | | |
| Relative risk | $\alpha D$ | – | 5 370.978 | 42 690 | Additive risk | $\alpha D$ | – | 5 380.678 | 42 690 |
| | $\alpha D + \beta D^2$ | – | 5 370.502 | 42 689 | | $\alpha D + \beta D^2$ | – | 5 380.323 | 42 689 |
| | $\alpha D$ | Sex | 5 370.934 | 42 689 | | $\alpha D$ | Sex | 5 380.655 | 42 689 |
| | $\alpha D$ | City | 5 370.978 | 42 689 | | $\alpha D$ | City | 5 380.657 | 42 689 |
| | $\alpha D$ | ln[*y*] | 5 370.302 | 42 689 | | $\alpha D$ | ln[*y*] | 5 379.040 | 42 689 |
| | $\alpha D$ | ln[*e*] | 5 370.676 | 42 689 | | $\alpha D$ | ln[*e*] | 5 377.081 | 42 689 |
| | $\alpha D$ | ln[*a*] | 5 369.410 | 42 689 | | $\alpha D$ | ln[*a*] | 5 374.957 | 42 689 |
| | $\alpha D$ | ln[*y*], ln[*e*] | 5 369.538 | 42 688 | | $\alpha D$ | ln[*y*], ln[*e*] | 5 376.990 | 42 688 |
| | $\alpha D$ | ln[*y*], ln[*a*] | 5 369.357 | 42 688 | | $\alpha D$ | ln[*y*], ln[*a*] | 5 374.490 | 42 688 |
| | $\alpha D$ | ln[e], ln[*a*] | 5 369.380 | 42 688 | | $\alpha D$ | ln[e], ln[*a*] | 5 374.843 | 42 688 |
| | $\alpha D$ | ln[*y*], ln[*e*], ln[*a*] | 5 369.355 | 42 687 | | $\alpha D$ | ln[*y*], ln[*e*], ln[*a*] | 5 373.229 | 42 687 |
| | **$\alpha D$** | – | **5 370.978** | **42 690** | | **$\alpha D$** | **ln[*a*]** | **5 374.957** | **42 689** |
| | $\beta D^2$ | – | 5 375.591 | 42 690 | | $\beta D^2$ | ln[*a*] | 5 376.808 | 42 689 |
| | $\alpha D + \beta D^2$ | – | 5 370.502 | 42 689 | | $\alpha D + \beta D^2$ | ln[*a*] | 5 374.946 | 42 688 |
| | $(\alpha D + \beta D^2) \exp[\gamma D]$ | – | 5 370.347 | 42 688 | | $(\alpha D + \beta D^2) \exp[\gamma D]$ | ln[*a*] | 5 374.943 | 42 687 |
| | $\alpha D^k$ | – | 5 370.886 | 42 689 | | $\alpha D^k$ | ln[*a*] | 5 374.956 | 42 688 |
| | $\alpha D \exp[\gamma D]$ | – | 5 370.529 | 42 689 | | $\alpha D \exp[\gamma D]$ | ln[*a*] | 5 374.943 | 42 688 |

[a] $D$ = RBE 10 liver dose (Sv), $a$ = attained age, $e$ = age at exposure, $y$ = years since exposure ($= a - e$).

**Table D9 Fits of generalized ERR and EAR models to LSS lung cancer incidence data**

Using DS02 lung dose, adjusted for 35% GSD dose errors, truncated, using adjustment factors derived from DS86 [P2]

The optimal models are shown in boldface

| | *Dose response* | *Modifier*[a] | *Deviance* | *df* | | *Dose response* | *Modifier*[a] | *Deviance* | *df* |
|---|---|---|---|---|---|---|---|---|---|
| Background | – | – | 6 243.855 | 42 697 | | | | | |
| Relative risk | $\alpha D$ | – | 6 196.943 | 42 696 | Additive risk | $\alpha D$ | – | 6 224.174 | 42 696 |
| | $\alpha D + \beta D^2$ | – | 6 196.798 | 42 695 | | $\alpha D + \beta D^2$ | – | 6 222.681 | 42 695 |
| | $\alpha D$ | Sex | 6 181.503 | 42 695 | | $\alpha D$ | Sex | 6 219.857 | 42 695 |
| | $\alpha D$ | City | 6 196.531 | 42 695 | | $\alpha D$ | City | 6 223.862 | 42 695 |
| | $\alpha D$ | Sex, ln[*y*] | 6 178.245 | 42 694 | | $\alpha D$ | Sex, ln[*y*] | 6 209.186 | 42 694 |
| | $\alpha D$ | Sex, ln[*e*] | 6 181.439 | 42 694 | | $\alpha D$ | Sex, ln[*e*] | 6 199.128 | 42 694 |
| | $\alpha D$ | Sex, ln[*a*] | 6 179.834 | 42 694 | | $\alpha D$ | Sex, ln[*a*] | 6 180.250 | 42 694 |
| | $\alpha D$ | Sex, ln[*y*], ln[*e*] | 6 177.052 | 42 693 | | $\alpha D$ | Sex, ln[*y*], ln[*e*] | 6 185.259 | 42 693 |
| | $\alpha D$ | Sex, ln[*y*], ln[*a*] | 6 177.635 | 42 693 | | $\alpha D$ | Sex, ln[*y*], ln[*a*] | 6 180.195 | 42 693 |
| | $\alpha D$ | Sex, ln[*e*], ln[*a*] | 6 179.284 | 42 693 | | $\alpha D$ | Sex, ln[*e*], ln[*a*] | 6 180.249 | 42 693 |
| | $\alpha D$ | Sex, ln[*y*], ln[*e*], ln[*a*] | 6 177.013 | 42 692 | | $\alpha D$ | Sex, ln[*y*], ln[*e*], ln[*a*] | 6 180.036 | 42 692 |
| | **$\alpha D$** | **Sex** | **6 181.503** | **42 695** | | **$\alpha D$** | **Sex, ln[*a*]** | **6 180.250** | **42 694** |
| | $\beta D^2$ | Sex | 6 194.664 | 42 695 | | $\beta D^2$ | Sex, ln[*a*] | 6 191.337 | 42 694 |
| | $\alpha D + \beta D^2$ | Sex | 6 181.296 | 42 694 | | $\alpha D + \beta D^2$ | Sex, ln[*a*] | 6 180.227 | 42 693 |
| | $(\alpha D + \beta D^2) \exp[\gamma D]$ | Sex | 6 180.487 | 42 694 | | $(\alpha D + \beta D^2) \exp[\gamma D]$ | Sex, ln[*a*] | 6 179.547 | 42 693 |
| | $\alpha D^k$ | Sex | 6 181.414 | 42 694 | | $\alpha D^k$ | Sex, ln[*a*] | 6 180.247 | 42 693 |
| | $\alpha D \exp[\gamma D]$ | Sex | 6 181.342 | 42 694 | | $\alpha D \exp[\gamma D]$ | Sex, ln[*a*] | 6 180.232 | 42 693 |

[a] $D$ = RBE 10 lung dose (Sv), $a$ = attained age, $e$ = age at exposure, $y$ = years since exposure ($= a - e$).

**Table D10 Fits of generalized ERR and EAR models to LSS bone cancer incidence data**

Using DS02 skeletal dose, adjusted for 35% GSD dose errors, truncated, using adjustment factors derived from DS86 [P2]

The optimal models are shown in boldface

| | *Dose response* | *Modifier*[a] | *Deviance* | *df* | | *Dose response* | *Modifier*[a] | *Deviance* | *df* |
|---|---|---|---|---|---|---|---|---|---|
| Background | – | – | 249.461 | 42 705 | | | | | |
| Relative risk | $\alpha D$ | – | 244.791 | 42 704 | Additive risk | $\alpha D$ | – | 242.675 | 42 704 |
| | $\alpha D + \beta D^2$ | – | 235.120 | 42 703 | | $\alpha D + \beta D^2$ | – | 238.958 | 42 703 |
| | $\beta D^2$ | – | 241.039 | 42 704 | | $\beta D^2$ | – | 238.937 | 42 704 |
| | $\beta D^2$ | Sex | 237.389 | 42 703[b] | | $\beta D^2$ | Sex | 233.614 | 42 704[b] |
| | $\beta D^2$ | City | 240.989 | 42 703 | | $\beta D^2$ | City | 238.930 | 42 703 |
| | $\beta D^2$ | ln[*y*] | 240.840 | 42 703 | | $\beta D^2$ | ln[*y*] | 238.853 | 42 703 |
| | $\beta D^2$ | ln[*e*] | 238.839 | 42 703 | | $\beta D^2$ | ln[*e*] | 237.773 | 42 703 |
| | $\beta D^2$ | ln[*a*] | 236.222 | 42 703 | | $\beta D^2$ | ln[*a*] | 237.613 | 42 703 |
| | $\beta D^2$ | ln[*y*], ln[*e*] | 237.278 | 42 702 | | $\beta D^2$ | ln[*y*], ln[*e*] | 237.639 | 42 702 |
| | $\beta D^2$ | ln[*y*], ln[*a*] | 236.105 | 42 702 | | $\beta D^2$ | ln[*y*], ln[*a*] | 236.775 | 42 702 |
| | $\beta D^2$ | ln[*e*], ln[*a*] | 236.126 | 42 702 | | $\beta D^2$ | ln[*e*], ln[*a*] | 237.412 | 42 702 |
| | $\beta D^2$ | ln[*y*], ln[*e*], ln[*a*] | 236.103 | 42 701 | | $\beta D^2$ | ln[*y*], ln[*e*], ln[*a*] | 234.217 | 42 701 |
| | $\alpha D$ | ln[*a*] | 239.810 | 42 703 | | $\alpha D$ | – | 242.675 | 42 704 |
| | **$\beta D^2$** | **ln[*a*]** | **236.222** | **42 703** | | **$\beta D^2$** | – | **238.937** | **42 704** |
| | $\alpha D + \beta D^2$ | ln[*a*] | 236.023 | 42 702 | | $\alpha D + \beta D^2$ | – | 238.726 | 42 703 |
| | $(\alpha D + \beta D^2) \exp[\gamma D]$ | ln[*a*] | 236.010 | 42 701 | | $(\alpha D + \beta D^2) \exp[\gamma D]$ | – | 238.687 | 42 702 |
| | $\alpha D^k$ | ln[*a*] | 235.332 | 42 702 | | $\alpha D^k$ | – | 237.824 | 42 703 |
| | $\alpha D \exp[\gamma D]$ | ln[*a*] | 236.299 | 42 702 | | $\alpha D \exp[\gamma D]$ | – | 238.761 | 42 703 |

[a] $D$ = RBE 10 stomach dose (Sv), $a$ = attained age, $e$ = age at exposure, $y$ = years since exposure (= $a - e$).

[b] Adjustment for sex did not converge.

**Table D11 Fits of generalized ERR and EAR models to LSS non-melanoma skin cancer incidence data**
Using DS02 skin dose, adjusted for 35% GSD dose errors, truncated, using adjustment factors derived from DS86 [P2]
The optimal models are shown in boldface

| | *Dose response* | *Modifier*[a] | *Deviance* | *df* | | *Dose response* | *Modifier*[a] | *Deviance* | *df* |
|---|---|---|---|---|---|---|---|---|---|
| Background | – | – | 2 234.237 | 42 700 | | | | | |
| Relative risk | $\alpha D$ | – | 2 181.366 | 42 699 | Additive risk | $\alpha D$ | – | 2 168.251 | 42 699 |
| | $\alpha D + \beta D^2$ | – | 2 177.636 | 42 698 | | $\alpha D + \beta D^2$ | – | 2 165.586 | 42 698 |
| | $\alpha D$ | Sex | 2 181.355 | 42 698 | | $\alpha D$ | Sex | 2 168.195 | 42 698 |
| | $\alpha D$ | City | 2 177.123 | 42 698 | | $\alpha D$ | City | 2 167.379 | 42 698 |
| | $\alpha D$ | City, ln[*y*] | 2 175.065 | 42 697 | | $\alpha D$ | ln[*y*] | 2 147.974 | 42 698 |
| | $\alpha D$ | City, ln[*e*] | 2 161.213 | 42 697 | | $\alpha D$ | ln[*e*] | 2 167.670 | 42 698 |
| | $\alpha D$ | City, ln[*a*] | 2 164.305 | 42 697 | | $\alpha D$ | ln[*a*] | 2 162.436 | 42 698 |
| | $\alpha D$ | City, ln[*y*], ln[*e*] | 2 160.926 | 42 696 | | $\alpha D$ | ln[*y*], ln[*e*] | 2 147.854 | 42 697 |
| | $\alpha D$ | City, ln[*y*], ln[*a*] | 2 151.978 | 42 696 | | $\alpha D$ | ln[*y*], ln[*a*] | 2 147.973 | 42 697 |
| | $\alpha D$ | City, ln[*e*], ln[*a*] | 2 159.020 | 42 696 | | $\alpha D$ | ln[*e*], ln[*a*] | 2 154.636 | 42 697 |
| | $\alpha D$ | City, ln[*y*], ln[*e*], ln[*a*] | 2 151.122 | 42 695 | | $\alpha D$ | ln[*y*], ln[*e*], ln[*a*] | 2 147.312 | 42 696 |
| | $\alpha D$ | ln[*y*], ln[*a*] | 2 153.145 | 42 697 | | $\alpha D$ | ln[*y*] | 2 147.974 | 42 698 |
| | $\beta D^2$ | ln[*y*], ln[*a*] | 2 149.904 | 42 697 | | $\beta D^2$ | ln[*y*] | 2 143.777 | 42 698 |
| | **$\beta D^2 \exp[\gamma D]$** | **ln[*y*], ln[*a*]** | **2 144.933** | **42 696** | | **$\beta D^2 \exp[\gamma D]$** | **ln[*y*]** | **2 138.579** | **42 697** |
| | $\alpha D + \beta D^2$ | ln[*y*], ln[*a*] | 2 148.971 | 42 696 | | $\alpha D + \beta D^2$ | ln[*y*] | 2 143.230 | 42 697 |
| | $(\alpha D + \beta D^2) \exp[\gamma D]$ | ln[*y*], ln[*a*] | 2 144.247 | 42 695 | | $(\alpha D + \beta D^2) \exp[\gamma D]$ | ln[*y*] | 2 138.072 | 42 696 |
| | $\alpha D^k$ | ln[*y*], ln[*a*] | 2 147.698 | 42 696 | | $\alpha D^k$ | ln[*y*] | 2 141.524 | 42 697 |
| | $\alpha D^k \exp[\gamma D]$ | ln[*y*], ln[*a*] | 2 138.531 | 42 695 | | $\alpha D^k \exp[\gamma D]$ | ln[*y*] | 2 133.231 | 42 696 |
| | $\alpha D \exp[\gamma D]$ | ln[*y*], ln[*a*] | 2 150.861 | 42 696 | | $\alpha D \exp[\gamma D]$ | ln[*y*] | 2 145.470 | 42 697 |

[a] $D$ = RBE 10 stomach dose (Sv), $a$ = attained age, $e$ = age at exposure, $y$ = years since exposure ($= a - e$).

**Table D12 Fits of generalized ERR and EAR models to LSS female breast cancer incidence data**

Using DS02 breast dose, adjusted for 35% GSD dose errors, truncated, using adjustment factors derived from DS86 [P2]

The optimal models are shown in boldface

| | *Dose response* | *Modifier*[a] | *Deviance* | *df* | | *Dose response* | *Modifier*[a] | *Deviance* | *df* |
|---|---|---|---|---|---|---|---|---|---|
| Background | – | – | 4 020.486 | 22 293 | | | | | |
| Relative risk | $\alpha D$ | – | 3 893.514 | 22 292 | Additive risk | $\alpha D$ | – | 3 912.142 | 22 292 |
| | $\alpha D + \beta D^2$ | – | 3 893.512 | 22 291 | | $\alpha D + \beta D^2$ | – | 3 911.963 | 22 291 |
| | $\alpha D$ | City | 3 893.155 | 22 291 | | $\alpha D$ | City | 3 911.940 | 22 291 |
| | $\alpha D$ | ln[*y*] | 3 891.953 | 22 291 | | $\alpha D$ | ln[*y*] | 3 900.082 | 22 291 |
| | $\alpha D$ | ln[*e*] | 3 891.686 | 22 291 | | $\alpha D$ | ln[*e*] | 3 911.871 | 22 291 |
| | $\alpha D$ | ln[*a*] | 3 881.872 | 22 291 | | $\alpha D$ | ln[*a*] | 3 910.297 | 22 291 |
| | $\alpha D$ | ln[*y*], ln[*e*] | 3 887.062 | 22 290 | | $\alpha D$ | ln[*y*], ln[*e*] | 3 899.895 | 22 290 |
| | $\alpha D$ | ln[*y*], ln[*a*] | 3 881.870 | 22 290 | | $\alpha D$ | ln[*y*], ln[*a*] | 3 899.476 | 22 290 |
| | $\alpha D$ | ln[*e*], ln[*a*] | 3 881.793 | 22 290 | | $\alpha D$ | ln[*e*], ln[*a*] | 3 904.857 | 22 290 |
| | $\alpha D$ | ln[*y*], ln[*e*], ln[*a*] | 3 881.543 | 22 289 | | $\alpha D$ | ln[*y*], ln[*e*], ln[*a*] | 3 898.853 | 22 289 |
| | **$\alpha D$** | **ln[*a*]** | **3 881.872** | **22 291** | | **$\alpha D$** | ln[*y*] | **3 900.082** | **22 291** |
| | $\beta D^2$ | ln[*a*] | 3 910.535 | 22 291 | | $\beta D^2$ | ln[*y*] | 3 925.959 | 22 291 |
| | $\alpha D + \beta D^2$ | ln[*a*] | 3 881.854 | 22 290 | | $\alpha D + \beta D^2$ | ln[*y*] | 3 900.082 | 22 290 |
| | $(\alpha D + \beta D^2) \exp[\gamma D]$ | ln[*a*] | 3 881.852 | 22 290 | | $(\alpha D + \beta D^2) \exp[\gamma D]$ | ln[*y*] | 3 900.081 | 22 290 |
| | $\alpha D^k$ | ln[*a*] | 3 881.871 | 22 290 | | $\alpha D^k$ | ln[*y*] | 3 900.082 | 22 290 |
| | $\alpha D \exp[\gamma D]$ | ln[*a*] | 3 881.852 | 22 290 | | $\alpha D \exp[\gamma D]$ | ln[*y*] | 3 900.081 | 22 290 |

[a] $D$ = RBE 10 stomach dose (Sv), $a$ = attained age, $e$ = age at exposure, $y$ = years since exposure ($= a - e$).

**Table D13 Fits of generalized ERR and EAR models to LSS urinary bladder cancer incidence data**

Using DS02 bladder dose, adjusted for 35% GSD dose errors, truncated, using adjustment factors derived from DS86 [P2]

The optimal models are shown in boldface

| | *Dose response* | *Modifier*[a] | *Deviance* | *df* | | *Dose response* | *Modifier*[a] | *Deviance* | *df* |
|---|---|---|---|---|---|---|---|---|---|
| Background | – | – | 2 564.693 | 42 703 | | | | | |
| Relative risk | $\alpha D$ | – | 2 550.130 | 42 702 | Additive risk | $\alpha D$ | – | 2 563.278 | 42 702 |
| | $\alpha D + \beta D^2$ | – | 2 549.083 | 42 701 | | $\alpha D + \beta D^2$ | – | 2 563.008 | 42 701 |
| | $\alpha D$ | Sex | 2 548.109 | 42 701 | | $\alpha D$ | Sex | 2 563.114 | 42 701 |
| | $\alpha D$ | City | 2 549.908 | 42 701 | | $\alpha D$ | City | 2 561.614 | 42 702 |
| | $\alpha D$ | ln[*y*] | 2 549.988 | 42 701 | | $\alpha D$ | ln[*y*] | 2 563.754 | 42 701 |
| | $\alpha D$ | ln[*e*] | 2 549.643 | 42 701 | | $\alpha D$ | ln[*e*] | 2 559.100 | 42 701 |
| | $\alpha D$ | ln[*a*] | 2 550.118 | 42 701 | | $\alpha D$ | ln[*a*] | 2 549.723 | 42 701 |
| | $\alpha D$ | ln[*y*], ln[*e*] | 2 549.591 | 42 700 | | $\alpha D$ | ln[*y*], ln[*e*] | 2 550.912 | 42 700 |
| | $\alpha D$ | ln[*y*], ln[*a*] | 2 549.868 | 42 700 | | $\alpha D$ | ln[*y*], ln[*a*] | 2 549.721 | 42 700 |
| | $\alpha D$ | ln[*e*], ln[*a*] | 2 549.424 | 42 700 | | $\alpha D$ | ln[*e*], ln[*a*] | 2 549.596 | 42 700 |
| | $\alpha D$ | ln[*y*], ln[*e*], ln[*a*] | 2 549.338 | 42 699 | | $\alpha D$ | ln[*y*], ln[*e*], ln[*a*] | 2 549.268 | 42 699 |
| | ***αD*** | – | **2 550.130** | **42 702** | | ***αD*** | **ln[*a*]** | **2 549.723** | **42 701** |
| | $\beta D^2$ | – | 2 556.176 | 42 702 | | $\beta D^2$ | ln[*a*] | 2 555.112 | 42 701 |
| | $\alpha D + \beta D^2$ | – | 2 549.083 | 42 701 | | $\alpha D + \beta D^2$ | ln[*a*] | 2 549.309 | 42 700 |
| | $(\alpha D + \beta D^2) \exp[\gamma D]$ | – | 2 548.656 | 42 700 | | $(\alpha D + \beta D^2) \exp[\gamma D]$ | ln[*a*] | 2 549.095 | 42 699 |
| | $\alpha D^k$ | – | 2 548.300 | 42 701 | | $\alpha D^k$ | ln[*a*] | 2 546.591 | 42 700 |
| | $\alpha D \exp[\gamma D]$ | – | 2 548.656 | 42 701 | | $\alpha D \exp[\gamma D]$ | ln[*a*] | 2 549.095 | 42 700 |

[a] $D$ = RBE 10 stomach dose (Sv), $a$ = attained age, $e$ = age at exposure, $y$ = years since exposure ($= a - e$).

**Table D14 Fits of generalized ERR and EAR models to LSS central nervous system cancer incidence data**
Using DS02 brain dose, adjusted for 35% GSD dose errors, truncated, using adjustment factors derived from DS86 [P2]
The optimal models are shown in boldface

| | *Dose response* | *Modifier*[a] | *Deviance* | *df* | | *Dose response* | *Modifier*[a] | *Deviance* | *df* |
|---|---|---|---|---|---|---|---|---|---|
| Background | – | – | 1 888.619 | 42 688 | | | | | |
| Relative risk | $\alpha D$ | – | 1 881.012 | 42 687 | Additive risk | $\alpha D$ | – | 1 877.645 | 42 687 |
| | $\alpha D + \beta D^2$ | – | 1 880.237 | 42 686 | | $\alpha D + \beta D^2$ | – | 1 877.488 | 42 686 |
| | $\alpha D$ | Sex | 1 873.972[b] | 42 686 | | $\alpha D$ | Sex | 1 875.613 | 42 686 |
| | $\alpha D$ | City | 1 880.600 | 42 686 | | $\alpha D$ | City | 1 877.585 | 42 686 |
| | $\alpha D$ | ln[*y*] | 1 880.237 | 42 686 | | $\alpha D$ | ln[*y*] | 1 876.777 | 42 686 |
| | $\alpha D$ | ln[*e*] | 1 874.928 | 42 686 | | $\alpha D$ | ln[*e*] | 1 875.032 | 42 686 |
| | $\alpha D$ | ln[*a*] | 1 871.623 | 42 686 | | $\alpha D$ | ln[*a*] | 1 877.331 | 42 686 |
| | $\alpha D$ | ln[*y*], ln[*e*] | 1 871.959 | 42 685 | | $\alpha D$ | ln[*y*], ln[*e*] | 1 874.096 | 42 685 |
| | $\alpha D$ | ln[*y*], ln[*a*] | 1 870.675 | 42 685 | | $\alpha D$ | ln[*y*], ln[*a*] | 1 873.782 | 42 685 |
| | $\alpha D$ | ln[*e*], ln[*a*] | 1 870.773 | 42 685 | | $\alpha D$ | ln[*e*], ln[*a*] | 1 874.513 | 42 685 |
| | $\alpha D$ | ln[*y*], ln[*e*], ln[*a*] | 1 870.739 | 42 684 | | $\alpha D$ | ln[*y*], ln[*e*], ln[*a*] | 1 873.761 | 42 684 |
| | **$\alpha D$** | **ln[*e*]** | **1 874.928** | **42 686** | | **$\alpha D$** | **–** | **1 877.645** | **42 687** |
| | $\beta D^2$ | ln[*e*] | 1 875.056 | 42 686 | | $\beta D^2$ | – | 1 880.184 | 42 687 |
| | $\alpha D + \beta D^2$ | ln[*e*] | 1 874.681 | 42 685 | | $\alpha D + \beta D^2$ | – | 1 877.488 | 42 686 |
| | $(\alpha D + \beta D^2) \exp[\gamma D]$ | ln[*e*] | 1 873.774 | 42 684 | | $(\alpha D + \beta D^2) \exp[\gamma D]$ | – | 1 877.472 | 42 685 |
| | $\alpha D^k$ | ln[*e*] | 1 874.055 | 42 685 | | $\alpha D^k$ | – | 1 877.512 | 42 686 |
| | $\alpha D \exp[\gamma D]$ | ln[*e*] | 1 874.769 | 42 685 | | $\alpha D \exp[\gamma D]$ | – | 1 877.472 | 42 686 |

[a] $D$ = RBE 10 stomach dose (Sv), $a$ = attained age, $e$ = age at exposure, $y$ = years since exposure ($= a - e$).
[b] Adjustment for sex did not converge.

**Table D15 Fits of generalized ERR and EAR models to LSS thyroid cancer incidence data**

Using DS02 thyroid dose, adjusted for 35% GSD dose errors, truncated, using adjustment factors derived from DS86 [P2]
The optimal models are shown in boldface

| | *Dose response* | *Modifier*[a] | *Deviance* | *df* | | *Dose response* | *Modifier*[a] | *Deviance* | *df* |
|---|---|---|---|---|---|---|---|---|---|
| Background | – | – | 2 972.807 | 42 700 | | | | | |
| Relative risk | $\alpha D$ | – | 2 916.527 | 42 699 | Additive risk | $\alpha D$ | – | 2 910.634 | 42 699 |
| | $\alpha D + \beta D^2$ | – | 2 914.496 | 42 698 | | $\alpha D + \beta D^2$ | – | 2 908.782 | 42 698 |
| | $\alpha D$ | Sex | 2 913.918 | 42 698 | | $\alpha D$ | Sex | 2 899.530 | 42 698 |
| | $\alpha D$ | City | 2 916.496 | 42 698 | | $\alpha D$ | City | 2 910.449 | 42 698 |
| | $\alpha D$ | ln[*y*] | 2 916.154 | 42 698 | | $\alpha D$ | Sex, ln[*y*] | 2 899.455 | 42 697 |
| | $\alpha D$ | ln[*e*] | 2 898.013 | 42 698 | | $\alpha D$ | Sex, ln[*e*] | 2 893.558 | 42 697 |
| | $\alpha D$ | ln[*a*] | 2 894.746 | 42 698 | | $\alpha D$ | Sex, ln[*a*] | 2 897.871 | 42 697 |
| | $\alpha D$ | ln[*y*], ln[*e*] | 2 892.908 | 42 697 | | $\alpha D$ | Sex, ln[*y*], ln[*e*] | 2 893.514 | 42 696 |
| | $\alpha D$ | ln[*y*], ln[*a*] | 2 892.942 | 42 697 | | $\alpha D$ | Sex, ln[*y*], ln[*a*] | 2 896.769 | 42 696 |
| | $\alpha D$ | ln[*e*], ln[*a*] | 2 890.965 | 42 697 | | $\alpha D$ | Sex, ln[*e*], ln[*a*] | 2 892.970 | 42 696 |
| | $\alpha D$ | ln[*y*], ln[*e*], ln[*a*] | 2 890.845 | 42 696 | | $\alpha D$ | Sex, ln[*y*], ln[*e*], ln[*a*] | 2 891.211 | 42 695 |
| | ***αD*** | **ln[*e*], ln[*a*]** | **2 890.965** | **42 697** | | ***αD*** | **Sex, ln[*e*]** | **2 893.558** | **42 697** |
| | $\beta D^2$ | ln[*e*], ln[*a*] | 2 915.645 | 42 697 | | $\beta D^2$ | Sex, ln[*e*] | 2 916.066 | 42 697 |
| | $\alpha D + \beta D^2$ | ln[*e*], ln[*a*] | 2 888.188 | 42 696 | | $\alpha D + \beta D^2$ | Sex, ln[*e*] | 2 891.262 | 42 696 |
| | $(\alpha D + \beta D^2) \exp[\gamma D]$ | ln[*e*], ln[*a*] | 2 887.650 | 42 695 | | $(\alpha D + \beta D^2) \exp[\gamma D]$ | Sex, ln[*e*] | 2 890.593 | 42 695 |
| | $\alpha D^k$ | ln[*e*], ln[*a*] | 2 890.066 | 42 696 | | $\alpha D^k$ | Sex, ln[*e*] | 2 892.870 | 42 696 |
| | $\alpha D \exp[\gamma D]$ | ln[*e*], ln[*a*] | 2 888.517 | 42 696 | | $\alpha D \exp[\gamma D]$ | Sex, ln[*e*] | 2 891.520 | 42 696 |

[a] $D$ = RBE 10 stomach dose (Sv), $a$ = attained age, $e$ = age at exposure, $y$ = years since exposure ($= a - e$).

**Table D16 Fits of generalized ERR and EAR models to LSS incidence data for all other solid cancers**
Using DS02 colon dose, adjusted for 35% GSD dose errors, truncated, using adjustment factors derived from DS86 [P2]
The optimal models are shown in boldface

| | *Dose response* | *Modifier*[a] | *Deviance* | *df* | | *Dose response* | *Modifier*[a] | *Deviance* | *df* |
|---|---|---|---|---|---|---|---|---|---|
| Background | – | – | 11 364.635 | 42 692 | | | | | |
| Relative risk | $\alpha D$ | – | 11 344.768 | 42 691 | Additive risk | $\alpha D$ | – | 11 347.376 | 42 691 |
| | $\alpha D + \beta D^2$ | – | 11 344.767 | 42 690 | | $\alpha D + \beta D^2$ | – | 11 347.354 | 42 690 |
| | $\alpha D$ | Sex | 11 343.408 | 42 690 | | $\alpha D$ | Sex | 11 343.055 | 42 690 |
| | $\alpha D$ | City | 11 342.650 | 42 690 | | $\alpha D$ | City | 11 340.930 | 42 690 |
| | | | | | | $\alpha D$ | City, Sex | 11 337.593 | 42 689 |
| | $\alpha D$ | ln[*y*] | 11 342.282 | 42 690 | | $\alpha D$ | City, ln[*y*] | 11 333.001 | 42 689 |
| | $\alpha D$ | ln[*e*] | 11 340.399 | 42 690 | | $\alpha D$ | City, ln[*e*] | 11 340.378 | 42 690 |
| | $\alpha D$ | ln[*a*] | 11 341.457 | 42 690 | | $\alpha D$ | City, ln[*a*] | 11 337.533 | 42 689 |
| | $\alpha D$ | ln[*y*], ln[*e*] | 11 339.811 | 42 689 | | $\alpha D$ | City, ln[*y*], ln[*e*] | 11 331.184 | 42 688 |
| | $\alpha D$ | ln[*y*], ln[*a*] | 11 335.856 | 42 689 | | $\alpha D$ | City, ln[*y*], ln[*a*] | 11 332.288 | 42 688 |
| | $\alpha D$ | ln[*e*], ln[*a*] | 11 339.688 | 42 689 | | $\alpha D$ | City, ln[*e*], ln[*a*] | 11 336.321 | 42 688 |
| | $\alpha D$ | ln[*y*], ln[*e*], ln[*a*] | 11 334.509 | 42 688 | | $\alpha D$ | City, ln[*y*], ln[*e*], ln[*a*] | 11 330.040 | 42 687 |
| | **$\alpha D$** | **ln[*y*], ln[*a*]** | **11 335.856** | **42 689** | | **$\alpha D$** | **ln[*y*]** | **11 336.354** | **42 690** |
| | $\beta D^2$ | ln[*y*], ln[*a*] | 11 339.390 | 42 689 | | $\beta D^2$ | ln[*y*] | 11 340.330 | 42 690 |
| | $\alpha D + \beta D^2$ | ln[*y*], ln[*a*] | 11 335.793 | 42 688 | | $\alpha D + \beta D^2$ | ln[*y*] | 11 336.318 | 42 689 |
| | $(\alpha D + \beta D^2) \exp[\gamma D]$ | ln[*y*], ln[*a*] | 11 333.923 | 42 687 | | $(\alpha D + \beta D^2) \exp[\gamma D]$ | ln[*y*] | 11 334.796 | 42 688 |
| | $\alpha D^k$ | ln[*y*], ln[*a*] | 11 335.328 | 42 688 | | $\alpha D^k$ | ln[*y*] | 11 336.195 | 42 689 |
| | $\alpha D \exp[\gamma D]$ | ln[*y*], ln[*a*] | 11 335.811 | 42 688 | | $\alpha D \exp[\gamma D]$ | ln[*y*] | 11 336.327 | 42 689 |

[a] $D$ = RBE 10 stomach dose (Sv), $a$ = attained age, $e$ = age at exposure, $y$ = years since exposure (= $a - e$).

**Table D17 Forms of optimal background models assumed in fits of generalized ERR and EAR models to LSS mortality data** [P10] **and LSS solid cancer incidence data** [P48]

| *Cancer site* | *Background model* $\ln[h_0(a,e,c,s)]$[a] |
|---|---|
| **LSS mortality data** | |
| All solid | $\kappa_0 + \kappa_1 \cdot s + \kappa_2 \cdot \ln[a] + \kappa_3 \cdot \ln[a]^2 + \kappa_4 \cdot \ln[a]^3 + \kappa_5 \cdot \ln[a]^4 + \kappa_6 \cdot \ln[a-e] + \kappa_7 \cdot \ln[a-e]^2 + \kappa_8 \cdot e + \kappa_9 \cdot e^2 + \kappa_{10} \cdot s \cdot \ln[a] + \kappa_{11} \cdot s \cdot \ln[a]^2 + \kappa_{12} \cdot s \cdot \ln[a]^3 + \kappa_{13} \cdot s \cdot \ln[a-e] + \kappa_{14} \cdot s \cdot \ln[a-e]^2 + \kappa_{15} \cdot \ln[a-e] \cdot \ln[a] + \kappa_{16} \cdot \ln[a-e] \cdot \ln[a]^2 + \kappa_{17} \cdot \ln[a-e] \cdot \ln[a]^3 + \kappa_{18} \cdot \ln[a-e]^2 \cdot \ln[a] + \kappa_{19} \cdot \ln[a-e]^2 \cdot \ln[a]^2 + \kappa_{20} \cdot e \cdot \ln[a] + \kappa_{21} \cdot e \cdot \ln[a]^2 + \kappa_{22} \cdot e \cdot \ln[a]^3$ |
| Leukaemia | $\kappa_0 + \kappa_1 \cdot s + \kappa_2 \cdot c + \kappa_3 \cdot \ln[a] + \kappa_4 \cdot \ln[a]^2 + \kappa_5 \cdot e + \kappa_6 \cdot e^2$ |
| **LSS solid cancer incidence data** | |
| Oesophageal | $\kappa_0 + \kappa_1 \cdot s + \kappa_2 \cdot \ln[a] + \kappa_3 \cdot \ln[a]^2 + \kappa_4 \cdot e + \kappa_5 \cdot e^2$ |
| Stomach | $\kappa_0 + \kappa_1 \cdot s + \kappa_2 \cdot c + \kappa_3 \cdot \ln[a] + \kappa_4 \cdot \ln[a]^2 + \kappa_5 \cdot \ln[a]^3 + \kappa_6 \cdot \ln[a]^4 + \kappa_7 \cdot \ln[a-e] + \kappa_8 \cdot s \cdot \ln[a] + \kappa_9 \cdot s \cdot \ln[a]^2 + \kappa_{10} \cdot c \cdot \ln[a] + \kappa_{11} \cdot s \cdot \ln[a-e] + \kappa_{12} \cdot \ln[a-e] \cdot \ln[a] + \kappa_{13} \cdot \ln[a-e] \cdot \ln[a]^2 + \kappa_{14} \cdot \ln[a-e] \cdot \ln[a]^3 + \kappa_{15} \cdot \ln[a-e] \cdot \ln[a]^4$ |
| Colon | $\kappa_0 + \kappa_1 \cdot s + \kappa_2 \cdot \ln[a] + \kappa_3 \cdot \ln[a]^2 + \kappa_4 \cdot \ln[a]^3 + \kappa_5 \cdot \ln[a-e] + \kappa_6 \cdot \ln[a-e]^2 + \kappa_7 \cdot s \cdot \ln[a] + \kappa_8 \cdot s \cdot \ln[a]^2 + \kappa_9 \cdot s \cdot \ln[a]^3 + \kappa_{10} \cdot \ln[a-e] \cdot \ln[a] + \kappa_{11} \cdot \ln[a-e] \cdot \ln[a]^2 + \kappa_{12} \cdot \ln[a-e] \cdot \ln[a]^3$ |
| Liver | $\kappa_0 + \kappa_1 \cdot s + \kappa_2 \cdot \ln[a] + \kappa_3 \cdot \ln[a]^2 + \kappa_4 \cdot \ln[a-e] + \kappa_5 \cdot \ln[a-e]^2 + \kappa_6 \cdot e + \kappa_7 \cdot s \cdot \ln[a] + \kappa_8 \cdot s \cdot \ln[a]^2 + \kappa_9 \cdot s \cdot \ln[a-e] + \kappa_{10} \cdot s \cdot \ln[a-e]^2 + \kappa_{11} \cdot \ln[a-e] \cdot \ln[a] + \kappa_{12} \cdot \ln[a-e] \cdot \ln[a]^2 + \kappa_{13} \cdot \ln[a-e]^2 \cdot \ln[a] + \kappa_{14} \cdot \ln[a-e]^2 \cdot \ln[a]^2 + \kappa_{15} \cdot e \cdot \ln[a] + \kappa_{16} \cdot e \cdot \ln[a]^2 + \kappa_{17} \cdot e \cdot \ln[a-e]$ |
| Lung | $\kappa_0 + \kappa_1 \cdot s + \kappa_2 \cdot \ln[a] + \kappa_3 \cdot \ln[a]^2 + \kappa_4 \cdot \ln[a]^3 + \kappa_5 \cdot \ln[a-e] + \kappa_6 \cdot \ln[a-e]^2 + \kappa_7 \cdot e + \kappa_8 \cdot s \cdot \ln[a] + \kappa_9 \cdot s \cdot \ln[a]^2 + \kappa_{10} \cdot s \cdot \ln[a-e] + \kappa_{11} \cdot s \cdot \ln[a-e]^2$ |
| Bone | $\kappa_0 + \kappa_1 \cdot s + \kappa_2 \cdot c + \kappa_3 \cdot \ln[a]$ |
| Non-melanoma skin | $\kappa_0 + \kappa_1 \cdot s + \kappa_2 \cdot \ln[a] + \kappa_3 \cdot \ln[a]^2 + \kappa_4 \cdot \ln[a]^3 + \kappa_5 \cdot \ln[a-e] + \kappa_6 \cdot s \cdot \ln[a] + \kappa_7 \cdot s \cdot \ln[a]^2 + \kappa_8 \cdot s \cdot \ln[a]^3$ |

| *Cancer site* | *Background model* $\ln[h_0(a,e,c,s)]$[a] |
|---|---|
| Female breast | $\kappa_0 + \kappa_1 \cdot c + \kappa_2 \cdot \ln[\min(a,50)] + \kappa_3 \cdot \ln[\max(a,50)] + \kappa_4 \cdot \ln[\min(a,50)]^2 + \kappa_5 \cdot \ln[a-e] + \kappa_6 \cdot \ln[a-e]^2 + \kappa_7 \cdot e + \kappa_8 \cdot \ln[a-e] \cdot \ln[\min(a,50)] + \kappa_9 \cdot \ln[a-e]^2 \cdot \ln[\min(a,50)] + \kappa_{10} \cdot e \cdot \ln[a-e] + \kappa_{11} \cdot e \cdot \ln[a-e]^2$ |
| Urinary bladder | $\kappa_0 + \kappa_1 \cdot s + \kappa_2 \cdot \ln[a] + \kappa_3 \cdot \ln[a]^2 + \kappa_4 \cdot \ln[a]^3 + \kappa_5 \cdot \ln[a-e]$ |
| Brain and central nervous system | $\kappa_0 + \kappa_1 \cdot s + \kappa_2 \cdot \ln[a] + \kappa_3 \cdot \ln[a]^2 + \kappa_4 \cdot \ln[a]^3 + \kappa_5 \cdot \ln[a]^4 + \kappa_6 \cdot \ln[a-e] + \kappa_7 \cdot \ln[a-e]^2 + \kappa_8 \cdot e + \kappa_9 \cdot e^2 + \kappa_{10} \cdot s \cdot \ln[a] + \kappa_{11} \cdot s \cdot \ln[a]^2 + \kappa_{12} \cdot \ln[a-e] \cdot \ln[a] + \kappa_{13} \cdot \ln[a-e] \cdot \ln[a]^2 + \kappa_{14} \cdot \ln[a-e] \cdot \ln[a]^3 + \kappa_{15} \cdot \ln[a-e] \cdot \ln[a]^4 + \kappa_{16} \cdot \ln[a-e]^2 \cdot \ln[a] + \kappa_{17} \cdot \ln[a-e]^2 \cdot \ln[a]^2 + \kappa_{18} \cdot \ln[a-e]^2 \cdot \ln[a]^3 + \kappa_{19} \cdot e \cdot \ln[a] + \kappa_{20} \cdot e \cdot \ln[a]^2$ |
| Thyroid | $\kappa_0 + \kappa_1 \cdot s + \kappa_2 \cdot c + \kappa_3 \cdot \ln[a] + \kappa_4 \cdot \ln[a-e] + \kappa_5 \cdot e + \kappa_6 \cdot e^2 + \kappa_7 \cdot s \cdot e + \kappa_8 \cdot e \cdot \ln[a]$ |
| All other solid | $\kappa_0 + \kappa_1 \cdot s + \kappa_2 \cdot \ln[a] + \kappa_3 \cdot \ln[a]^2 + \kappa_4 \cdot \ln[a]^3 + \kappa_5 \cdot \ln[a]^4 + \kappa_6 \cdot \ln[a-e] + \kappa_7 \cdot \ln[a-e]^2 + \kappa_8 \cdot e + \kappa_9 \cdot e^2 + \kappa_{10} \cdot s \cdot \ln[a] + \kappa_{11} \cdot s \cdot \ln[a]^2 + \kappa_{12} \cdot s \cdot \ln[a]^3 + \kappa_{13} \cdot s \cdot \ln[a-e] + \kappa_{14} \cdot s \cdot \ln[a-e]^2 + \kappa_{15} \cdot s \cdot e + \kappa_{16} \cdot s \cdot e^2$ |

[a] $a$ = attained age, $e$ = age at exposure, $c$ = city (Hiroshima, Nagasaki), $s$ = sex (male, female).

# Appendix E. Risk models fitted to the atomic bombing survivor data by Bayesian Markov Chain Monte Carlo methods, and their use to obtain uncertainty bounds on population risk

E1. In this appendix we detail the models used to fit the current LSS cancer mortality [P10] by Bayesian Markov chain Monte Carlo (MCMC) methods. The models fitted are of the general form described in section IV of the main text, generalized ERR models. Generalized ERR models were fitted in which the expected cancer mortality rate at age *a*, for sex *s* and city *c*, following exposure at age *e* to a dose D of radiation is given by:

$$h_0(a,e,c,s)\cdot[1+F(D)\cdot\phi(a,e,c,s)] = h_0(a,e,c,s)\cdot[1+ERR(D,a,e,c,s)] \tag{E.1}$$

E2. In modelling the latest solid cancer mortality data [P10] the following generalized ERR model was used, in which the cancer mortality rate for age *a*, age at exposure *e*, city *c*, sex *s* and "true" colon dose *D* is given by:

$$h_0(a,e,c,s)\cdot\left[\begin{array}{l}1+(\alpha\cdot D+\beta\cdot D^2)\cdot\exp[\gamma\cdot D]\cdot \\ \exp[\kappa_1\cdot 1_{s=female}+\kappa_2\cdot\ln[a-e]+\kappa_3\cdot\ln[a]]\end{array}\right] \tag{E.2}$$

This is a generalized ERR model that is linear–quadratic–exponential in dose, and that incorporates adjustment to the ERR for sex *s*, attained age *a* and time since exposure $a - e$. It is very similar to model (14) described in section IV of the main text, differing only in the exponential cell sterilization term $\exp[\gamma\cdot D]$. In addition, a variant of this model was fitted in which the cell sterilization term $\gamma$ was set to 0, i.e. the model is linear–quadratic in dose.

E3. Likewise, for leukaemia mortality the following generalized ERR model was used, in which the leukaemia mortality rate for age *a*, age at exposure *e*, city *c*, sex *s* and "true" bone marrow dose *D* is given by:

$$h_0(a,e,c,s)\cdot\left[1+(\alpha\cdot D+\beta\cdot D^2)\cdot\exp[\gamma\cdot D]\cdot\exp[\kappa_3\cdot\ln[a]+\kappa_4\cdot\ln[e]]\right] \tag{E.3}$$

This is a generalized ERR model that is linear–quadratic–exponential in dose and that incorporates adjustment to the ERR for attained age *a* and age at exposure *e*. It is very similar to model (17) described in section IV, differing only in the exponential cell sterilization term, $\exp[\gamma\cdot D]$, and in the additional adjustment for age at exposure, $\exp[\kappa_4\cdot\ln[e]]$. In addition, a variant of this model was fitted in which the cell sterilization term $\gamma$ was set to 0, i.e. the model is linear–quadratic in dose. The parametric forms of the background models $h_0(a,e,c,s)$ used in models (E.2) and (E.3) are as described in table D17 in appendix D.

E4. The natural modelling of measurement error in Bayesian MCMC methods is at the individual level. The stratification creates groups of subjects, and so requires transfer of the modelling of measurement error on the individual dose to the measurement error on the mean dose over the stratum. At an individual level, the "true" dose distribution in each of the two cities (Hiroshima, Nagasaki) is modelled by an extended Weibull distribution, as described in appendix C. The probability density of the distribution of true dose *D* in each sex (*s* = male, female) and city (*c* = Hiroshima, Nagasaki) is modelled by the superposition of an extended Weibull density function (similar to that used previously by Little [L32, L49]), with an additional uniform density on the true dose interval [0.0, 0.01] given by:

$$\begin{aligned} w_{sc}(D) &= \omega_{1sc}\cdot\left[\omega_{2sc}\cdot\omega_{3sc}\cdot D^{\omega_{3sc}-1}+\omega_{4sc}\right]\cdot\exp\left[-\omega_{2sc}\cdot D^{\omega_{3sc}}-\omega_{4sc}\cdot D\right] \\ &+[1-\omega_{1sc}]\cdot 100\cdot 1_{D<0.01} \end{aligned} \tag{E.4}$$

E5. As in appendix C, a "classical" measurement error model is employed, since the main component of the measurement error comes from the declaration by the survivor of their location and orientation with respect to the hypocentre at the time of explosion [R12, R20]. Therefore the distribution of the "nominal" dose *d*, given the "true" individual dose *D*, is assumed here to be log-normal with median *D*. As in appendix C, and following the example of Pierce and colleagues [P2, P11, P16] and Little and colleagues [B18, L17, L29, L32, L33, L34, L35, L37], the "nominal" dose is assumed here to be log-normally distributed with 35% GSD errors.

E6. A two-stage method is used for modelling the stratum-specific dosimetric uncertainties, very similar to the method used by Little and colleagues in references [B18, L17] and described in more detail there. In the first stage, for each stratum *i* (defined by city, sex and age at exposure group) and dose group *j*, the distribution of the "true" mean dose $\overline{\dot{D}_{ij}}$ is computed by Monte Carlo integration according to an iterative procedure that we now describe.

(a) Individual "nominal" doses are first sampled in the dose interval, using a trapezoidal distribution adapted to the width of the dose interval and parameterized so that the resulting distribution has the mean value specified on the data file.

(b) Individual "true" doses are then sampled for each of the $n_{ij}$ individuals in the stratum, conditional on the sampled individual "nominal" doses, the current extended Weibull exposure distribution (E.4) and the (fixed) log-normal error model.

(c) The extended Weibull distribution parameters (E.4) are resampled.

(d) Steps (a–c) are repeated 5,500 times.

(e) By averaging all the $n_{ij}$ individual contributions, the mean "true" organ dose for the stratum, $\overline{\dot{D}_{ij}}$, is thereby simulated. The 5000 iterations (discarding the initial "burn-in" 500 iterations) of this whole process yield a sample of the stratum mean "true" organ dose $\overline{\dot{D}_{ij}}$.

(f) 500 replicates of steps (a–e) yield a sample of the stratum mean "true" organ dose $\overline{\dot{D}_{ij}}$, from which are computed the sample mean, $\mu ij$, and normalized variance, $\sigma_{ij}^{\,2} n_{ij}^{\,-1}$, of the mean "true" organ dose in the stratum.

(g) This true stratum mean dose distribution is then approximated by a normal or gamma distribution having mean $\mu ij$ and variance $\sigma_{ij}^{\,2} n_{ij}^{\,-1}$. For groups of 5 subjects or less, the distribution of $\overline{\dot{D}_{ij}}$ is skewed, so that a gamma distribution is used, whereas for larger groups the normal distribution is a good approximation to the distribution of $\overline{\dot{D}_{ij}}$.

Steps (a–g) were performed using a FORTRAN program. This procedure was necessitated by the grouped nature of the data, in particular by the fact that individual "nominal" doses were not available. In the second stage, the derived distribution of all the $\overline{\dot{D}_{ij}}$ is then used together with the ERR–EAR disease models (E.2) and (E.3) to derive the posterior distribution of the parameters of these ERR–EAR models. The Bayesian sampling was performed using WinBUGS [S89]. A total of 50,000 samples were taken for leukaemia and solid cancer, after 50,000 samples were discarded in each case to allow the Markov chains to reach their stationary equilibrium distributions; convergence of the Markov chains was assessed using the Gelman–Rubin statistic [G28]. Each set of model parameter values from this 50,000 sample was used to calculate a measure of population cancer risk for the current Chinese, Japanese, Puerto Rican, United States and United Kingdom populations, using the four risk measures detailed in appendix B and in section I.G of the main text. These samples of 50,000 parameter values are therefore associated with a sample of population cancer risks for these current five populations. Tables E1 and E2 contain the parameter estimates (with 90% Bayesian CI) for the fitted models (linear–quadratic–exponential and linear–quadratic) for solid cancers and leukaemia.

**Table E1 Means and 90% Bayesian uncertainty intervals on the posterior distribution of solid cancer and leukaemia generalized linear–quadratic–exponential ERR models to LSS mortality data** [P10]

All models are fitted by two-step Bayesian MCMC techniques. Uncertainty intervals computed from the last 50,000 samples from chains, the first 50,000 samples of which had been discarded. $D$ = radiation dose (Sv), $a$ = attained age, $e$ = age at exposure, $s$ = sex.

| **Solid cancer generalized ERR model (adjustment for sex, attained age and years since exposure), linear–quadratic–exponential dose response** | |
|---|---|
| $h_0(a,e,c,s)\cdot\left[1+(\alpha\cdot D+\beta\cdot D^2)\cdot\exp[\delta\cdot D]\cdot\exp[\kappa_1\cdot 1_{s=female}+\kappa_2\cdot\ln[(a-e)/25]+\kappa_3\cdot\ln[a/50]]\right]$ | |
| $\alpha=$ | 0.164 (–0.170, 0.497) Sv$^{-1}$ |
| $\beta=$ | 0.683 (–0.079, 1.548) Sv$^{-2}$ |
| $\delta=$ | –0.412 (–0.864, 0.403) Sv$^{-1}$ |
| $\kappa_1=$ | 0.575 (0.225, 0.944) |
| $\kappa_2=$ | 1.020 (0.518, 1.579) |
| $\kappa_3=$ | –2.764 (-3.558, –1.982) |
| **Leukaemia generalized ERR model (adjustment for attained age and age at exposure), linear–quadratic–exponential dose response** | |
| $h_0(a,e,c,s)\cdot\left[1+(\alpha\cdot D+\beta\cdot D^2)\cdot\exp[\delta\cdot D]\cdot\exp[\kappa_1\cdot\ln[a/50]+\kappa_2\cdot\ln[e/25]]\right]$ | |
| $\alpha=$ | –0.139 (–2.161, 2.350) Sv$^{-1}$ |
| $\beta=$ | 7.368 (0.169, 13.180) Sv$^{-2}$ |
| $\delta=$ | –0.466 (–0.840, 0.014) Sv$^{-1}$ |
| $\kappa_1=$ | –1.838 (–2.746, –0.977) |
| $\kappa_2=$ | 0.192 (–0.260, 0.681) |

**Table E2 Means and 90% Bayesian uncertainty intervals on the posterior distribution of solid cancer and leukaemia generalized linear–quadratic ERR models to LSS mortality data** [P10]

All models are fitted by two-step Bayesian MCMC techniques. Uncertainty intervals computed from the last 50,000 samples from chains, the first 50,000 samples of which had been discarded $D$ = radiation dose (Sv), $a$ = attained age, $e$ = age at exposure, $s$ = sex.

| **Solid cancer generalized ERR model (adjustment for sex, attained age and years since exposure), linear–quadratic dose response** | |
|---|---|
| $h_0(a,e,c,s)\cdot\left[1+(\alpha\cdot D+\beta\cdot D^2)\cdot\exp[\kappa_1\cdot 1_{s=female}+\kappa_2\cdot\ln[(a-e)/25]+\kappa_3\cdot\ln[a/50]]\right]$ | |
| $\alpha=$ | 0.347 (0.161, 0.566) $Sv^{-1}$ |
| $\beta=$ | 0.121 (0.004, 0.246) $Sv^{-2}$ |
| $\kappa_1=$ | 0.613 (0.256, 1.005) |
| $\kappa_2=$ | 1.024 (0.531, 1.589) |
| $\kappa_3=$ | –2.711 (–3.500, –1.944) |
| **Leukaemia generalized ERR model (adjustment for attained age and age at exposure), linear–quadratic dose response** | |
| $h_0(a,e,c,s)\cdot\left[1+(\alpha\cdot D+\beta\cdot D^2)\cdot\exp[\kappa_1\cdot\ln[a/50]+\kappa_2\cdot\ln[e/25]]\right]$ | |
| $\alpha=$ | 1.599 (0.134, 3.313) $Sv^{-1}$ |
| $\beta=$ | 2.125 (0.927, 3.381) $Sv^{-2}$ |
| $\kappa_1=$ | –1.980 (–2.878, –1.120) |
| $\kappa_2=$ | 0.233 (–0.221, 0.725) |

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# ANNEX B

## Epidemiological evaluation of cardiovascular disease and other non-cancer diseases following radiation exposure

## Contents

# INTRODUCTION

1. The risks of cancer associated with exposure to ionizing radiation have been extensively studied and documented. Epidemiological data on the carcinogenic effects of exposure to ionizing radiation are the subject of continuing reviews by UNSCEAR (see annex A to this report, "Epidemiological studies of radiation and cancer", and, for example, references [U2, U4, U6]). The effects of exposure to radiation expressed as diseases other than cancer were most recently reviewed in the 1982 [U8] and 1993 UNSCEAR Reports [U5]. In these reports, the effects expressed as diseases other than cancer were regarded as "deterministic", resulting from "direct" changes occurring in cells. The deterministic model assumes the presence of a minimum dose—the threshold dose—below which radiation effects are not detected, although a threshold dose is difficult to define and may vary according to tissues, biological end points and measuring techniques [U8]. In 1992, the analysis of mortality data from the Life Span Study (LSS) cohort of survivors of the atomic bombings in Japan demonstrated a statistically significant association between radiation dose and some diseases other than cancer (non-cancer diseases) [S1]. Excess non-cancer disease mortality risks in the LSS were evident at levels of dose lower than those hitherto considered as a threshold, e.g. 4–5 Gy, for various deterministic effects. While some of these non-cancer diseases are neoplastic though benign in nature, significant excess risks are mostly seen for mortality from stroke, heart disease, and diseases of the respiratory and digestive systems, which are of a non-neoplastic nature.

2. The Committee considered it necessary to assess the epidemiological evidence of radiation effects expressed as diseases other than cancer at low doses, because the phenomenon is potentially important for radiation risk assessment at these dose levels, and there is a considerable lack of consistency among the available epidemiological data. The Committee considered it important to focus on cardiovascular disease as the major end point of interest, because cardiovascular disease is among the most common diseases in many populations worldwide and thus may be important for radiation risk assessment.

3. This annex first provides an overview of current epidemiological data on mortality from broad categories of non-cancer diseases obtained from studies of populations exposed to radiation at doses of less than 1–2 Gy. In assessing the evidence on radiation effects, the annex considers several methodological issues that are especially relevant for non-cancer data, such as cohort selection, quality of the mortality data, confounding and publication bias. It then provides a general overview of data currently available on major non-cancer disease categories from various irradiated populations. The annex goes on to consider radiation effects on diseases of the circulatory system and specifically on cardiovascular (heart) disease. Although the primary focus of this annex is the effect of exposure to low doses of radiation, the risks of cardiovascular disease associated with exposure to high doses are also addressed. This is because much is known about the clinical and biological effects of exposure at high dose levels, and this may be helpful for considering possible biological mechanisms of effects at low dose levels.

# I. GENERAL ISSUES IN ASSESSING DATA ON NON-CANCER DISEASES

4. Annex A of this report describes features that are important in conducting or interpreting epidemiological studies. In addition, when assessing published epidemiological data on non-cancer diseases, several methodological issues are especially relevant. These include the selection of exposed populations (including the "healthy worker" effect and the presumed "healthy survivor" effect), the quality of the mortality data, the confounding effects of non-radiation risk factors and publication bias.

## A. Cohort selection

5. The nature of an exposed population needs to be considered when study subjects are irradiated for medical reasons. Data on non-cancer diseases are reported from some of the medically exposed cohorts that have been studied to assess cancer risks. Groups of individuals with certain non-neoplastic medical conditions for which they were irradiated may have underlying rates of non-cancer diseases that may not be representative of the general population rates, even if the underlying cancer rates of these individuals are not affected by their medical conditions. For example, thyroid hormone exerts a major influence on the cardiovascular system, and patients with hyperthyroidism often have cardiovascular symptoms [L9]. Angina pectoris and congestive heart failure may develop when there is underlying heart disease. Women with some benign gynaecological disorders are in a hyper-oestrogenic status, and thus may have an increased underlying risk of cardiovascular disease. When the observed number of cases (or deaths) with the disease of interest is compared with the number expected from the general population (external comparison), estimates of the risk may be biased. However, comparison of disease rates in exposed and unexposed persons within the same cohort population (internal comparison) is less likely to produce biased risk estimates.

6. The "healthy worker effect" is an observed decrease in mortality in cohorts of workers when comparison is made with the general population. This effect occurs because of the initial selection process by which healthy people are more likely to be employed than unhealthy ones. Decreased mortality in workers may also occur for several other reasons, for example the beneficial effect from better health care (referred to as the "worker healthier effect"), or continuing selection due to healthier people remaining employed (referred to as the "healthy worker survivor effect") [C7]. The healthy worker effect is known to be particularly strong for chronic non-malignant diseases, such as cardiovascular disease, compared with cancer or precancerous conditions that are dormant or clinically less evident at the time of beginning or during employment. The empirical estimates are that the healthy worker effect represents a 20–30% reduction in comparison with the mortality rate of the whole population [C8]. Several features of the healthy worker effect are notable. The effect is greatest during the initial period of follow-up and diminishes with increasing follow-up time, and the length of time during which the effect persists has been reported to range from 5 to 30 years or longer [B9]. The magnitude of the healthy worker effect also varies among different occupational groups, and may be particularly large in nuclear worker cohorts because of the strict health selection associated with security clearances in the industry [B9]. Thus a simple ratio of the observed to the expected number of deaths, or standardized mortality ratio (SMR), is not a useful measure of radiation risk for non-cancer disease in occupational cohorts.

7. It has been suspected that a selection process that is similar to that underlying the healthy worker effect may have occurred in the cohort of the atomic bombing survivors [P4, S1]. This effect, called the "healthy survivor effect" is apparently different in nature from the healthy worker survivor effect seen in those who remain employed. Rather, several features suggest that it is similar in nature to the healthy worker effect caused by the selection of healthier persons at the time of cohort entry.

## B. Quality of the mortality data

8. Mortality follow-up is the principal method used in most studies of radiation-exposed cohorts. Imprecise reports of the causes of death on death certificates often lead to misclassification of diseases from or with which subjects died. Since mortality rates for cancer generally increase with increasing radiation dose, the misclassification of death from cancer as death from non-cancer disease on death certificates can spuriously produce a dose-related increase in mortality rates for non-cancer disease or overstate the effect of radiation on non-cancer disease rates. In the analysis by Sposto et al. [S6] of the LSS death certificate data, correcting for the misclassification of cancer deaths as non-cancer deaths using autopsy diagnoses reduced the estimate of excess relative risk (ERR) for non-cancer disease by about 20% (although the non-cancer dose response still remained significant after this correction). The problem of

misclassification of causes of death is likely to exist in many of the radiation-exposed cohorts studied, but the LSS is the only study to date in which the impact of disease misclassification on the estimates for risk of non-cancer disease has been evaluated.

### C. Confounding effects

9. Cardiovascular disease and the other non-cancer diseases with which this report is concerned are multifactorial diseases involving lifestyle and other personal factors. Underlying rates for major non-cancer diseases, especially circulatory diseases, are relatively high and vary among people with different socio-economic status, from different geographical locations and with different lifestyles. Because the risk of non-cancer effects associated with radiation exposure is relatively small—about one third the risk of cancer, as indicated by the atomic bombing survivor data—the power to detect radiation effects is reduced and the likelihood of the influence of confounding factors is increased. Simple comparisons of exposed versus unexposed groups are susceptible to confounding as well as selection bias and should be given limited credibility, while radiation dose–response analyses provide more credible evidence regarding the effect of radiation exposure.

### D. Publication bias

10. Cancer has been the primary focus of epidemiological research on radiation effects. Radiation effects expressed as non-cancer diseases have been less systematically studied and reported. Only occasionally have associations of radiation with non-cancer diseases been reported as supplemental findings of studies designed to assess cancer risks. Findings related to non-cancer effects may have been reported because they are statistically significant or "interesting". On the other hand, non-cancer data may simply not have been analysed because the investigators were not interested in the data. Reviews of studies in the social and medical sciences show that studies with significant results or favourable results are more likely to be published, but the magnitude and nature of publication bias and other related biases are uncertain [S5]. Favourable results may be those findings that are congruent with ruling paradigms at the time. This also suggests that when positive results are unexpected, they may be rigorously analysed, while null results, when expected, may not be critically examined. For example, unexpected positive findings may cause investigators to examine the possible sources of bias or confounding, but null findings that are expected may be accepted at face value. While there is a concern for a potential publication bias in published non-cancer data, the direction of biases in published data is unpredictable.

# II. NON-CANCER DATA IN RADIATION-EXPOSED COHORTS

11. The objectives of this annex include the identification of cohort studies that may provide epidemiological information for assessing the relationship of radiation exposure and non-cancer diseases and to judge the usefulness and consistency of their findings for various non-cancer disease categories. Table 1 lists cohort populations exposed to mostly low-linear-energy-transfer (LET) radiation and records any major non-cancer findings. These cohorts were selected from those considered in the UNSCEAR 2000 Report (table 2 in annex I, "Epidemiological evaluation of radiation-induced cancer") [U2], supplemented and updated by a separate literature search. The cohorts in table 1 were selected a priori on the basis of considerations of population size and reported radiation doses to relevant organs, and then data on non-cancer mortality were sought in published material.

12. In table 1, the LSS cohort of the survivors of the atomic bombings in Japan is presented together with the Adult Health Study (AHS) cohort, which is a subset of the LSS.[1] Cohort populations irradiated for treatment of cancer include those treated for cervical cancer, childhood cancer and childhood lymphoma. These patients received doses ranging between <1 Gy and 10 Gy to various organs, and they represent high-dose exposure populations. Table 1 excludes a large number of studies of cardiovascular disease risks following high-dose radiotherapy for Hodgkin's lymphoma or breast cancer, as these will be the focus of detailed examination later in this annex. Patients with a variety of benign diseases (childhood skin haemangioma, benign lesions in the locomotor system, ankylosing spondylitis, tinea capitis, post-partum mastitis, thymic enlargement, tonsil enlargement, benign breast disease, benign gynaecological disorders, lymphoid hyperplasia and peptic ulcer disease) who were irradiated at a range of moderate doses are considered next. Individuals irradiated for diagnostic purposes (fluoroscopic examination, scoliosis) were exposed to relatively low doses, as were occupationally exposed populations, and these are considered separately. The atomic bombing survivors and occupationally exposed populations are characterized by whole-body radiation exposure, whereas medically exposed populations had localized exposures with varying doses to different target organs. This should be kept in mind when comparing findings for different populations or when examining different non-cancer diseases within the same population.

13. Table 1 presents associations reported from these studies regarding radiation exposure and major non-cancer disease categories (infectious diseases, circulatory diseases, respiratory system diseases, digestive system diseases, genito-urinary system diseases and other diseases). The associations are described in terms of whether they were significantly positive (P, increased risk associated with radiation exposure), significantly inverse (I, reduced risk associated with radiation exposure), not significant (NS, no significant association) or lacking data on non-cancer disease (–). The types of analysis used in obtaining the results are described as follows: "dose–response analysis", including analyses using dose categories; "internal comparison" based on only a comparison of exposed versus unexposed groups with no dose data; or "external comparison" with SMRs or observed/expected (O/E) ratios for the exposed cohort only.

14. Of these cohort studies, 60% provided mortality or morbidity data for heart disease, cerebrovascular disease or diseases of the circulatory system as a whole. The use of different disease categories in different studies makes it difficult to assess the consistency of the associations. On the basis of dose–response analysis or trend analysis using dose categories, significant associations of radiation and circulatory disease (heart disease, cerebrovascular disease or both) were reported from nine cohort studies (atomic bombing survivors for both heart disease and cerebrovascular disease; peptic ulcer patients for coronary heart disease; scoliosis patients for diseases of the circulatory system; and six occupational cohort studies, i.e. the International Agency for Research on Cancer (IARC) three-country nuclear worker study for circulatory disease; studies in the United Kingdom on workers at Sellafield for ischaemic heart disease and at Springfields uranium production facility for cerebrovascular disease; the Canadian National Dose Registry study for circulatory disease; and studies on Chernobyl recovery operations workers for both ischaemic heart disease and cerebrovascular disease). The lack of a significant association for circulatory disease was reported from eight cohort studies (two populations of patients with benign gynaecological disorders and six occupational studies: in the United Kingdom, the National Registry for Radiation Workers (NRRW) and the studies of the Capenhurst uranium workers and the Chapelcross workers; in the United States, the

[1] Authors of atomic bombing survivor studies have provided dose estimates in terms of weighted colon doses, which are the sum of the gamma-ray dose estimate and 10 times the neutron dose estimate. Early papers often used grays (Gy) for the units of these weighted doses, while more recent papers use sieverts (Sv). Throughout this annex, the Committee uses the convention of sieverts for the units of the weighted colon doses when addressing the specific results of the atomic bombing survivor studies.

Hanford–Oak Ridge National Laboratory (ORNL)–Rocky Flats weapons plant study and the study at Hanford only; and in the Russian Federation, the study of workers at the Mayak nuclear complex). In one of the two studies of patients with benign gynaecological disorders, the association of heart disease with radiation exposure was of borderline significance. In the United States nuclear power utility worker study, dose–response analyses for circulatory disease and ischaemic heart disease showed significant associations, but trend analyses using dose categories showed the associations as not significant.

15. Fewer data were available for other non-cancer diseases. About half of the studies provide data on digestive diseases, 47% on respiratory diseases, 36% on infectious diseases and 33% on genito-urinary diseases. The specific disease categories analysed differed among the studies.

16. In addition to the evidence from the studies of the survivors of the atomic bombings, a significant association for diseases of the digestive system was reported from the follow-up of patients receiving X-ray monitoring for scoliosis, though no data were presented [D9], and from two occupational cohorts (the Springfields uranium production workers when exposures were lagged for 20 years, and the Chernobyl recovery operations workers). No significant association was found in seven cohort studies (the benign gynaecological disorder patients and six occupational cohorts: the IARC three-country cohort and the NRRW, Sellafield, Chapelcross, Capenhurst and Hanford cohorts).

17. A significant association for diseases of the respiratory system has been reported from studies on five cohorts: the atomic bombing survivors, patients with scoliosis (though data were not presented), NRRW workers (for respiratory diseases unrelated to smoking), Sellafield workers (for pneumonia) and Chapelcross workers (for bronchitis). The lack of a significant association was found for nine cohorts: benign gynaecological disorder patients, IARC three-country cohort, Chapelcross workers, Springfields uranium workers, Capenhurst uranium workers, Canadian National Dose Registry study, Hanford–ORNL–Rocky Flats workers, Hanford workers and Chernobyl recovery operations workers.

18. Data on infectious diseases or genito-urinary diseases were very scarce, with only one study reporting a significant association for each disease category: patients with scoliosis (for infectious diseases) and patients with benign gynaecological disorders (for genito-urinary diseases). The absence of a significant association was reported from several other cohort studies.

**Table 1 Studies on radiation-exposed cohorts and reported associations with non-cancer diseases**

| *Study* | *Number of subjects* | *Doses: range and mean (Sv)* | *Non-cancer disease associations found*[a] | | | | | | | *Type of analyses performed for non-cancer diseases* |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | *All non-cancer diseases* | *Infectious diseases* | *Circulatory diseases* | *Respiratory diseases* | *Digestive diseases* | *Genito-urinary diseases* | *Other diseases* | |
| **Exposure to atomic bombings** | | | | | | | | | | |
| LSS [P4, S21] | 50 113 exposed persons<br>36 459 unexposed persons | Individual estimates for several organs: colon dose[b], 0–4 Sv; mean 0.29 (exposed persons) | P | NS | P (stroke, heart disease) | P | P | NS | P (blood disease); I (suicide) | Dose–response analysis; confounding effects examined |
| AHS [K5, W5, Y3] | 9 641 persons (subset of LSS) | Mean[b] 0.83 Sv (exposed persons) | – | – | P (hypertension, myocardial infarction) | – | P (liver disease, cirrhosis) | P (renal and ureteral stones) | P (uterine myoma, thyroid disease) | Dose–response analysis |
| **Treatment of malignant disease** | | | | | | | | | | |
| Cervical cancer cohort [B10] | 82 616 exposed women<br>99 424 unexposed women | Typical doses: oesophagus, 0.14–0.28; stomach, 0.7–1.2 [T1] | – | – | – | – | – | – | | Non-cancer diseases not analysed |
| Hodgkin's lymphoma late mortality [H1] | 2 001 exposed persons<br>231 unexposed persons | Mediastinum, <30–44 | – | – | P (myocardial infarction, other heart disease) | – | – | – | | Internal comparison (two dose categories: 0–30 Gy, >30 Gy) |
| Childhood cancers [D6] (France and United Kingdom) | 3 109 exposed persons<br>1 291 unexposed persons | Individual doses: breast, 0.7–11; digestive tract, 0.5–13; brain, 0.3–25 | – | – | – | – | – | – | | Non-cancer diseases not analysed |
| Childhood Hodgkin's lymphoma [B11] | 1 380 persons | Individual doses: oesophagus, 1.5–3.95; stomach, 10–28 [T1] | – | – | – | – | – | – | | Non-cancer diseases not analysed |
| **Treatment of benign disease** | | | | | | | | | | |
| Childhood skin haemangioma, Stockholm [L7, L8] | 14 351 exposed persons | Individual organ doses, mean: lung, 0.15 | – | – | – | – | – | – | | Non-cancer diseases not analysed |
| Childhood skin haemangioma, Gothenburg | 11 914 exposed persons | | – | – | – | – | – | – | | Non-cancer diseases not analysed |
| Benign lesions in locomotor system [D7] | 20 024 exposed persons | Individual red bone marrow doses, mean: <0.2–>0.5 | – | – | – | – | – | – | | Non-cancer diseases not analysed |

| *Study* | *Number of subjects* | *Doses: range and mean (Sv)* | *Non-cancer disease associations found*[a] | | | | | | | *Type of analyses performed for non-cancer diseases* |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | *All non-cancer diseases* | *Infectious diseases* | *Circulatory diseases* | *Respiratory diseases* | *Digestive diseases* | *Genito-urinary diseases* | *Other diseases* | |
| Ankylosing spondylitis [D3, L1] | 13 914 exposed persons | 1 in 15 sample of the population, mean: gastrointestinal tract, 2.43; heart, 2.49; pulmonary region, 1.64 | NS | – | P (cerebrovascular disease, other circulatory diseases) | P (bronchitis) | P (peptic ulcer, other genito-urinary diseases) | – | P (violence) | O/E ratios, external comparisons |
| Israel tinea capitis [R11] | 10 834 exposed persons<br>16 226 unexposed persons | Individual doses, mean: brain, 1.5; thyroid, 0.09 | | NS | NS | NS | NS | NS | NS | Internal comparison (exposed versus unexposed or sibling) |
| New York tinea capitis [S11] | 2 226 exposed persons<br>1 387 unexposed persons | Individual doses | NS | NS | NS | – | – | – | | Internal comparison (exposed versus unexposed) |
| New York postpartum mastitis [S12] | 571 exposed persons<br>993 unexposed persons | Individual doses: breast, 0.6–11.5 | – | – | – | – | – | – | | Non-cancer diseases not analysed |
| Rochester thymic irradiation [H10] | 2 652 exposed persons<br>4 823 unexposed persons | Individual doses, mean: breast, 0.69 | – | – | – | – | – | – | | Non-cancer diseases not analysed |
| Tonsil irradiation [S13, S14] | 2 634 exposed persons | Individual doses, mean: thyroid, 0.58 | – | – | – | – | – | – | | Non-cancer diseases not analysed |
| Swedish benign breast disease [M10] | 1 216 exposed persons<br>1 874 unexposed persons | Individual doses, mean: lung, 0.75; liver, 0.66; stomach, 0.66; oesophagus, 0.23 | – | – | – | – | – | – | | Non-cancer diseases not analysed |
| Metropathia haemorrhagica [D8, S3] | 2 067 exposed persons | Individual doses, mean: lung, 0.04 | – | – | NS (ischaemic heart disease) | – | – | NS (diseases of genitals, breasts, ovaries, etc.) | | Internal comparisons (three dose categories) |
| Benign gynaecological disorders [I2] | 4 483 exposed persons | Individual doses: lung, 0.04–0.06 | – | NS | NS | NS | NS | P | | Internal comparisons (four dose categories) |
| Lymphoid hyperplasia screening [P5] | 1 195 exposed persons<br>1 063 unexposed persons | Individual doses, mean: thyroid, 0.24 | – | – | – | – | – | – | | Non-cancer diseases not analysed |
| Peptic ulcer [C9, G1] | 1 831 exposed persons<br>1 778 unexposed persons | Individual doses, mean: heart, 2.1; left lung, 1.79; right lung, 0.55; left kidney, 14.2; right kidney, 2.07 | – | NS | P (coronary heart disease); NS (other heart disease, stroke) | NS | NS | NS | | Dose–response analysis for circulatory disease; internal comparison (exposed versus unexposed) for other diseases |

| *Study* | *Number of subjects* | *Doses: range and mean (Sv)* | *Non-cancer disease associations found*[a] | | | | | | | *Type of analyses performed for non-cancer diseases* |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | *All non-cancer diseases* | *Infectious diseases* | *Circulatory diseases* | *Respiratory diseases* | *Digestive diseases* | *Genito-urinary diseases* | *Other diseases* | |
| **Diagnostic examinations** | | | | | | | | | | |
| Massachusetts tuberculosis fluoroscopy [D4] | 6 285 exposed persons<br>7 100 unexposed persons | Individual exposures, mean: lung, 0.84 | NS (all except tuberculosis and respiratory) | NS (tuberculosis) | NS | NS | NS | | | O/E ratios, internal comparisons (exposed and unexposed) |
| Canadian tuberculosis fluoroscopy [H11, H12] | 25 007 exposed persons<br>39 165 unexposed persons | Individual exposures: lung, 0–>3 | – | – | – | – | – | – | | Non-cancer diseases not analysed |
| Scoliosis [D9] | 5 573 women with scoliosis receiving repeated radiographic examinations | Individual doses, mean: bone marrow, 0.01; lung, 0.041 | | P (infectious diseases) | P (circulatory diseases) | P (respiratory diseases) | P (digestive diseases) | | P (musculoskeletal conditions) | Dose–response analysis |
| **Occupational exposures** | | | | | | | | | | |
| Nuclear workers in Japan [I4] | 119 484 workers | Recorded exposures to external radiation: mean cumulative dose, 0.0153 | NS | – | – | – | – | | P (external causes) | Dose–response analysis for total non-cancer mortality only |
| Nuclear workers in Canada, United Kingdom and United States [C6] | 95 673 workers (Hanford, 32 595; Rocky Flats, 6 638; ORNL, 6 591; Sellafield, 9 494; United Kingdom other than Sellafield, 29 000; Atomic Energy of Canada Limited, 11 535) | Recorded exposures to external radiation: mean cumulative dose, 0.04 | NS | | P (circulatory diseases) | NS | NS (liver cirrhosis) | | NS (external causes) | Dose–response analysis |
| NRRW, United Kingdom [M5] | 124 743 workers | Recorded exposures to external radiation: mean cumulative dose, 0.03 | | | NS (smoking-related diseases, including coronary heart disease, aortic aneurysm, bronchitis, emphysema, chronic obstructive pulmonary diseases) | P (non-smoking-related respiratory diseases) | NS | NS | I (unknown causes) | Dose–response analysis |

| *Study* | *Number of subjects* | *Doses: range and mean (Sv)* | *Non-cancer disease associations found*[a] | | | | | | | *Type of analyses performed for non-cancer diseases* |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | *All non-cancer diseases* | *Infectious diseases* | *Circulatory diseases* | *Respiratory diseases* | *Digestive diseases* | *Genito-urinary diseases* | *Other diseases* | |
| Sellafield, United Kingdom Atomic Energy Authority (UKAEA) and Atomic Weapons Establishment (AWE) [C10] | 40 761 monitored workers (Sellafield, 10 028; UKAEA, 9 389; AWE, 9 389) | Recorded exposures to external radiation: mean cumulative doses: Sellafield, 0.1329; AEA, 0.0406; AWE, 0.011 | NS | – | – | – | – | | | Dose–response analysis |
| Sellafield [O1] | 10 382 monitored workers | Recorded exposures to external radiation | – | I (tuberculosis) | P (ischaemic heart disease) | P (pneumonia) | NS | NS | P (mental disorders); I (accidents/ violence) | Dose–response analysis (ischaemic heart disease, pneumonia, mental disorders); internal comparisons (tuberculosis, digestive and genito-urinary diseases, accidents/ violence) |
| Chapelcross [M11] | 2 628 monitored workers | Recorded exposures to external radiation: mean cumulative dose, 0.0836 | – | – | NS | P (bronchitis) | NS | NS | | Internal comparisons (seven dose categories) |
| Springfields uranium production [M12] | 13 960 monitored workers | Recorded exposures to external radiation: mean cumulative dose, 0.0228 | – | NS | P (cerebrovascular disease) | NS | P | NS | P (nervous and sense organ diseases, prostatic hyper-trophy, accidents/ violence) | Internal comparisons (seven dose categories) |
| Capenhurst uranium enrichment [M7] | 3 244 monitored workers | Recorded exposures to external radiation: mean cumulative dose, 0.0098 | – | NS | NS | NS | NS | NS | | Internal comparisons (seven dose categories) |
| Canadian National Dose Registry [A2] | 206 620 monitored workers | Recorded exposures to external radiation: mean cumulative dose, 0.06 | – | NS | P (circulatory diseases) | NS | – | NS | P (accidents) | Dose–response analysis |
| Hanford, ORNL and Rocky Flats weapons plant [G6] | 44 943 monitored workers (Hanford, 32 643; ORNL, 6 348; Rocky Flats, 5 952) | Recorded exposures to external radiation: mean cumulative doses: Hanford, 0.026; ORNL, 0.022; Rocky Flats, 0.041 | NS | – | NS | NS | P (cirrhosis) | | NS (external causes) | Internal comparison (six dose categories) |

| *Study* | *Number of subjects* | *Doses: range and mean (Sv)* | *Non-cancer disease associations found*[a] | | | | | | | *Type of analyses performed for non-cancer diseases* |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | *All non-cancer diseases* | *Infectious diseases* | *Circulatory diseases* | *Respiratory diseases* | *Digestive diseases* | *Genito-urinary diseases* | *Other diseases* | |
| Hanford [G7] | 37 971 monitored workers | Recorded exposures to external radiation: mean cumulative dose, 0.0233 | NS | – | NS | NS | NS (cirrhosis) | | NS (external causes) | Internal comparison (five dose categories) |
| Portsmouth Naval Shipyard [R12] | 8 960 monitored workers | Recorded exposures to external radiation: <1.5 (range) | – | – | – | – | – | – | | – |
| Rocketdyne/ Atomics International [R13] | 4 563 monitored workers | Recorded exposures to external radiation: cumulative dose 0–0.2 | – | – | NS | NS | NS | NS | NS | External comparison, single SMR values |
| Mound facility [W6] | 3 229 monitored workers | Recorded exposures to external radiation: mean cumulative dose, 0.0297 | – | NS | NS | NS | NS | NS | NS (injuries) | External comparison, single SMR values |
| Nuclear power utilities, United States [H13] | 53 698 monitored workers | Recorded exposures to external radiation: mean cumulative dose, 0.0257 | P | NS | P (circulatory system, arteriosclerotic heart disease) | NS | NS | NS | | Circulatory disease data significant by dose–response analysis; not significant by trend tests using dose categories |
| Chernobyl recovery operations workers, Russian Federation [I1] | 68 309 workers | Assessed external radiation doses: 0–0.02+ | | NS | P (essential hypertension, cerebrovascular disease) NS (hypertensive heart disease, ischaemic heart disease) | NS | P | NS | P (endocrine/ metabolic diseases, mental disorders) | Dose–response analysis |
| Chernobyl recovery operations workers, Estonia [R14] | 4 742 workers | Recorded radiation doses: mean, 0.11 | – | – | NS | – | NS | – | P (suicide) | External comparisons, SMRs only |
| Mayak workers [B12] | 15 601 persons monitored for external radiation | Recorded doses to external radiation, mean: lung, 3.8–35 | – | – | NS (cardiovascular disease) | – | – | – | | Internal comparisons (three dose categories) |

| *Study* | *Number of subjects* | *Doses: range and mean (Sv)* | *Non-cancer disease associations found*[a] | | | | | | | *Type of analyses performed for non-cancer diseases* |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | *All non-cancer diseases* | *Infectious diseases* | *Circulatory diseases* | *Respiratory diseases* | *Digestive diseases* | *Genito-urinary diseases* | *Other diseases* | |
| Japanese radiologic technologists [Y2] | 9 179 radiologic technologists | Recorded exposures to external radiation | – | – | – | – | – | – | | – |
| Danish radiotherapy staff [A5] | 4 151 radiotherapy workers | Recorded exposures to external radiation | – | – | – | – | – | – | | – |
| Chinese X-ray workers [W2] | 27 011 X-ray workers | Recorded exposures to external radiation | – | – | – | – | – | – | | – |
| United States radiologic technologists [H3] | 90 284 radiologic technologists | Recorded doses to external radiation | | – | P (ischaemic heart disease, stroke) | – | – | – | | Internal comparisons using exposure surrogates (periods of employment); adjusted for confounding effects |
| United Kingdom radiologists [B4] | 2 698 radiologists | | NS | NS | NS | – | – | – | NS (external causes) | Internal comparisons using exposure surrogates (periods of employment) |
| United States radiologists [M2] | 6 500 radiologists | | | – | P (cardiovascular disease) | – | – | – | | Internal comparisons among different medical professions and calendar years |

*a* P = positive, I = inverse, NS = not significant; (–) indicates no published data.

*b* Dose estimates are provided in terms of weighted colon doses, which are the sum of the gamma-ray dose estimate and 10 times the neutron dose estimate. This annex uses as a convention sieverts for the units of weighted colon doses.

# III. DATA ON NON-CANCER MORTALITY FOR SURVIVORS OF THE ATOMIC BOMBINGS

19. This section examines the LSS data on non-cancer mortality in some additional detail, because the analyses of the mortality data on the LSS cohort represent the most thorough evaluation to date of the association between radiation exposure and non-cancer disease risks. The LSS mortality data provide evidence of a dose response for mortality from heart disease, stroke, respiratory diseases (largely pneumonia, 67%) and digestive diseases (including a large proportion of liver cirrhosis, 44%). Non-cancer risk estimates and dose responses for different disease categories presented in table 2 and figure I are derived from the analysis of the full follow-up period from 1950 to 1990 [S20]. The LSS non-cancer mortality data were updated more recently, to 1997, and were analysed in more detail [P4, Z1], as discussed later in this annex, but the overall risk estimates for the full follow-up period remained essentially unchanged. There is no evidence of a dose response for mortality from infectious diseases (largely tuberculosis) and other diseases (including diseases of the genito-urinary system). Several potential sources of bias and confounding have been considered [S20], including: *(a)* the possibility that the construction of this cohort five years after the bombings may have led to the selection of study subjects in a manner that would bias the non-cancer disease outcomes; *(b)* possible misclassification of causes of death that may give rise to a spurious association between non-cancer mortality and radiation dose; and *(c)* the possibility that radiation dose, which is closely correlated with distance from the hypocentre, may be confounded by other factors affecting non-cancer disease rates. The impact of these potential biases, which was analysed by pooling non-cancer mortality (excluding blood diseases), is discussed below.

**Figure I. Dose–response curve of mortality from all diseases except neoplasms and blood disease**
Both cities, both sexes, all ages at the time of bombing, 1950–1985. Bars indicate 90% confidence interval of relative risk [S20]

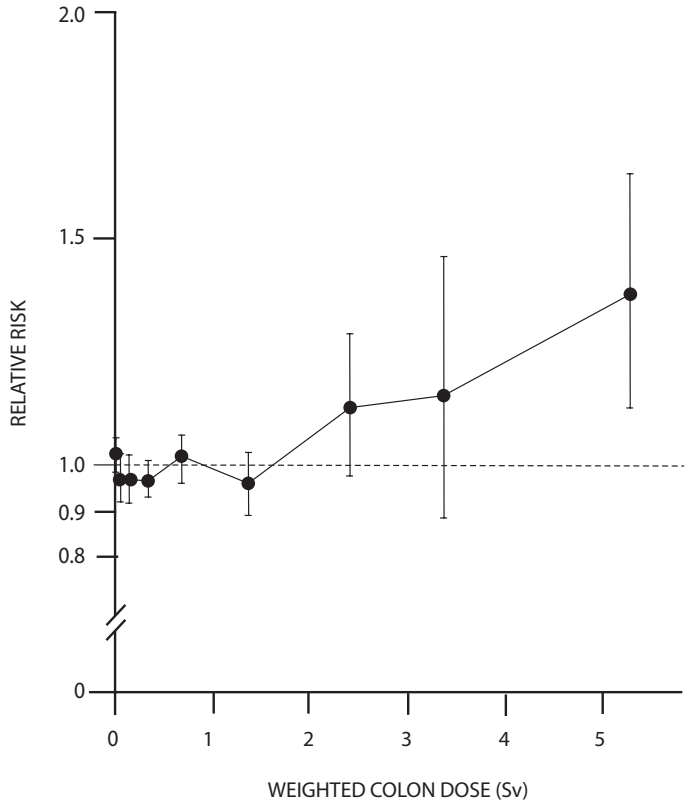


**Table 2 Number of deaths and ERR estimates for major categories of non-cancer disease**
Life Span Study 1950–1990 [S20]

| *Cause of death* | *Number of deaths* | *ERR per unit weighted colon dose[a] ($Sv^{-1}$)* | *90% confidence interval* | *p-value (1-sided)* |
|---|---|---|---|---|
| Stroke | 7 859 | 0.09 | (0.02, 0.17) | 0.02 |
| Cerebral haemorrhage | 3 687 | 0.03 | (–0.06, 0.14) | |
| Cerebral infarction | 1 611 | 0.07 | (–0.09, 0.25) | |
| Other | 2 561 | 0.20 | (0.06, 0.35) | |
| Heart diseases | 6 826 | 0.14 | (0.05, 0.22) | 0.003 |
| Coronary heart disease | 2 362 | 0.06 | (–0.06, 0.20) | |
| Hypertensive heart disease | 1 199 | 0.21 | (0.00, 0.45) | |
| Other | 3 265 | 0.17 | (0.05, 0.31) | |
| Respiratory diseases | 3 163 | 0.18 | (0.06, 0.31) | 0.005 |
| Pneumonia | 1 828 | 0.20 | (0.04, 0.37) | |
| Asthma | 397 | 0.08 | (–0.18, 0.45) | |
| Other | 938 | 0.19 | (–0.02, 0.43) | |
| Digestive diseases | 2 742 | 0.11 | (0.00, 0.24) | 0.05 |
| Liver cirrhosis | 920 | 0.18 | (0.00, 0.40) | |
| Other | 1 822 | 0.07 | (–0.07, 0.23) | |
| Infectious diseases | 1 705 | –0.002 | (–0.13, 0.15) | >0.50 |
| Tuberculosis | 1 368 | 0.01 | (–0.13, 0.19) | |
| Other | 337 | –0.07 | (<–0.10, 0.29) | |
| Other diseases | 4 822 | 0.01 | (–0.08, 0.11) | 0.41 |
| Chronic renal disease | 551 | 0.003 | (–0.22, 0.30) | |
| Senility | 1 906 | 0.09 | (–0.08, 0.29) | |
| Other | 2 365 | –0.02 | (–0.13, 0.10) | |

[a] The authors express the weighted colon dose in sieverts as the sum of the gamma-ray dose and 10 times the neutron dose.

### A. Misclassification

20. Using data from a large number of autopsies carried out in the LSS as the diagnostic reference, it was estimated that on average 20% of cancer deaths are misclassified on death certificates as being due to non-cancer causes ("cancer to non-cancer misclassification"), while 3.5% of deaths from causes other than cancer are mistakenly classified as cancer deaths ("non-cancer to cancer misclassification") [R5, S6]. Sposto et al. [S6] demonstrated that after correction for the cancer to non-cancer misclassification rates by age, sex, time and city, estimates for ERR of non-cancer mortality were reduced by about 20% relative to estimates that ignored the misclassification. In conclusion, in the LSS, disease misclassification on death certificates has an effect on estimates of risk for non-cancer disease, but the dose response for non-cancer disease remains highly significant even after correcting for this effect.

21. Because misclassification rates vary among different causes of death (they are especially high for respiratory diseases, for example), their impact on estimates for cause-specific mortality from non-cancer disease will vary but remains unassessed [R5]. Sposto et al. [S6] suggested two alternative ways to correct for misclassification for a specific disease entity. One was to create two disease categories, e.g. heart disease and all other causes combined, and to estimate the misclassification probabilities. Alternatively, more than two classifications could be used, pooling causes of death that are similar.

### B. Biases and confounders

22. Because radiation doses were dependent on the distance from the hypocentre, a spurious dose effect could arise if proximal and distal survivors differed with respect to socio-economic status, lifestyle or other risk factors. First, this question was directly examined by assessing the possible confounding effect of smoking and other factors [S20] using data obtained from mail surveys conducted

among the LSS cohort subjects during the 1960s and 1970s. Potential factors, such as educational level, occupation, physical activity at work, house size per person (as a surrogate measure of socio-economic level), marital status, smoking status, regular alcohol use and percentage of Japanese food in diet, were analysed. Non-cancer underlying mortality rates varied significantly with each of these factors. The magnitude of the effects of many of these factors was comparable to, or even larger than, the difference in risk associated with exposure to 1 Sv. For example, smoking at the time of the mail surveys increased the non-cancer mortality rates by 37%. However, the associations between these factors and dose were not strong enough to significantly alter the risk associated with radiation doses; for example, there was only a 2% difference in the frequency of smoking associated with exposure to 1 Sv versus 0 Sv. Statistical adjustment for smoking reduced the estimate of ERR per unit dose only from 0.083 $Sv^{-1}$ to 0.079 $Sv^{-1}$ (table 3). In no case did the failure to allow for any of the other factors have an appreciable impact on the risk estimate for non-cancer disease from radiation exposure. When five factors (smoking, marital status, education, occupation and house size per person) were all taken into account, the estimate for ERR per unit dose for non-cancer disease was reduced from 0.097 $Sv^{-1}$ to 0.087 $Sv^{-1}$. These findings indicate that the observed association between radiation and non-cancer mortality cannot be explained by the confounding effect of any of these factors, although the possibility of confounding by other unidentified or unmeasurable factors cannot be eliminated.

23. In further analysis [S20], the dose–response analyses for non-cancer disease were limited to the 61,000 proximal survivors (those exposed within 3 km of the hypocentre). The ERR estimate obtained from this subcohort was 0.11 $Sv^{-1}$, which was consistent with the estimate derived from the full cohort data. Furthermore, a significant radiation dose effect was found even when the analysis was limited to about 3,000 survivors who were between 0.9 and 1.2 km from the hypocentre, a span of 300 m in which weighted colon radiation dose estimates ranged from 0.35 to 5.8 Sv (median dose 1.1 Sv). It was considered implausible that there would be enough dose-correlated variation in socio-demographic characteristics over this narrow distance band to account for the observed dose response. It should be noted that atomic bombing survivors have shown a high prevalence of infection with the hepatitis C virus, an important cause of both liver cancer and liver cirrhosis [S19]. This may have played a cofactor role in the occurrence of liver disorders among exposed atomic bombing survivors.

### C. Selection effects

24. The presence of cohort selection effects was suggested by temporal patterns of the LSS underlying rates of non-cancer diseases. The underlying rates of non-cancer disease in the year 1950 were about 15% lower for proximal survivors (i.e. those who were within 3 km of the hypocentre, generally an urban area, but for whom doses were estimated as zero because of shielding) than for distal survivors with zero dose (who were between 3 and 10 km of the hypocentre, generally a rural area), but this difference diminished to about 2% in the late 1960s [P4]. While this small difference in the rates of non-cancer disease seemed to persist, and may reflect the urban–rural, socio-economic or other differences affecting underlying rates, the diminishing difference in rates with time in the earlier years was considered to be due to the selection of healthy survivors, resembling the healthy worker effect seen in studies of occupational cohorts. Thus proximal survivors included in the LSS may have been initially healthier than the general

**Table 3 Risk estimates for non-cancer disease due to radiation with and without adjustment for potential confounders**
Life Span Study 1950–1990 [S20]

| *Risk factor* | *Number of subjects with data available* | *ERR per unit dose*[a] *($Sv^{-1}$)* | |
|---|---|---|---|
| | | *Unadjusted* | *Adjusted* |
| Highest education level | 38 035 | 0.086 | 0.088 |
| Occupation | 36 766 | 0.098 | 0.097 |
| Physical activity at work | 7 364 | 0.088 | 0.097 |
| House size per person | 26 562 | 0.071 | 0.068 |
| Current marital status | 37 543 | 0.104 | 0.097 |
| Current smoking status | 38 975 | 0.083 | 0.079 |
| Current alcohol use | 34 470 | 0.133 | 0.144 |
| Per cent of Japanese food in diet | 7 292 | 0.085 | 0.084 |

[a] Weighted colon dose.

population, since they were able to survive the effects of the bombings and/or the difficult living conditions in the two cities in the immediate post-war period.

### D. Dose response and risk estimates

25. The shape of the dose–response curve for non-cancer diseases is influenced by making allowance for the presumed healthy survivor effect, which depends on time and distance, and causes a small but persistent urban–rural difference in underlying rates [P4]. Because the effect is more pronounced in the earlier years of follow-up, the analysis restricted to the period before 1968 reveals significant curvature in the dose response (figure II, left panel), while there is no evidence of non-linearity in the later period, 1968–1997 (figure II, right panel). The small urban–rural (proximal–distal) differences in underlying rates add a smaller curvature to the dose response in the full cohort compared with the proximal survivors in both the pre-1968 and the 1968–1997 periods (figure II, left and right panels).

26. Figure III shows fitted linear and smoothed dose–response curves for the 1968–1997 period with no adjustment for proximal–distal differences in underlying rates [P4]. There is no indication of significant non-linearity in the dose response. However, there is considerable uncertainty regarding the dose response or even the existence of an effect at doses of below about 0.5 Sv. There is no evidence against a threshold of zero, and the maximum-likelihood estimate of the threshold in the adjusted analysis is about 0.15 Sv, with an upper 90% confidence bound of about 0.55 Sv. For the period before 1968, the data suggest a non-linear dose response. The non-linearity in the early LSS data is reduced but not totally accounted for by adjustments based on proximal–distal comparisons; this may be due to a residual proximal–distal effect that remains after the simple adjustment above [P4].

27. The non-cancer mortality data for the period of 1950–1967 show that a linear–quadratic or quadratic dose–response model may be adequate [P4]. However, since the distance-dependent selection effects among the proximal survivors are likely to have biased the estimates of values for dose–response parameters for this period, generalization of these estimates to other populations or different exposure situations may not be warranted.

28. Analysing the same LSS non-cancer mortality data for the period 1968–1997, Little used a variety of generalized relative risk models assuming 25%, 35% and 45% geometric standard deviation (GSD) dosimetric errors [L10]. When linear–threshold, quadratic–threshold, or linear–quadratic–threshold relative risk models were fitted, there was no evidence of threshold models significantly different from the linear, quadratic or linear–quadratic models. These findings were true irrespective of the assumed dosimetric errors. There was also little evidence of excess risk below 0.5 Sv. In general, these findings were true for the four major disease categories considered, i.e. stroke, coronary heart disease, digestive disease and respiratory disease.

29. Because the ERR for mortality from non-cancer disease is considerably smaller than that for mortality from solid cancers, and because underlying rates of non-cancer

**Figure II. Fitted curves of mortality from non-cancer diseases in the LSS cohort for early (1950–1967, left panel) and late (1968–1997, right panel) periods of follow-up [P4]**

Solid curve fits use only proximal survivor data; dashed curve fits are based on the full cohort without allowance for selection effects

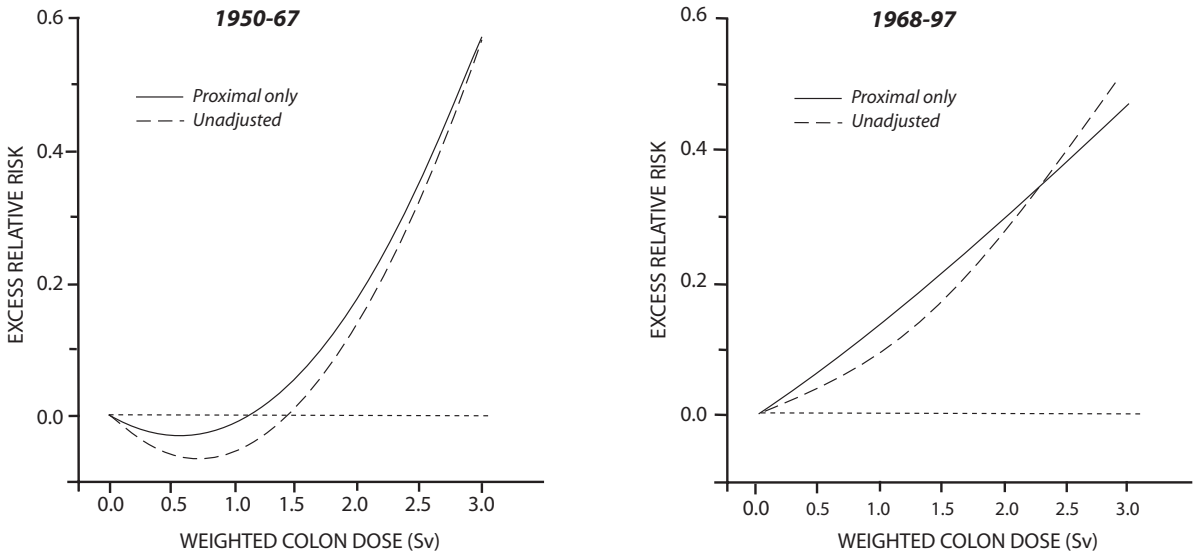
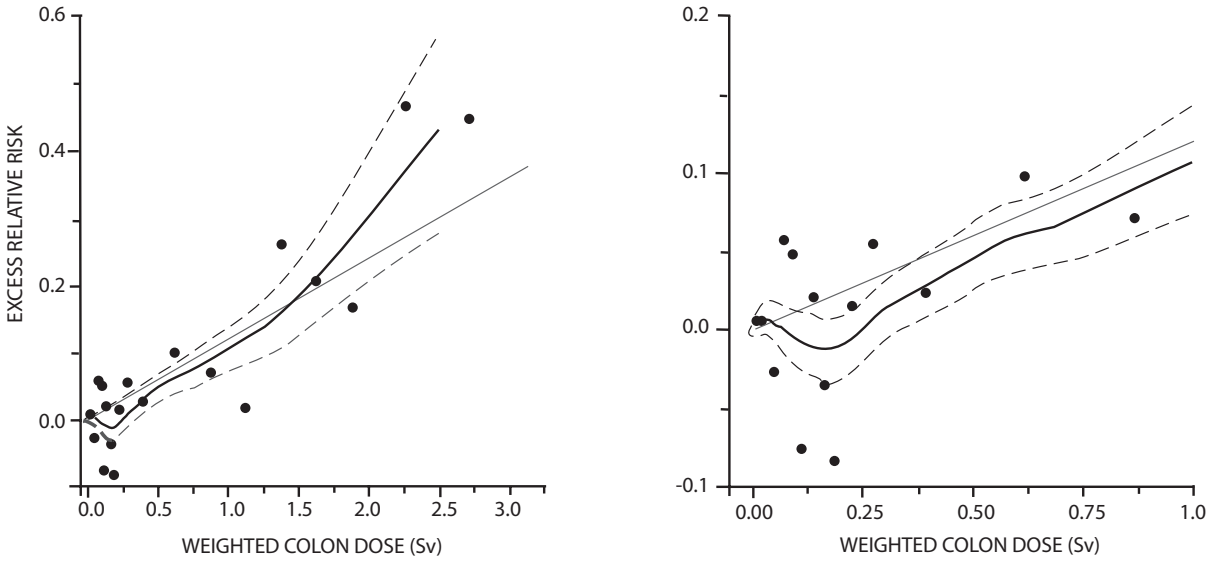


**Figure III. Mortality from non-cancer disease in the LSS cohort versus dose for the period 1968–1997 [P4]**
Individual points are dose-category-specific ERR estimates. The thin straight solid line is the fitted linear ERR model without any effect of age at exposure, sex or attained age. The thick solid curve provides a smoothed estimate derived from the individual points, with the two dashed curves indicating ±1SE (standard error). The right panel represents the same data as in the left panel, but shows the low-dose portion of the fitted curve in greater detail

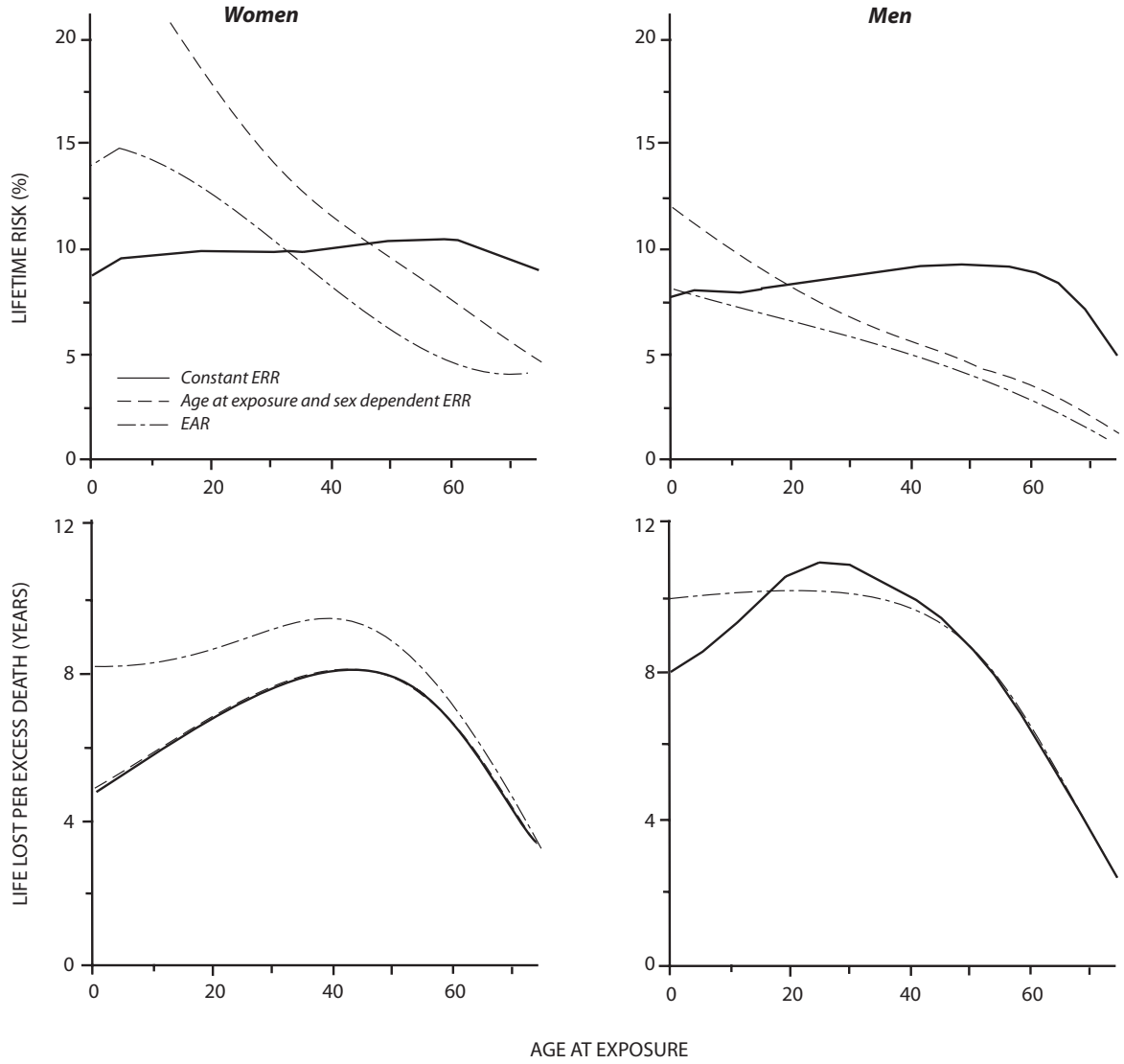



disease are much higher than rates of cancer, any modifying effect of age, time and sex on the risk is difficult to detect. The ERR for non-cancer disease decreases with increasing age at exposure, decreases with attained age and is lower for men than for women, although none of these effects is statistically significant [P4]. Others [L10, Z1] who have analysed the LSS data have also found that age at exposure has no significant effect on the risk of non-cancer disease.

30. There are two main sources of uncertainty in the current LSS dose–response data for estimating the lifetime risk of non-cancer disease due to radiation exposure. First, because of the uncertainty about how the risk varies with age, sex and age at exposure, three different risk models are used: *(a)* the constant ERR model; *(b)* an alternative ERR model with age-at-exposure and sex effects; and *(c)* an excess absolute risk (EAR) model with no age-at-exposure effects. Age-specific underlying rates of non-cancer disease have declined rapidly in Japan, but the time-constant ERR model provides lifetime risk estimates that are insensitive to age at exposure. In contrast, the other two models (ERR and EAR) depend on age at exposure, and predict decreasing risks with increasing age (figure IV). In any case, the results suggest that the lifetime risks of non-cancer disease among those exposed as children may be half the risks or less than those for solid cancer, while persons exposed at age 50 may have lifetime risks of non-cancer disease equal to those for solid cancer [P4]. Second, because there is great uncertainty about the shape of the dose–response relationship at low doses, the current estimates for lifetime risk are presented for exposure at 1 Sv, where the estimates are little affected by the shape of the dose–response curve. The magnitude of the risk of non-cancer disease at lower dose levels, e.g. 0.5 Sv, is at present very uncertain.

**Figure IV. Estimates of lifetime risk (two upper graphs) and of years of life lost per excess death (two lower graphs) at 1 Sv weighted colon dose (from LSS Report 13 [P4])**

The two left-hand graphs show the estimates for women, the two right-hand graphs those for men. Estimates represented by the dark solid curves are based on constant ERR models. Estimates based on age-at-exposure and sex-specific ERR models (dashed curves) or on an EAR model (dash-dotted curves) are also shown



# IV. CIRCULATORY DISEASES

31. Diseases of the circulatory system (circulatory diseases) are leading causes of morbidity and mortality among adults worldwide, and are the cause of 30–50% of all deaths in many countries. In comparison, malignant neoplasms are the cause of 15–30% of all deaths. Atherosclerosis is a generalized underlying condition for the majority of circulatory diseases in adult populations and has three major clinical manifestations: cerebrovascular disease, coronary (or ischaemic) heart disease and peripheral vascular disease. Coronary heart disease and stroke are the major causes of death from circulatory diseases. Risk factors for atherosclerotic disease traditionally have included high blood pressure, cigarette smoking, hypercholesterolaemia (especially increased low-density lipoprotein (LDL) cholesterol) and diabetes. Factors such as obesity, family history of premature coronary heart disease and oestrogen replacement therapy have also been associated with coronary heart disease. Heavy alcohol intake increases mortality from coronary heart disease, but moderate intake appears to have a protective effect against the disease [T6].

32. Diseases of the heart may be broadly categorized as ischaemic heart disease (most importantly myocardial infarction), hypertensive heart disease, valvular heart disease, non-ischaemic (primary) myocardial disease and congenital heart disease. These different types of heart disease markedly differ in pathogenesis, aetiology, clinical presentation and prognosis. Ischaemic heart disease is the late manifestation of coronary atherosclerosis and is responsible for the majority (80–90%) of the cardiac deaths in most countries [S18]. The effects of radiation exposure at low doses on this category of heart disease and underlying atherosclerotic changes are of special concern in this annex. Hypertensive heart disease occurs in response to systemic hypertension, leading to heart dysfunction or congestive heart failure, among others. Valvular heart disease may be caused by congenital disorders or by various acquired diseases, including rheumatic heart disease. Primary myocardial disease may occur as a result of inflammatory disease (myocarditis), immunological disease, systemic metabolic disorders, muscular dystrophies, genetic abnormalities or other unknown causes. These different categories of heart disease can be coded using the International Classification of Diseases (ICD) scheme adopted by most epidemiological follow-up studies.

33. In the literature, the term “cardiovascular disease” is used interchangeably to refer to the broad category that includes all diseases of the circulatory system or more specifically to heart disease. This annex follows the nomenclature used in the International Classification of Diseases and Related Health Problems (ICD-10) [W7]. “Circulatory disease” will be used to refer to the entire group of diseases of the circulatory system (I00–I99), including any form of heart disease (I00–I02, I05–I09, I10–I15, I20–I25, I26–I28, I30–I52), cerebrovascular disease (I60–I69), and diseases of the arteries, diseases of other vessels and diseases not elsewhere classified (I60–I69, I70–I79, I80–I89). “Heart disease” will refer to any form of disease of the heart as defined above. “Ischaemic heart disease” (I20–I29), which is often used synonymously with coronary heart disease in the literature, will include angina pectoris, myocardial infarction and its complications. “Cerebrovascular disease” (I60–I69) includes stroke, haemorrhagic infarction or unspecified, and its sequelae. “Stroke” is used synonymously with this disease category.

## A. Patients receiving radiotherapy for cancer

34. The heart at one time was considered to be a radiation-resistant organ; only isolated examples of radiation-induced carditis were available in the early literature. This was in part due to the limitations on thoracic irradiation posed by the much greater radiosensitivity of the lungs. In the mid-1960s, cases of radiation-induced heart disease began to be reported from a large series of Hodgkin’s lymphoma patients who had survived irradiation of the mantle field. Therapeutic doses were very high, exceeding 30–40 Gy in most cases. Damage to the heart is considered to be due to tissue destruction from such high doses. The changes in heavily irradiated patients can involve all structures of the heart (including the pericardium, myocardium, valves, conduction system and coronary arteries), but most characteristically the pericardium, and can include pericardial effusion, fibrosis and constrictive pericarditis [A3, F1]. The term “radiation-induced heart disease” has been used to refer to such conditions [S2]. Initially, coronary heart disease or myocardial infarction was only occasionally reported, but starting in the early 1990s, an excess risk of myocardial infarction after radiation treatment began to be noted in patients with Hodgkin’s lymphoma or breast cancer. Much information has since been accumulated on the risk of coronary heart disease subsequent to cancer radiotherapy.

### 1. Hodgkin’s lymphoma patients

35. Until 1960, the treatment of Hodgkin’s lymphoma was usually considered palliative, but starting around 1960,

curative treatment of this disease began to evolve rapidly with new radiotherapy and chemotherapy regimens. With the introduction of megavoltage radiotherapy, techniques to treat extensive fields became available. With the development of mantle field irradiation and total lymphoid irradiation, radiotherapy became the cornerstone of the treatment of Hodgkin's lymphoma [C1]. Megavoltage equipment delivered a dose to deeper parts of the body. In the 1960s, doses of 40–44 Gy were often given to involved fields [K1, N1]. Before 1960, if radiation was employed at all, smaller doses were used to treat early-stage Hodgkin's lymphoma, although at some medical centres doses of 25–30 Gy were administered to involved nodal and proximal areas [D1].

36. In the late 1970s and early 1980s, it became apparent that radiotherapy given to extended fields at high doses could induce late mortality from lung damage, myocardial infarction and second cancers. Modifications were then introduced to reduce radiotherapy fields and doses whenever possible. From the mid-1970s to 1994, 30–40 Gy was commonly given when radiotherapy was used without cytotoxic drugs, while an average of 30 Gy was administered when used in combination with chemotherapy [D2]. Before the early 1970s, similar therapy was given to paediatric and adult Hodgkin's lymphoma patients. Thereafter, treatment of Hodgkin's lymphoma in children was modified to use lower doses (15–25 Gy to involved fields); therapy regimens for fully developed adolescents still incorporated larger doses (35–44 Gy) [M1].

37. Some earlier literature linked coronary artery disease to cancer treatment [K2]. Among the earliest follow-up studies was one by Boivin et al. [B1]. In a cohort of 4,665 Hodgkin's lymphoma patients treated at 11 cancer treatment centres in the United States and Canada (Boston, Houston, Montreal and Toronto), 124 cases who died either directly from or with coronary heart disease were compared with 489 controls randomly selected from the entire cohort. The age-adjusted relative risk of death with any coronary heart disease after radiotherapy was non-significantly elevated (1.87), but the relative risk of death with myocardial infarction was significantly elevated (2.56). When the analysis was restricted to coronary heart disease as the direct cause of death, the age-adjusted relative risk associated with radiotherapy was significantly increased (3.11). The patients included both children and adults diagnosed between 1940 and 1985. Cardiac radiation doses were not available. The relative risk for those treated in the early period (before 1965–1970), when high-dose orthovoltage irradiation was used, was higher, but not significantly, than for those treated in later years.

38. To date, the most detailed analysis of risk of mortality from heart disease after radiotherapy for Hodgkin's lymphoma comes from the cohort study of 2,232 paediatric and adult patients irradiated during 1960–1990 at Stanford University Medical Centre (table 4) [H1]. The patients were followed on average for 9.5 years; 1,609 patients received mediastinal irradiation from mantle therapy; 369 received less extensive, limited field irradiation; 23 received irradiation for recurrent disease; and 231 received no mediastinal irradiation. Mean mediastinal doses were lower among patients treated before 10 years of age (21.5 Gy) and after 50 years of age (28.7 Gy) than for other age groups (36.7–40.5 Gy). Of the 88 deaths from heart disease, 55 were from acute myocardial infarction and 33 from other cardiac diseases.

39. The relative risk (RR) of death from acute myocardial infarction calculated on the basis of comparison with the United States Life Tables was 3.2 for the entire cohort, with no significant sex difference. The RR was higher for patients treated with radiation alone (RR = 4.1, mean dose 50.7 Gy) than for those treated with both chemotherapy and radiation (RR = 2.7, mean dose 43.3 Gy) or for those who received no mediastinal irradiation (RR = 1.7) (table 4). A significantly elevated RR of 3.5 was found for patients irradiated at ≥30 Gy (mediastinum dose); the RR of 4.2 for those irradiated at <30 Gy was derived from only two subjects.

40. Of the 33 deaths from cardiac diseases other than acute myocardial infarction, about half (15) were deaths from chronic pancarditis or pericarditis. The RR of other cardiac deaths was elevated both for patients treated with radiation alone (RR = 3.2) and for those treated with chemotherapy and radiation (RR = 3.6) (table 4).

41. In this cohort, very few patients were treated with combination chemotherapy, mostly MOPP, without radiotherapy. The relative risk for all cardiac disease mortality for this group of patients was elevated (1.6), but not significantly, and this was consistent with the earlier analysis by the same investigators, which indicated the absence of an excess risk of coronary heart disease in Hodgkin's lymphoma patients treated with chemotherapy [H14].

42. Several risk-modifying effects were noted. As discussed in more detail later, the most notable were the effects of age at treatment. A higher risk of heart disease, both myocardial infarction and other heart diseases, was found among patients treated at young ages, especially at less than 20 years. Also, the relative risk of acute myocardial infarction and other cardiac diseases increased with time after treatment. Blocking to limit cardiac exposure (subcarinal block) reduced the relative risk of cardiac diseases other than myocardial infarction from 5.3 to 1.4, but not that of acute myocardial infarction (RR = 3.7 versus 3.4). Subcarinal blocking reduces the volume of the heart exposed to irradiation but does not provide protection to the proximal part of the coronary arteries [A3].

43. Although information on smoking was not available for the entire cohort of Hodgkin's lymphoma patients, a subset of the subjects participated in a questionnaire and interview study. Among the Hodgkin's lymphoma patients, 52.6% had never smoked cigarettes and 24.5% had formerly

**Table 4 Risks of death from myocardial infarction and other cardiac diseases after treatment for Hodgkin's lymphoma**
Stanford Study [H1]

| *Group (number of patients at risk)* | *Acute myocardial infarction* | | | *Other cardiac diseases* | | |
|---|---|---|---|---|---|---|
| | *Number observed/expected* | *Relative risk (95% CI)* | *Absolute risk* | *Number observed/expected* | *Relative risk (95% CI)* | *Absolute risk* |
| All patients | 55/17.3 | 3.2 (2.3, 4.0) | 17.8 | 33/11.5 | 2.9 (1.9, 3.9) | 10.2 |
| Male (1 316) | 47/14.3 | 3.3 (2.3, 4.2) | 27.0 | 24/8.3 | 2.9 (1.7, 4.1) | 13.0 |
| Female (916) | 8/3.0 | 2.6 (1.2, 5.0) | 5.5 | 9/3.2 | 2.8 (1.4, 5.1) | 6.4 |
| Radiation alone[a] (1 183) | 35/8.4 | 4.1 (1.2, 5.5) | 25.7 | 17/3.3 | 3.2 (1.9, 4.0) | 11.4 |
| Combined treatment (1 119)[a] | 14/5.2 | 2.7 (1.5, 3.8) | 9.7 | 12/3.3 | 3.6 (2.0, 6.1) | 9.6 |
| Mediastinum radiation treatment: | | | | | | |
| None (254) | 6/3.6 | 1.7 (0.7, 3.5) | —[b] | 4/2.9 | 1.4 (0.4, 3.4) | —[b] |
| 0–30 Gy (131) | 2/0.5 | 4.2 (0.7, 13.8) | —[b] | 0/0.3 | —[b] | —[b] |
| >30 Gy (1 830) | 47/13.3 | 3.5 (2.5, 4.5) | 18.6 | 29/8.4 | 3.5 (2.2, 4.7) | 11.4 |
| Before 1972 (553) | 26/7.0 | 3.7 (2.3, 5.1) | 24.7 | 23/4.3 | 5.3 (3.1, 7.5) | 24.2 |
| After 1972 (1 448) | 23/6.8 | 3.4 (2.0, 4.8) | 13.9 | 6/4.3 | 1.4 (0.6, 2.9) | —[b] |
| Age at irradiation, years: | | | | | | |
| <20 (487) | 6/0.14 | 44.1 (17.8, 91.6) | 11.3 | 4/0.19 | 21.5 (6.8, 52) | 7.3 |
| 20–29 (749) | 8/1.1 | 7.3 (3.4, 13.8) | 9.0 | 7/0.79 | 8.8 (3.8, 17.4) | 8.1 |
| 30–39 (448) | 14/2.7 | 5.1 (2.9, 7.4) | 27.4 | 7/1.5 | 4.8 (0.5, 5.1) | 13.4 |
| 40–49 (169) | 9/3.0 | 3.0 (1.4, 5.5) | 43.6 | 3/1.6 | 1.9 (0.5, 5.1) | —[b] |
| >50 (148) | 12/6.8 | 1.8 (1.0, 3.0) | —[b] | 8/4.6 | 1.7 (0.8, 3.3) | —[b] |
| Years after treatment: | | | | | | |
| 0–4 (NA)[c] | 12/6.0 | 2.0 (1.1, 3.3) | 6.4 | 6/4.1 | 1.5 (0.6, 3.0) | —[b] |
| 5–9 (NA) | 17/4.7 | 3.6 (2.2, 4.5) | 20.1 | 10/3.1 | 3.2 (1.6, 5.7) | 11.3 |
| 10–14 (NA) | 11/3.7 | 3.0 (1.6, 5.2) | 20.5 | 5/2.4 | 2.1 (0.8, 4.6) | —[b] |
| 15–19 (NA) | 11/2.2 | 5.0 (2.6, 8.7) | 54.2 | 8/1.4 | 5.8 (2.7, 10.9) | 40.7 |
| >20 (NA) | 4/0.7 | 5.6 (1.8, 13.6) | 70.6 | 4/0.5 | 8.8 (2.8, 21.3) | 76.1 |

[a] Includes mediastinum.
[b] Risk was not significantly elevated.
[c] NA = number of patients at risk not available.

smoked cigarettes. These figures were comparable to those reported for United States adults (of whom 51.2% had never smoked and 24.1% were former smokers), so it seems unlikely that the increased risk of acute myocardial infarction observed among the cohort of Hodgkin's lymphoma patients is explained by their smoking habits.

44. Other studies, generally of cohorts smaller in size than the Stanford cohort, have also reported increased risk (as measured by SMR) of mortality from myocardial infarction after radiotherapy for Hodgkin's lymphoma (table 5) [A7, C2, H9, K3, M6, R1]. Radiation doses received by the Hodgkin's lymphoma patients in these studies were in the range 35–45 Gy, except for the paediatric patients who were treated in 1980–1900 and received 20 Gy [H9].

45. Elevated SMRs ranging from 2 to 5 are in general agreement with the relative risks (which are actually SMRs) reported from the Stanford study [H1]. The very high SMR of 22 for cardiac death in paediatric patients irradiated between the ages of 3 and 22 years [H9] involved six deaths from cardiac disease, five of which were from myocardial infarction and occurred in males receiving 35–37 Gy from extended radiotherapy. Three of these six cases had received concomitant cyclophosphamide chemotherapy, which may also have contributed to cardiac myocyte injury.

46. Most results reported from follow-up of irradiated Hodgkin's lymphoma patients are based on external comparisons, with a few studies using limited internal comparisons. Nevertheless, the reported SMRs, which are sometimes

**Table 5 Risks of heart disease after radiotherapy for Hodgkin's lymphoma, other than the Stanford study**

| *Study and year* | *Study population* | *Age at treatment (years)* | *Length of follow-up (years)* | *Dose (Gy)* | *Results*[a] |
|---|---|---|---|---|---|
| King et al., 1996 [K3] | 326 patients treated between 1954 and 1989; Rochester, New York, United States | 25.6 (mean); 5–72 (range) | 13.3 (mean); 3–37 (range) | Central cardiac dose: 44.3 (mean); 35–60.4 (range) | Increased SMR (2.8) for fatal myocardial infarction among the irradiated patients |
| Reinders et al., 1999 [R1] | 258 patients treated between 1965 and 1980; Netherlands | 28 (median); 5–78 (range) | 14.2 (median); 0.7–26 (range) | Mediastinum inferior dose: 37.2 (mean) | SMR = 5.3 for ischaemic heart disease among the irradiated patients |
| Cosset et al., 1991 [C2] | 499 patients treated between 1971 and 1984; Villejuif, France | Not available | Not available | Mediastinal dose: 39–41 (68%); 35–37 (11%); 41–43 (7%) | Increased RR of 3.25 for pericarditis among patients irradiated at >41 Gy; no elevated RR of myocardial infarction |
| Mauch et al., 1995 [M6] | 794 patients treated between 1969 and 1988; Boston, Massachusetts, United States | 24 (median); 3–69 (range) | 11 (median) | Mediastinal dose: 35–40 Gy | Increased SMR of 2.2 for cardiac deaths for the cohort |
| Aleman et al., 2003 [A7] | 1 261 patients treated between 1965 and 1987; Netherlands | <40 | 17.8 (median) | Not available | Cardiovascular SMR: 7.2 (RT), 5.5 (RT and CT), 5.9 (salvage treatment); Myocardial infarction SMR: 1.3 (RT), 0.7 (RT and CT), 2.0 (salvage treatment) |
| Hudson et al., 1998 [H9] | 387 paediatric patients diagnosed between 1968 and 1990; Memphis, Tennessee, United States | 14.4 (median); 3–25 (range) | 15.1 (median) | Mediastinal dose: 35–44 Gy (1968–1979); 20 Gy (1980–1990) | Increased SMR (22.2) for cardiac disease |

[a] RT: radiotherapy; CT: chemotherapy.

referred to as relative risks in these studies, are in the range 2–5 in different populations (with the exception of paediatric patients), providing consistent evidence of the effects of high-dose radiotherapy (at about 30–40 Gy) on ischaemic heart disease. Modern radiotherapy for Hodgkin's lymphoma has incorporated newer techniques, exposing a smaller volume of the heart to a much lower dose, but little is known about the effects of the lower-dose radiotherapy currently in use (from 15 to 25 Gy). More information could be expected from follow-up studies of patients treated with modern radiotherapy, but analysis will be complicated by the combined use of doxorubicin and related drugs, which have been shown to have long-term cardiotoxic effects [K8, L11].

### 2. Childhood cancer patients

47. The long-term risk of heart disease following radiotherapy and chemotherapy for childhood cancer has been reported [A3], but few studies have examined a dose response. In a clinical follow-up of 229 patients treated for a variety of cancers before the age of 15 years at the Institut Gustave Roussy, Villejuif, France, between 1968 and 1985, cardiac disorders were diagnosed in 89 patients, including 24 with heart failures and 65 with other asymptomatic, echocardiographic changes (abnormal fractional shortening, ejection fraction and end systolic meridonal wall stress) [G10]. All these children had received anthracyclins and 125 had received radiotherapy. Radiation doses delivered to seven points in the heart were estimated for all patients who had received radiotherapy [D10]. Adjusted for potential confounders, the cardiac disorder risk was found to be linearly related to radiation dose; the RR was 1.63 for radiation doses of >0–5 Gy, 6.48 for doses of 5–20 Gy and 4.40 for doses of >20 Gy compared with patients with no radiotherapy [P6]. There was no indication of an interaction between radiation dose and cumulative dose of anthracyclins known to be cardiotoxic.

### 3. Breast cancer patients

48. Today, the majority of breast cancers diagnosed in women in most Western countries are detected at an early stage. Surgery is the primary treatment, but subsequently adjuvant therapy (including radiotherapy, chemotherapy or

hormonal treatment) is also given. The treatment fields used in irradiating the breast or chest wall include a portion of the heart. The radiation dose to the heart depends on the radiation treatment technique used. Especially in older series of post-mastectomy radiotherapy, a large portion of the heart was irradiated [F2, R2]. Early randomized trials of treatment for breast cancer, as discussed below, have demonstrated that radiotherapy is an effective treatment modality for reducing mortality from breast cancer, but they have also provided evidence of increased mortality from cardiovascular disease associated with the radiotherapy.

49. Recent radiation techniques used in conjunction with breast-conserving surgery deliver radiation to a smaller portion of the heart. The strategy for breast-conserving treatment is to remove the bulk of the tumour surgically and to use moderate doses of radiation to eradicate any residual cancer. The volume of the heart irradiated has been significantly reduced in patients treated with modern techniques (mostly megavoltage radiotherapy after conservative surgery) compared with patients treated with earlier techniques (mostly by post-mastectomy orthovoltage radiation) [F2]. However, even with contemporary megavoltage radiotherapy, left-side breast cancer may result in exposure of the left anterior descending coronary artery to a substantial radiation dose, because the artery lies within or near the target field [F2]. Several studies, also reviewed below, have attempted specifically to evaluate the risk associated with modern radiotherapy.

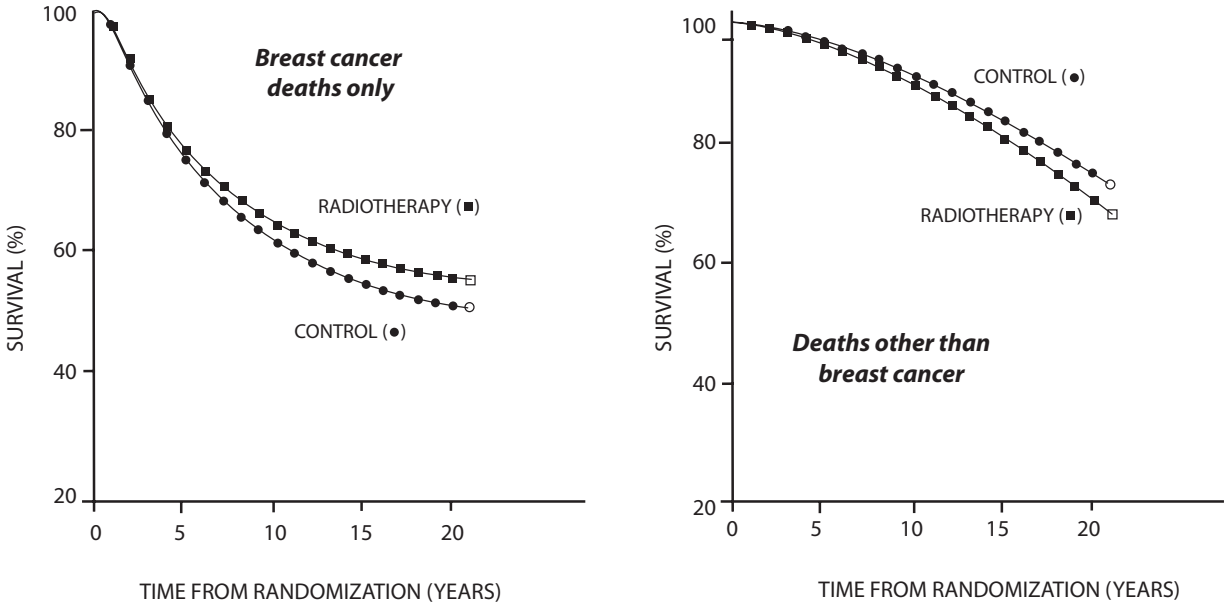
50. There are two major sources of data useful for assessing the risk of heart disease following radiotherapy in breast cancer patients: randomized clinical trials and laterality studies. In randomized clinical trials, breast cancer patients were randomly assigned to radiotherapy and other methods of treatment. Because of the random selection, results are expected to be unbiased, and thus well-executed randomized trials are regarded as the most credible. In "laterality studies", the risk of cardiac disease is calculated by comparing the disease rates after radiotherapy for left-sided breast cancer with that for right-sided breast cancer. This takes into account the fact that radiotherapy given for left-sided breast cancer exposes a larger volume of the heart to radiation and with a higher dose than treatment for right-sided breast cancer. Laterality studies are observational (not randomized), but they offer the advantage that differences in heart disease risk between left-sided and right-sided breast cancer patients are unlikely to be explained by possible confounding or patient selection.

*(a) Randomized clinical trials*

51. An increased risk of mortality from cancer other than breast cancer among irradiated breast cancer patients was initially suggested by Cuzick et al. [C3, C4], who reviewed data from several early breast cancer clinical trials—one comparing radical mastectomy without radiotherapy against simple mastectomy with radiotherapy in patients treated during 1951–1975, and the other evaluating post-operative adjuvant radiotherapy in breast cancer patients treated during 1949–1979. The data showed a detrimental impact on long-term (10–15 year) survival associated with radiotherapy, which was attributed to excess cardiovascular mortality [H2, H4, J3].

52. Radiotherapy regimens used in the initial series varied with respect to the energy of the beam, fields irradiated, duration of treatment and dose range. Cuzick et al. [C5]

**Figure V. Effect of radiotherapy on cause-specific survival in breast cancer patients in the EBCTCG [E3]**



subsequently extended the follow-up and showed that among the survivors of ≥10 years, cardiac-related deaths were increased in the radiotherapy arm by 82% compared with the control arm.

53. Since 1984–1985, data from randomized trials in early breast cancer, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), have been evaluated periodically. Results have shown reduced mortality from breast cancer in the adjuvant radiotherapy group [E2]. Mortality from diseases other than breast cancer, however, was increased among those who received radiotherapy. The meta-analysis of data from follow-up of the radiotherapy to 1995 in 40 unconfounded randomized trials involved 19,583 women with early breast cancer and showed that radiotherapy increased mortality from causes other than breast cancer by 21.2%; the 20-year survival was 69.5% among those who were allocated to radiotherapy compared with 73.8% among controls (figure V) [E3].

54. Vascular mortality was significantly increased by radiotherapy (radiotherapy/control death rate ratio = 1.30, standard error 0.09) (table 6). The relative excess of vascular deaths appeared to be similar during and after the first decade of follow-up, but the absolute rates were about three times higher in the latter period, reflecting the increasing underlying mortality with increasing follow-up time. No information was available, however, on radiation doses or on laterality of breast cancer (as a surrogate for cardiac exposure).

55. The latest analysis of the EBCTCG data involves 42,000 women in 78 randomized comparisons allowing analysis of 15 or more years of follow-up data [E4]. As with the previous analysis, there was a significant excess of mortality from non-cancer diseases in irradiated women, mainly involving heart disease (radiotherapy/control death rate ratio = 1.27, $p = 0.001$). The excess seemed to be less during the first 5 years of follow-up but was significant for the periods 5–14 years and 15 years or more after follow-up. The mean dates of randomization were 1975 and 1970, respectively, for those who died 5–14 years and 15 or more years after randomization. This is consistent with the possibly greater hazards of the radiotherapy regimens in the early 1970s versus the lower late hazards of modern radiotherapy.

56. More recent data, from the Danish Breast Cancer Cooperative Group, are relevant for assessing the risk associated with the most recent therapy techniques. In this trial, 3,083 women who were at high risk of breast cancer recurrence after mastectomy were randomly assigned to adjuvant systemic treatment with or without radiotherapy [H7]. Breast cancer patients were treated with electron-based techniques that minimized the portion of the heart volume irradiated. In the 12-year follow-up, the relative hazard (radiotherapy/non-radiotherapy ratio of the cumulative hazard function) of morbidity and mortality from ischaemic heart disease among women treated with radiotherapy was 0.86 (95% CI: 0.6, 1.3), which was not significantly different from that of 0.84 (95% CI: 0.4, 1.8) among those without radiotherapy (figure VI). The volume of the heart irradiated was considered small, but the exact heart volume in the radiation field was unknown. The conservative estimate was that less than 15 mm of the anterior surface of the heart received an absorbed dose per day of 1.7–1.9 Gy, given in 25 fractions, 5 fractions per week. The number of subjects (46 morbidity cases and 12 deceased cases with ischaemic heart disease) was rather small, and the authors cautioned that further follow-up would be necessary to assess the long-term effects on the heart.

### *(b) Laterality studies*

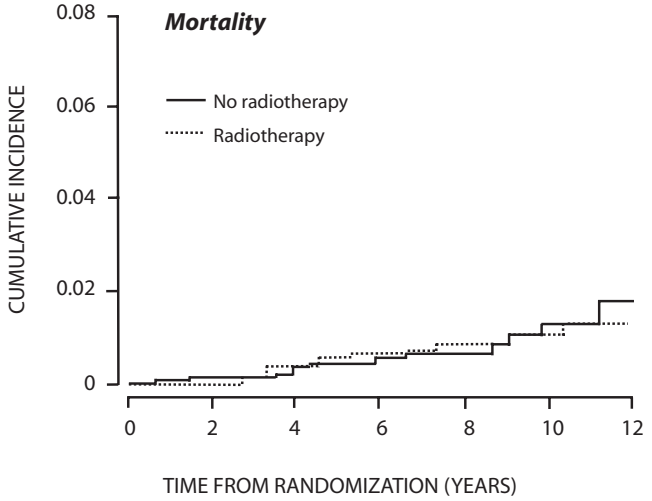
57. Laterality studies are methodologically innovative, taking advantage of the heart being closer to the left breast than the right. However, left- versus right-sided comparisons may lead to an underestimate of the radiation-related risk, because the heart also receives a low dose of scattered radiation from radiotherapy for the right-sided breast. In addition, most of the laterality studies lack information on the radiotherapy used, and radiation doses are rarely estimated.

58. Table 7 summarizes the main results regarding the risk of heart disease from laterality studies. The largest study of myocardial infarction after adjuvant radiotherapy for left- versus right-sided breast cancer was conducted by Paszat

**Table 6 Non-cancer causes of death**
Early Breast Cancer Trialists' Collaborative Group [E3]

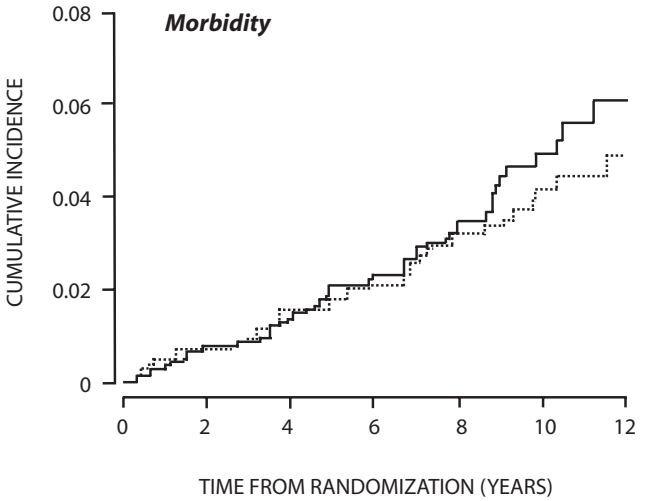
| *Underlying cause of death when breast cancer had not recurred* | *Number of deaths* | | *Radiotherapy/control ratio of annual death rates (standard error)* |
|---|---|---|---|
| | *Allocated to radiation treatment* | *Adjusted control* | |
| Vascular | 437 | 322 | 1.30 (0.09) |
| Non-vascular | 382 | 313 | 1.15 (0.09) |
| Unknown | 339 | 292 | 1.09 (0.09) |
| Total | 1 158 | 927 | 1.18 (0.05) |
| Follow-up duration ($10^3$ woman-years before recurrence) | 82.1 | 74.8 | |

**Figure VI. Cumulative mortality (left) and morbidity (right) for ischaemic heart disease among patients treated with/without radiotherapy, from the Danish Breast Cancer Cooperative Group study of high-risk breast cancer patients after adjuvant post-mastectomy systemic treatment with/without radiotherapy [H7]**




Patients at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| No radiotherapy | 1 521 | 1 316 | 1 052 | 666 | 645 | 340 | 154 |
| Radiotherapy | 1 525 | 1 322 | 1 099 | 946 | 737 | 410 | 194 |




Patients at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| No radiotherapy | 1 521 | 1 311 | 1 043 | 657 | 631 | 329 | 151 |
| Radiotherapy | 1 525 | 1 316 | 1 092 | 939 | 727 | 402 | 188 |

et al. [P1]. This was based on over 200,000 breast cancer patients identified by the Surveillance, Epidemiology and End Results (SEER) registries in the United States. The subjects were women aged 20 years or older and diagnosed between 1973 and 1992. A total of 703 deaths from myocardial infarction occurred during the follow-up, which averaged 74 months. Analysis of actuarial probability of deaths showed a greater likelihood of fatal myocardial infarction among women given adjuvant radiotherapy for left-sided breast cancer than for right-sided breast cancer (figure VII, two left-hand graphs). In contrast, there was no significant difference in the probability of death from myocardial infarction among non-irradiated women between left-sided and right-sided breast cancer (figure VII, two right-hand graphs). Since no individual information was available on the specific type of radiotherapy, the authors compared data for two time periods, 1973–1982 and 1983–1992, assuming major differences in radiation treatment practices (see table 7) between the two periods. The relative risk of myocardial infarction after irradiation for left-sided breast cancer patients was significant among those who were diagnosed before age 60 years during the earlier time period (table 7) but not among those aged 60 years or more at diagnosis, during either the earlier or the later period. Cardiac events were too few among breast cancer patients of less than 60 years of age and diagnosed in the later period, when use of post-lumpectomy (breast-conserving surgery) radiation treatment was more frequent.

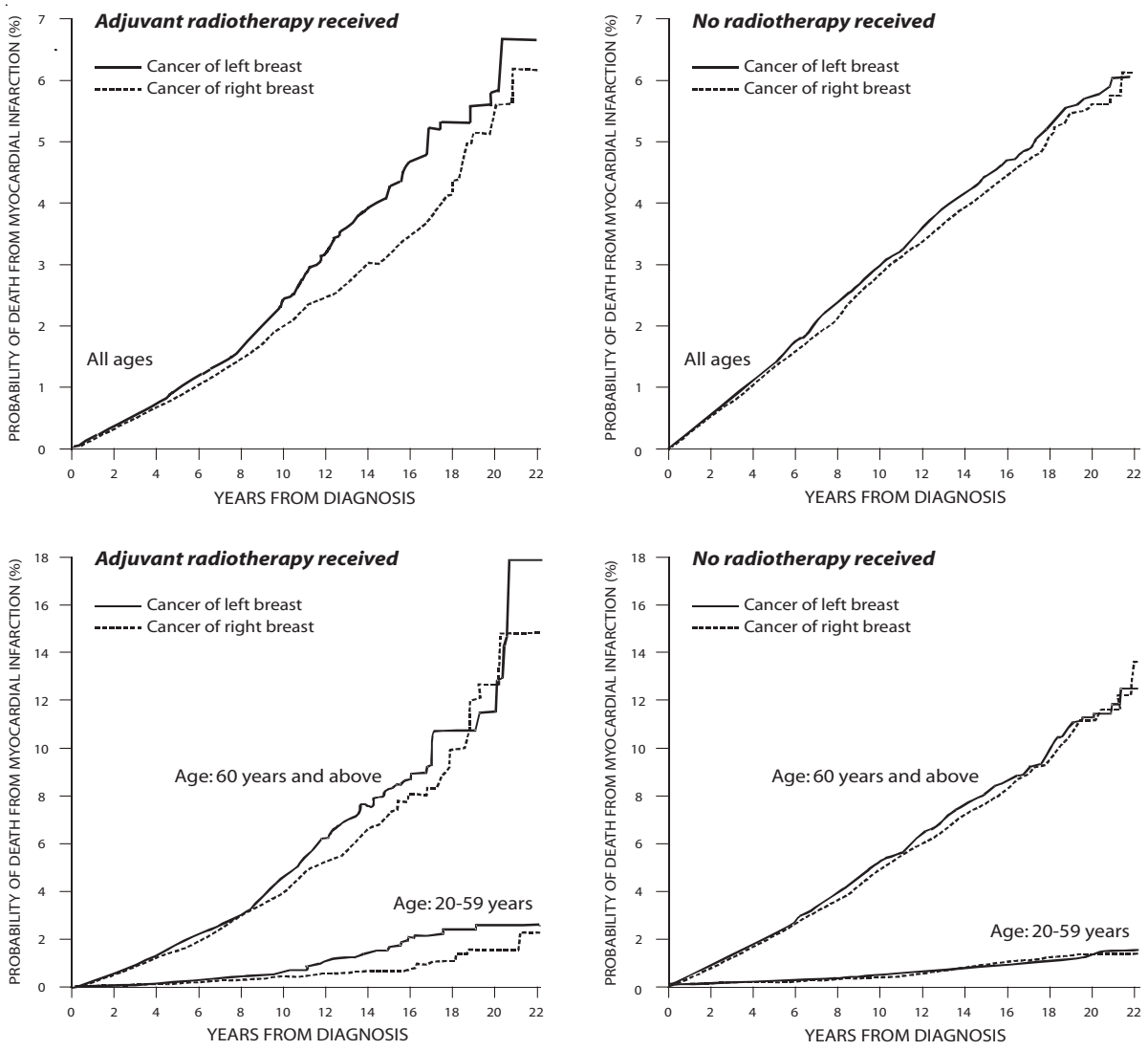
59. Rutqvist and Johansson [R3] analysed mortality data among about 55,000 breast cancer patients reported to the Swedish Cancer Registry during 1970–1985. The registry does not record information on treatment, but previous population-based surveys had indicated that about 50% of all breast cancer patients received radiotherapy, usually with supervoltage techniques. The relative risk of death from myocardial infarction was significantly elevated for left- versus right-sided tumours (1.09; 95% CI: 1.02, 1.17). The relative risk appeared to increase with follow-up time, but was not significant. Assuming that about half of all breast cancer patients in this study had radiotherapy, the relative risk associated with radiation was estimated to be 1.2. This magnitude of relative risk from the Swedish study was slightly lower than that previously reported from the United Kingdom Cancer Research Campaign (CRC) trial, in which the relative risk associated with treatment for left-sided tumours showed a twofold excess over that for right-sided tumours (2.26 versus 1.20) [H2]. However, in the latter study, the relative risk associated with orthovoltage radiation was higher (1.86) than that with megavoltage techniques (1.27). The Swedish relative risk value was similar to the value reported from the CRC trial for cardiac death associated with supervoltage radiation (1.35 for left-sided tumours).

60. Analysing mortality data for 89,407 women aged 18–79 years with unilateral breast cancer in Sweden between 1970 and 1996, Darby et al. [D5] reported an increased relative risk of death from cardiovascular disease (RR = 1.10) occurring more than 10 years after treatment (table 7). No information was available regarding the specific radiation techniques used, but most of the cardiovascular deaths involved women treated for breast cancer in the 1970s. For women treated in the 1980s, when radiation

## Table 7 Breast cancer laterality studies

| *Study and year* | *Number of breast cancer patients, years treated and country* | *Follow-up duration (years)* | *Treatment, breast tumour dose (Gy)* | *Heart disease* | |
|---|---|---|---|---|---|
| | | | | *Number of deaths or cases* | *Relative risk (left- versus right-sided breast cancer)* |
| **Mortality follow-up** | | | | | |
| Paszat et al., 1998 [P1] | 206 523 women<br>1973–1992<br>United States | Mean 6.2 | 1973–1982, adjuvant radiotherapy;<br>1983–1992, mostly post-lumpectomy radiotherapy | Total 361, aged 60+, 1973–1982;<br>Total 125, aged 20–59, 1973–1982;<br>Total 218, aged 60+, 1983–1992;<br>Total 19, aged 20–59, 1983–1992 | RR = 1.98 for age 20–59, 1973–1982;<br>RR = 1.17 for age 60+, 1973–1982 (NS);<br>RR = 1.02 for age 60+, 1983–1992 (NS) |
| Rutqvist and Johansson, 1990 [R3] | 54 617 women<br>1970–1986<br>Sweden | Median 9;<br>range 1–17 | Usually supervoltage technique | 1 803 (left)<br>1 566 (right) | RR (myocardial infarction) = 1.09 |
| Darby et al., 2003 [D5] | 89 407 women<br>1970–1996<br>Sweden | <10<br><br>10+ | Unknown | 5 739<br><br>3 426 | RR (all cardiovascular disease) = 1.01 (95% CI: 0.96, 1.07) at <10 years, 1.10 at 10+ years after diagnosis |
| Nixon et al., 1998 [N2] | 745 women<br>1968–1986<br>United States | Maximum 12 | Breast-conserving surgery plus megavoltage, tangential;<br>typically 45–50 | Total 18 (9 left-sided; 9 right-sided) | RR (cardiac death) = 1.04 (NS) |
| Rutqvist et al., 1998 [R4] | 684 women<br>1976–1987<br>Sweden | Mean 9;<br>range 3–16 | Breast-conserving surgery plus tangential photon field;<br>46–54 (96%),<br>10–16 (1.9%) | Total 12<br>(7 left-sided;<br>5 right-sided) | RR = 0.86 (NS) |
| Vallis et al., 2002 [V1] | 2 128 women<br>1982–1988<br>Toronto, Canada | Median 10.2;<br>range 7.7–15.1 | Post-lumpectomy radiotherapy (coplanar tangential);<br>typically 40 | Total 49<br>(26 left-sided;<br>23 right-sided) | RR = 1.1 (NS), all ages;<br>RR = 1.6 for age <60;<br>RR = 0.9 for age 60+ |
| Paszat et al., 1999 [P2] | 3 006 women<br>1982–1997<br>Ontario, Canada | Median 8.8 | Post-lumpectomy radiotherapy;<br>mean 43 | Total 74<br>(44 left-sided;<br>30 right-sided) | RR = 2.10 (all ages);<br>RR = 8.76 (age 60+ versus 20–59) |
| Giordano et al., 2005 [G8] | 27 283 women<br>1973–1988<br>United States | 15 | | Not available | All patients (in situ, localized, regional disease):<br>RR = 1.28 (13.1% versus 10.2%) for 1973–1979;<br>RR = 1.08 (9.4% versus 8.7%) (NS) for 1980–1984;<br>RR = 1.04 (5.8% versus 5.2%) (NS) |
| **Morbidity follow-up** | | | | | |
| Patt et al., 2005 [P7] | 16 270 women<br>(8 363 with left-sided breast cancer)<br>1986–1993<br>United States | mean 9.5;<br>range 0–15 | Primary surgical therapy and adjuvant radiotherapy | Total:<br>Ischaemic heart disease<br>(825 left-sided;<br>769 right-sided) | Hazard ratio = 1.05 (NS) |

**Figure VII. Probability of death from myocardial infarction in women of all ages (upper panels) and in women aged 20–59 years or 60+ years (lower panels) with cancer of the left or right breast who received adjuvant radiotherapy or no radiotherapy [P1]**




doses to the breast were presumably lower, the relative risk was still elevated (1.1), but had a wide confidence interval.

61. Several studies (discussed below) attempted to assess the risk of myocardial infarction specifically associated with radiotherapy given after conservative surgery of the breast. The results are mixed. An absence of significantly increased relative risk of myocardial infarction following radiotherapy treatments for left- versus right-sided breast cancer has been reported by: Nixon et al. [N2], who followed 745 breast cancer patients in Boston, United States, for up to 12 years; Rutqvist et al. [R4], who followed 684 Swedish breast cancer patients from 3 to 16 years; and Vallis et al. [V1], who followed 2,128 breast cancer patients in Toronto, Canada, for about 8 to 15 years (table 7). The numbers of cases with myocardial infarction in these studies are generally small (fewer than 50).

62. An increased risk of myocardial infarction was reported from another study by Paszat et al. [P2], which included 3,000 breast cancer patients in Ontario, Canada, with a record of lumpectomy as maximal breast surgery and a record of post-lumpectomy radiotherapy. The relative risk of mortality from myocardial infarction for women who received post-lumpectomy radiotherapy for a left-sided cancer was 2.10 (95% CI: 1.11, 3.95) compared with those with right-sided cancer (table 7). The increased likelihood of mortality from myocardial infarction among the left-sided breast cancer patients was significant among women aged 60 years and older (table 7). There is an overlap in the breast cancer patients included in this study and the one by Vallis et al. [V1] cited above, which did not find an increased risk of myocardial infarction. While the subjects in the [P2] study were identified from a province-wide registry, the [V1] study included patients seen at a specialized

cancer centre. The patients included in the [V1] study had carcinoma in situ as well as invasive cancers and tended to be younger. Thus there may have been some differences in cardiac dose or dose volume between the two series of breast cancer patients.

63. More recently, Giordano et al. [G8] followed 27,283 women treated with adjuvant radiation for breast cancer identified from the SEER programme in the United States. These patients were stratified into three subcohorts on the basis of the year of diagnosis: 1973–1979, 1980–1984 and 1985–1989. To ensure an equal time of follow-up for the different subcohorts, follow-up was censored at 12–15 years. Among the women diagnosed between 1973 and 1979, there was a statistically significant difference in the 15-year mortality from ischaemic heart disease between patients with left-sided (13.1%) and right-sided (10.2%) breast cancer. No significant difference was found for women diagnosed between 1980 and 1984 (9.4% versus 8.7% for left- and right-sided, respectively) or between 1985 and 1989 (5.8% versus 5.2% for left- and right-sided, respectively). Thus the differences in rate for women with left- and right-sided breast cancer have diminished with time, but continued follow-up will be necessary to determine whether excess cardiovascular mortality disappears completely [C11, G8].

64. Also using the SEER database, Patt et al. followed 16,270 women with breast cancer who received adjuvant radiotherapy during 1986–1993 [P7]. The subjects were followed for up to 15 years by linkage to the Medicare database. This database provides morbidity information from hospitalization for individuals aged 65 years and older, but the completeness of coverage is not clear. No significant differences were found in left- versus right-sided breast cancer patients for hospitalization for ischaemic heart disease (9.7% versus 9.6%) or other heart disease, with the age-adjusted hazard ratios for ischaemic heart disease being 1.05 (95% CI: 0.94, 1.16).

65. Data on cardiac risks following breast cancer radiotherapy have also been reviewed by Taylor et al. [T3] and Prosnitz et al. [P9]. Both reviews concluded that modern radiotherapy techniques for breast cancer have reduced radiation exposure to the heart, but it is not clear whether current regimens are free from cardiac risks. Taylor et al. pointed out that none of the observational studies (mostly laterality studies) of breast cancer patients receiving radiotherapy have attempted to reconstruct dosimetric calculations for dose–response analysis for heart disease.

66. Subclinical vascular abnormalities have also been observed following thoracic irradiation. In breast cancer patients treated with modern radiotherapy, myocardial perfusion scintigraphy studies demonstrated perfusion defects to occur more frequently for left- than for right-sided breast cancers up to 18 years after radiotherapy [G9]. The frequency of perfusion defects was correlated with the volume of the left ventricle exposed to the radiation field, as these defects occurred in 25% of patients who had from 1 to 5% of the left ventricle in the tangent field compared with 55% of patients with >50% of the left ventricle in the field [M15]. The clinical significance of perfusion defects is unclear, but the findings suggest that subtle cardiac injury may still occur even with modern techniques [P8].

### 4. Testicular seminoma patients

67. About 15–25% of patients with stage I seminoma have metastases to the drainage lymphatics, and are treated with elective irradiation to the lumbar periaortic and ipsilateral ilioinguinal lymph nodes. Some patients are given bilateral pelvic irradiation. Previously, elective irradiation frequently was given to the mediastinum and supraclavicular areas of stage I patients, and elective mediastinal irradiation was administered to most patients with stage II disease. Currently, for patients with stage I disease, megavoltage irradiation is recommended using daily doses of 1.8–2 Gy, for a total of 20–25 Gy over 2–3 weeks, to the primary zone of nodal drainage in the lumbar and periaortic and ipsilateral ilioinguinal regions. When elective mediastinal irradiation is administered, 20 Gy is given over 2–3 weeks. For patients with stage II seminoma with metastases in lymph nodes below the diaphragm, irradiation is similar to that used in stage I patients, but the dose is increased to 30–40 Gy over 4–5 weeks. Elective mediastinal irradiation is administered to all stage II B patients [W3].

68. Early data from irradiated seminoma patients showed variable findings regarding heart disease risk [B6, P3, W4]. A more recent study of 124 patients with seminoma treated between 1968 and 1984 reported an increased risk of heart disease after mediastinal irradiation [L2]. Of the 124 patients, 57 had mediastinal as well as infradiaphragmatic irradiation, while others had treatment limited mostly to the infradiaphragmatic field only. The median dose to the mediastinum among the patients was 2.4 Gy. Four patients, all in the group that received mediastinal irradiation, developed heart disease (three with myocardial infarction or related heart disease and one with constrictive carditis), and two died from sudden death thought to be of cardiac origin. No cardiac disease was observed in the group not treated with mediastinal irradiation.

69. Huddart et al. [H8] analysed long-term risks of cardiovascular disease in a larger follow-up (up to 20 years) study of 992 testicular seminoma patients (390 with chemotherapy only, 130 with chemotherapy and radiotherapy, 230 with radiotherapy and 242 with surveillance only) treated between 1982 and 1992 at the Royal Marsden National Health Service Trust in the United Kingdom [H8]. The relative risk of cardiac events (myocardial infarction, angina or related cardiovascular episode) was significantly elevated (RR = 2.40) among patients treated with radiotherapy, with or without chemotherapy, compared with the reference surveillance group. No significant differences were found in smoking behaviour or cholesterol levels

between different treatment groups, but patients receiving radiotherapy and chemotherapy had a higher frequency of history of hypertension than the surveillance group. On the basis of computed tomography scans in six patients, the mean cardiac dose was estimated to be 0.76 Gy (range: 0.54–1.35 Gy), with a mean maximum cardiac dose of 3.36 Gy (range: 0.82–14.1 Gy), and on average 14% of the cardiac volume received a dose of 0.9 Gy or more, indicating that direct cardiac irradiation was uncommon. Only 30 patients received mediastinal irradiation, while the majority of the remaining patients received infradiaphragmatic radiotherapy. The risk of cardiovascular disease remained elevated after excluding patients who had mediastinal irradiation. These data suggest an elevated cardiac risk associated with partial irradiation and/or low scattered doses, although radiation-induced nephropathy (from infradiaphragmatic irradiation) could be an alternative explanation for the excess heart disease risk. This finding, however, is at odds with a more recent study of a larger cohort of 2,512 5-year survivors of testicular cancer in the Netherlands [V3]. After a medical follow-up of 18.4 years, 694 cardiovascular events occurred, including 141 acute myocardial infarctions. Mediastinal irradiation was associated with a 3.7-fold increase in myocardial infarction risk compared with surgery alone, but infradiaphragmatic irradiation was not associated with an increase in myocardial infarction risk.

### 5. Dose response and factors affecting risk

70. Dose–volume histograms and "normal tissue complication probability" models have been used to describe the cardiac response to irradiation. In these models, an organ is thought to consist of multiple functional subunits arranged serially or in parallel. For serially structured organs, such as the gastrointestinal tract or nervous tissue, damage to one portion of the organ may render the entire organ dysfunctional [H5]. In organs with parallel structure (e.g. lung and liver), damage to a small number of functional subunits may not impair the entire organ function, because the remaining subunits operate independently from the damaged subunits, and clinical injury occurs when a critical volume of the organ is damaged. When the dose distribution is inhomogeneous or when part of the organ is irradiated, the probability of a specific organ response can be estimated by a normal tissue complication probability model [G4]. In the case of the heart, little is known about structures within the heart that are liable to radiation-induced damage. However, dose–response curves have been constructed for radiation-induced heart disease, including coronary heart disease, assuming that the entire heart volume is equally radiosensitive. Applying the relative seriality model to the Stockholm and Oslo randomized trial data, Gagliardi et al. [G3] estimated a threshold dose of 20 Gy for ischaemic heart disease mortality. The serial assumption may not be valid because, as the Hodgkin's lymphoma data suggest (see the section on partial irradiation below), there may be differences in sensitivity to radiation by tissue type and location [H1].

71. In a study of a small number of Swedish breast cancer patients enrolled in a randomized trial of pre- or post-operative radiation therapy (45 Gy over 5 weeks) versus surgery alone [R2], the different radiotherapy techniques used were classified into three groups depending on the calculated dose volume: low (right-sided tangential $^{60}$Co fields), intermediate (electron fields) and high (left-sided tangential $^{60}$Co fields). The subset of patients who received the highest dose volume had significantly increased risk of death from ischaemic heart disease compared with surgical controls (table 8). Mortality from ischaemic heart disease in the groups with low and intermediate dose volume was similar to that among non-irradiated controls. No other differences were statistically significant. Since the dose and the irradiated heart volume were correlated, it was not possible to determine whether the dose, the volume or both were important for the increased cardiac mortality.

**Table 8 Mortality by estimated radiation dose volume in breast cancer patients with adjuvant radiation therapy versus surgery alone**

Rates in the table are deaths per 1000 persons per year; absolute numbers of deaths are given in parentheses [R2]

| *Cause of death* | *Surgery alone (n = 321)* | *Radiation therapy: radiation dose volume* | | | *Trend test* |
|---|---|---|---|---|---|
| | | *Low (n = 164)* | *Intermediate (n = 314)* | *High (n = 161)* | |
| Breast cancer | 33.9 (120) | 26.1 (51) | 25.6 (93) | 31.2 (57) | Not significant |
| Other cancer | 4.2 (15) | 3.6 (7) | 3.6 (13) | 1.6 (3) | Not significant |
| Ischaemic heart disease | 2.3 (8) | 1.5 (3) | 2.2 (8) | 7.1 (13) | $p < 0.05$ |
| Other cardiovascular disease | 2.8 (10) | 2.6 (5) | 2.5 (9) | 1.6 (3) | Not significant |
| Other causes | 2.5 (9) | 2.0 (4) | 3.0 (11) | 3.3 (6) | Not significant |
| All causes | 45.7 (162) | 35.8 (70) | 36.9 (134) | 44.9 (82) | Not significant |

*(a) Partial irradiation*

72. Gagliardi et al. [G3] reviewed data from two randomized breast cancer trials: the Oslo breast cancer trial of post-operative radiotherapy as an adjuvant to radical mastectomy [H4] and the Stockholm breast cancer trial of adjuvant pre- or post-operative radiotherapy versus surgery alone [R2]. The end points used were mortality from myocardial infarction in the Oslo trial and mortality from ischaemic heart disease in the Stockholm trial. Based on three-dimensional dose distributions reconstructed for different treatment techniques in 10 model breast cancer patients [G3], the dose–response curves were quite similar for different cardiac volumes irradiated (100%, 66% and 33%), suggesting that volume dependence is small.

73. Eriksson et al. [E1] further compared the dose response for heart disease mortality obtained from 157 Hodgkin's lymphoma patients with the five mean dose–volume histograms for breast cancer patients studied by Gagliardi et al. [G3]. The dose–response curve from the breast cancer radiotherapy was much steeper than that from the Hodgkin's lymphoma treatment. This was thought to be due to the different portions of the heart irradiated for the two types of treatment; the typical irradiation geometry for the Hodgkin's lymphoma treatment is almost complementary to that of the breast cancer treatment. These findings suggest the presence of heterogeneity in tissue response to radiation within the heart.

74. Heterogeneity in tissue response was also suggested by the Stanford study of Hodgkin's lymphoma [H1], in which subcarinal blocking was associated with a reduction of the relative risk for non-myocardial infarction from 5.3 to 1.4, but not of the relative risk for myocardial infarction (3.7 versus 3.4). Subcarinal blocking reduces the irradiated volume for the entire heart but does not protect the proximal part of the major coronary arteries from irradiation. This finding, however, is also consistent with possible susceptibility to coronary artery injury at lower radiation doses [H1].

*(b) Dose fractionation*

75. Cosset et al. [C2] followed 499 patients irradiated for Hodgkin's lymphoma during 1971–1984 at the Institut Gustave Roussy; 75% of the patients were treated using 4 weekly fractions of 2.5 Gy, 6% received 3 weekly fractions of 3 Gy, 16% received 3 weekly fractions of 3.3 Gy, and the remaining patients received an unusual fraction schedule and thus were not analysed. The 5-year cumulative incidence of pericarditis increased significantly with increasing total cumulative dose (4.1%, 5.8% and 10.4% in dose groups 35–37 Gy, 39–41 Gy and 41–43 Gy, respectively). After adjustment for fractionation, the same increasing trend was observed but was no longer significant. Multivariate analysis adjusting for age, sex, mediastinal involvement and type of chemotherapy showed the pericarditis risk to be significantly increased with total doses of 41 Gy or higher and at 3.0 Gy or higher per fraction. Although the cumulative incidence of myocardial infarction in the irradiated patients was significantly increased compared with that in 138 Hodgkin's lymphoma patients without mediastinal radiotherapy, neither a dose nor a fractionation effect could be demonstrated, possibly owing to there being only a small number of events (13 cases of myocardial infarction). The data suggest that dose fractionation may reduce the risk of radiation-induced pericarditis, but the effect of dose fractionation on the risk of coronary heart disease is not clear. In the study of irradiated Hodgkin's lymphoma patients, Reinders et al. [R1] failed to construct the "biologically equivalent dose", accounting for variations in total dose, fraction dose and treatment techniques, as a predictor of ischaemic heart disease risk, but this may have been in part due to the small variation in these parameters.

*(c) Age and time*

76. The earlier case–control study by Boivin et al. of Hodgkin's lymphoma patients [B1] found the relative risks of myocardial infarction associated with mediastinal irradiation to be homogeneous among subgroups classified by age at diagnosis of Hodgkin's lymphoma (0–39, 40–59 and 60+ years) or by number of years after diagnosis (0–4, 5–9 and 10+ years). However, variations in the radiation-related risk of heart disease were evident in the Stanford Hodgkin's lymphoma data [H1], which included a large number of patients treated at a wide range of ages and follow-up years. Most remarkably, the relative risk of acute myocardial infarction was highest (RR = 44) among those treated at an age of <20 years and decreased significantly with increasing age at treatment (irradiation) (see table 4). The absolute risk, i.e. the excess number of cases per 10,000 persons, increased significantly with increasing age at treatment, reflecting the increasing underlying rate for this disease with increasing age. The relative risk of acute myocardial infarction was already significantly elevated during the first 5 years after the initiation of therapy and remained elevated 20 years or more after treatment, and the risk increased with time after treatment (table 4). Generally similar patterns were observed for the risk of heart disease other than myocardial infarction. The relative risk of heart disease other than myocardial infarction was highest among patients treated at an age of <20 years, decreased significantly with increasing age at treatment (table 4), and increased significantly with increasing years after treatment.

77. Because of the narrow age range of breast cancer patients, ages at irradiation were grouped into two age categories, i.e. <60 and 60+ years, in most studies of breast cancer patients. In the study by Paszat et al. of breast cancer patients who received adjuvant radiotherapy [P1], the relative risk (left-sided versus right-sided breast cancer) of fatal myocardial infarction was significantly elevated for women diagnosed at ages 20–59 years and treated during 1973–1982 (RR = 1.98). The relative risk for women diagnosed at ages 60+ years was elevated but not significantly so. This is in disagreement with the results from another study by Paszat

et al. of the Ontario, Canada, cohort of Hodgkin's lymphoma patients [P2], which reported that the relative risk (left-sided versus right-sided breast cancer) of myocardial infarction after post-lumpectomy irradiation was increased for women diagnosed at age 60+ years (RR = 8.76) but not for women who were diagnosed at <60 years of age.

*(d) Smoking and other risk factors*

78. Animal studies have provided varying results as to whether general atherogenic risk factors modify the effect of radiation on coronary heart disease. In an early study by Fajardo and Stewart [F3, S15], irradiation of the heart in several hundred rabbits failed to produce coronary heart disease; a high-fat diet was found to be necessary for irradiation to induce atherosclerosis [A4]. However, in dogs, plaques developed with a normal diet [L4]. In general, however, results from these and other studies [A6, B3] are in agreement that the combination of irradiation and a high-fat diet accelerated atherogenesis.

79. Few human data are available on the possible modifying effects of non-radiation risk factors. In the study by Boivin et al. [B1], the relative risks of myocardial infarction after irradiation for Hodgkin's lymphoma did not differ with history of cigarette smoking (yes or no), hypertension, diabetes and previous coronary heart disease. Glanzmann et al. [G5] followed 352 irradiated Hodgkin's lymphoma patients with or without chemotherapy in Zurich, Switzerland, and found the incidence of ischaemic heart disease to be higher than expected in the subgroup with cardiovascular risk factors (18 observed versus 7.60 expected) but not in the subgroup without the risk factors (3 observed versus 3.13 expected).

## B. Patients receiving diagnostic radiation or radiotherapy for non-neoplastic diseases

80. Patients irradiated for diagnostic purposes or treatment of non-neoplastic conditions are exposed at doses lower than those treated with radiation for cancer. Among the numerous patient populations in this category that have been studied, populations of special interest are patients with thymic enlargement, mastitis, skin haemangioma, benign gynaecological disorders, tinea capitis and peptic ulcer (see table 1). Most of the study results on circulatory diseases are based on the comparison of observed numbers of events (mostly deaths) with expected numbers derived from the general population (i.e. external comparisons). Very few studies have compared disease rates between irradiated and non-irradiated patients in the cohort (i.e. internal comparisons). Causal inferences of findings from external comparisons alone are problematic because of the possibility that individuals with disease may have underlying disease rates that differ from those of the general population. Certain conditions for which patients were irradiated may also influence the subsequent risk of circulatory disease.

81. Ankylosing spondylitis patients received a total mean cardiac dose of 2.5 Gy, with a 10–90% range of 0.04–4.75 Gy, from a single course of X-ray treatment [L1]. Doses relevant for cerebrovascular disease are not clear but are assumed to be much lower if a mean thyroid dose of 0.99 Gy is used as the surrogate. Cerebrovascular and other circulatory diseases (presumably mostly heart disease) were among the causes of death that originally were considered to be normal among patients with spondylitis (referred to as Class D). The ratios of observed to expected deaths (O/E ratios) from cerebrovascular and other circulatory diseases (based on age-, sex- and period-adjusted mortality rates in England and Wales) were significantly elevated (the O/E ratios were 1.14 for cerebrovascular disease and 1.25 for other circulatory disease) (table 9). The finding was interpreted as not being attributable to the radiation treatment because: *(a)* increased mortality was observed in Class D for many other causes of death, including bronchitis, peptic ulcer, other gastrointestinal disease and violence; *(b)* a similar excess had been observed in another population of non-irradiated spondylitis patients [R7]; and *(c)* the increased risk of Class D diseases was more closely associated with attained age than with time since treatment, i.e. the risk tended to decrease with time. When relative risks were estimated by comparing the O/E ratios for the irradiated spondylitis cohort with those for a separate non-irradiated spondylitis cohort [R7], the calculated relative risks were below unity for cerebrovascular disease (RR = 0.66; 95% CI: 0.40, 1.10) and other circulatory diseases (RR = 0.97; 95% CI: 0.70, 1.33) [M13].

82. Between the 1940s and the 1960s, radiation therapy was frequently used at the University of Chicago, United States, to treat peptic ulcers. Radiotherapy for peptic ulcers consisted of daily fractions of 1.5 Gy given in one or two 6-day to 14-day courses, with a total mean cardiac dose of 2.10 Gy. The heart received scattered radiation, and it was estimated that up to 5% of the heart (the apex) was within the direct irradiation field. In the earlier analysis of mortality data of 3,609 peptic ulcer patients, a significantly increased relative risk of circulatory disease of 1.20 was observed among the irradiated group [G1]. The relative risk was based on the internal comparison of irradiated and non-irradiated patients with peptic ulcer and was adjusted for age, sex and other demographic variables as well as smoking. More recently, Carr et al. conducted an analysis of the dose–response relationship for mortality from coronary heart disease [C12]. Among those who survived 10 or more years after the treatment, the relative risk (adjusted for demographic variables, smoking and other risk factors) increased significantly, from 1.00 for the lowest cardiac dose category (mean volume-weighted dose of 1.6 Gy, with mean in-field dose of 7.6 Gy) to 1.51 for the highest cardiac dose category (mean volume-weighted dose of 3.9 Gy with mean in-field dose of 18.4 Gy) (table 9). There was no indication of a dose response for heart disease other than coronary heart disease. A statistically significant increased relative risk for coronary heart disease of 1.54 was seen for persons with a mean volume-weighted dose

**Table 9 Populations receiving diagnostic radiation or radiotherapy for non-cancer diseases**

| *Cohort, country* | *Cohort description* | *Dose (Gy)* | *Number of deaths* | *O/E ratio or relative risk* |
|---|---|---|---|---|
| **Heart disease** | | | | |
| Ankylosing spondylitis, United Kingdom [D3, L1] | 14 000 patients treated with a single course of X-rays | Heart: 2.49 (mean); 0.04–4.75 (10–90% range) | Circulatory disease other than cerebrovascular disease: 990 observed/794 expected | O/E = 1.25 |
| Peptic ulcer, United States [C12, G1] | 1 859 irradiated patients and 1 860 non-irradiated patients (men and women) | Heart: 1.6–3.9 (volume-weighted mean); 7.6–18.4 (assumed 5% in direct X-ray beam) | Coronary heart disease among 10+ year survivors: 551 exposed 546 unexposed | RR = 1 (referent, non-irradiated) RR = 1.00 (1.6 Gy, 7.6 Gy) RR = 1.23 (2.3 Gy, 10.6 Gy) RR = 1.54 (2.8 Gy, 12.9 Gy) RR = 1.51 (3.9 Gy, 18.4 Gy) (volume-weighted mean dose, in-field dose) |
| Metropathia haemorrhagica, Scotland, United Kingdom [D8, S3] | 2 068 women treated with X-irradiation for metropathia haemorrhagica | Bone marrow: 1.34 (mean); 0.07–1.9 (range) | Coronary heart disease: 102 observed/100.9 expected | O/E = 0.70 (<1.25 Gy) O/E = 1.27 (1.25–1.49 Gy) O/E = 1.17 (>1.5 Gy) |
| Menorrhagia, Manchester, United Kingdom [A1] | 2 049 women irradiated for menorrhagia | Ovary: 4.5–5; 12.5–15 (age <40 years) | Coronary heart disease: 44 observed/36.9 expected | O/E = 1.19, not significant |
| X-ray menopause, Cambridge, United Kingdom [B2] | 277 women with X-ray-induced menopause | Pelvis: approx. 7–10 | Coronary heart disease: 16 observed/9.68 expected | O/E = 1.65 ($p$ = 0.04) |
| **Cerebrovascular disease** | | | | |
| Ankylosing spondylitis, United Kingdom [D3, L1] | 14 000 patients treated with a single course of X-rays | Thyroid: 0.99 (mean); 0–2.06 (10–90% range) | Cerebrovascular disease: 231 observed/202 expected | O/E = 1.14 |
| **Circulatory disease** | | | | |
| Metropathia haemorrhagica, Sweden [R15] | 788 exposed and 1 219 unexposed women treated for benign bleeding disorders | Ovary: 6 | Circulatory system disease: 308 exposed 257 unexposed | O/E = 0.92 exposed O/E = 0.88 unexposed RR = 1.05 |
| New England benign gynaecological disorders, United States [I2] | 4 483 women irradiated for benign gynaecological disorders; 10 hospitals in New England, 1925–1965 | Bone marrow: 0.53–2.5 (tissue-weighted mean); Lung: 0.04–0.06 | Circulatory system disease: 1 685 observed/1 734.6 expected | O/E = 0.8 (0.01–0.25) O/E = 1.0 (0.26–0.50) O/E = 1.0 (0.51–0.75) O/E = 1.0 (≥0.76) O/E = 1.1 (unknown) |
| Scoliosis, United States [D9] | 5 573 women with scoliosis receiving repeated radiographic examinations | Lung: 0.041 (mean) | Circulatory system disease: number not reported | Significant dose response (no data presented) |
| Massachusetts tuberculosis fluoroscopy, United States [D4] | 6 285 patients (men and women) fluoroscopically examined for an average of 77 times; 7 100 unexposed non-irradiatedpatients | Lung: 0.84 (mean); | Circulatory system disease: Number (SMR) Female: 309 (1.0) exposed 440 (1.1) unexposed Male: 517 (1.0) exposed 925 (1.1) unexposed | RR = 0.9 for both women and men (estimated by ratio of SMR for exposed to unexposed) |

of 2.8 Gy or in-field dose of 12.9 Gy (to 5% of the heart volume). These relative risk values translate into an excess relative risk of 0.13–0.19 at 1 Gy (volume-weighted dose). It had previously been thought that peptic ulcer patients who were selected for radiotherapy may have had other conditions that made them unsuitable for surgical treatment, e.g. disposition for cardiovascular disease [G1], and that this may have caused the apparent increased rate of heart disease. However, such selection seemed unlikely. If such selection had occurred, the excess risk would have been observed sooner, within 10 years after treatment, and it was not.

83. During the 1930s and 1940s, the uterus and ovaries of female patients were irradiated to treat abnormal uterine bleeding. The conditions involved were mostly hyperplasia of the endometrium, uterine fibroids, endometrial and cervical polyps, and chronic cervicitis; the underlying cause

for many of these lesions was thought to be excessive secretion of oestrogen relative to progesterone from the ovaries. The target organ for radiotherapy was the ovary or uterus. Typical doses for women treated with X-rays were of the order of 6–15 Gy to the ovaries and 0.7–1.3 Gy to the bone marrow. Cardiac doses were not estimated but were presumably very low because the dose dropped sharply with increasing distance from the source and was very low for organs outside of the pelvis or abdomen [I2, I3]. Because the underlying condition (i.e. hyperoestrogenic status) may affect cardiovascular disease rates, a simple comparison of observed numbers of cardiovascular events in irradiated populations with numbers expected from rates in the general population is likely to be an inadequate measure of the risk associated with exposure.

84. Data on mortality from circulatory disease have been reported in several studies of patients with benign gynaecological disorders. Interpretation of the results presented in table 9 and summarized in the next paragraph is difficult because the underlying rates of circulatory disease may be influenced by the presumed hyperoestrogenic condition for which these patients were treated. Cell-killing effects of high-dose irradiation on the ovaries may affect the oestrogenic status, further complicating the assessment of radiation effects.

85. Early studies of women irradiated for gynaecological conditions generally reported mortality from heart disease close to the expected rate, although some studies suggested an increased risk of coronary heart disease after radiotherapy. In the cohort of 2,068 women X-irradiated for metropathia haemorrhagica at three Scottish radiotherapy centres, the observed number of deaths from coronary heart disease (102) was similar to the expected number (100.9) [D8, S3] (table 9). In this study, however, analysis based on internal comparison showed the ratio of observed to expected deaths from coronary heart disease to increase with an increasing bone marrow dose, with borderline significance for trend. The bone marrow dose ranged from 0.7 to 1.9 Gy [S3].

86. In another study of 2,049 women irradiated for menorrhagia at a Manchester (United Kingdom) hospital [A1], the observed number of deaths from coronary heart disease (44) was slightly higher than the expected number (36.9), but the difference was not significant. Radiation doses were not estimated for this group, but are presumed to be similar to those in the Scottish metropathia series. Significant excess mortality from coronary heart disease was found in a study of 277 women who had an X-irradiation-induced menopause in Cambridge, United Kingdom [B2]; 16 deaths were observed when 9.68 were expected (table 9). No internal comparison was carried out. Most of the higher than expected mortality occurred within 5 years after radiotherapy. Women in these series were mostly treated at ages close to their natural menopause, and therefore it was thought unlikely that results were explained by radiation-induced premature menopause.

87. The largest and most recent study of women irradiated for gynaecological disorders was conducted by Inskip et al. It originally involved 4,483 women irradiated at one of 10 hospitals in New England (Massachusetts or Rhode Island), United States, between 1925 and 1965 and followed up until 1985 [I2]. Cardiac doses were not estimated, but lung doses were estimated to be 0.04–0.06 Gy. The observed number of deaths (1,685) from circulatory disease was similar to the expected number (1,734.5) (SMR = 0.97; 95% CI: 0.93, 1.02). SMRs for circulatory disease did not differ with bone marrow dose (table 9). Bone marrow doses ranging from 0.1 to >0.76 Gy in this cohort were somewhat lower than the doses in the Scottish cohort. In a smaller study of patients irradiated for metropathia haemorrhagica in Sweden, the ratio of observed to expected deaths from circulatory disease was slightly higher in the exposed group than the unexposed group [R15]. The broad category of circulatory disease used is a weakness of the data from these two studies.

88. No evidence of excess risk of cardiovascular disease is available from a study of 6,285 tuberculosis patients who received multiple chest exposures to fluoroscopic X-rays at Massachusetts hospitals (fluoroscopy cohorts). Fluoroscopic examinations were given on average 77 times. Doses to the heart were not estimated, but doses to the lungs were estimated to be 0.84 Gy (mean). Doses relevant for cerebrovascular disease were not estimated. The SMRs for circulatory disease in the exposed patients were almost equal to the SMRs for the unexposed patients [D4], with ratios of the exposed to unexposed SMR being 0.9 for both men and women (table 9). However, no dose–response analysis was performed, and the disease category used was broad.

### C. Radiologists and radiologic technologists

89. Radiologists were among the earliest occupational groups exposed to excessive amounts of radiation. There are eight cohorts of radiologists and medical radiological personnel documented in the literature: three from the United States (radiologists, army X-ray technologists and radiologic technologists) and one each from Canada, China, Denmark, Japan and the United Kingdom. Of these, published data on mortality from circulatory disease are available from only three studies: United Kingdom radiologists, United States radiologists and United States Army technologists. The published Canadian medical radiation cohort data do not distinguish medical from non-medical workers and thus are reviewed in section D below, together with studies of other radiation workers.

90. The cohort of about 2,700 United Kingdom radiologists, the data for which were most recently updated by Berrington et al. [B4], includes radiologists who worked in the earliest years of radiological practices. Those who worked during 1897–1920 were largely pioneer British

radiologists who were exposed to excessive amounts of radiation. The authors estimated that radiologists in the 1920s and 1930s could have received exposures of 100 roentgens (equivalent to absorbed doses of approximately 1 Gy) each year [B5]. Smith and Doll previously stated that annual exposure in this population was 0.1 Gy before the 1950s and perhaps 0.05 Gy in the early 1950s [S4]. SMRs for specific causes of death were compared for different calendar years of first registration with a radiological society. The comparison indicates the declining levels of radiation exposure among radiologists over time. Compared with the rates of mortality in the general population, significantly lower than expected numbers of deaths from all causes were found among the radiologists (SMR = 0.77) and among those who first registered after 1920. Compared with the mortality rates for Social Class I (professional occupations) males or male medical practitioners, a significant deficit in all-cause mortality was found for the entire group (SMR = 0.94 and 0.92, respectively), and this was primarily driven by the deficit for those who registered most recently (i.e. during 1955–1979) (SMR = 0.69 and 0.68, respectively). The deficit in all-cause mortality appears largely to be due to a deficit in non-cancer mortality, as the numbers of deaths from cancer were generally close to expectation but were higher than expectation among those entering the profession in the early years, especially before 1920. The observed numbers of deaths from circulatory disease were generally close to or lower than expectation (table 10). Compared with the mortality for male medical practitioners, the number of deaths from circulatory disease was significantly lower than expected among those who first registered before 1920 (SMR = 0.79), during 1921–1935 (SMR = 0.83) and most recently (1955–1979) (SMR = 0.59) (table 10). The authors concluded that the absence of an elevated SMR for non-cancer diseases in the earliest radiologists indicated the lack of evidence of a radiation effect.

91. It has been reported elsewhere, however, that general medical practitioners have higher mortality on average, largely from diseases associated with smoking (ischaemic heart disease, respiratory disease and several types of cancer, etc.), when compared with hospital physicians and surgeons; on average general practitioners smoked 37% more cigarettes than did hospital physicians and surgeons [S4]. This complicates the interpretation of SMR values using medical practitioners as the comparison.

92. In the study of United States radiologists, mortality rates were compared between radiologists and other physician specialists (who were considered less exposed to radiation) stratified by different calendar years of entry into their specialty organization. In an earlier analysis of cause-specific mortality data, the authors noted a significant difference in the cardiovascular–renal disease mortality of radiologists (RSNA) and physicians (ACP) compared with that of ophthalmologists and otolaryngologists (AAOO) in the earliest subcohort (1920–1929) and of ophthalmologists in the 1930–1939 subcohort [M2]. Further analysis of mortality data [M3] showed that radiologists had 15% higher mortality from cardiovascular disease than did other physicians (table 10). Interpretation of the findings is difficult. On one hand, the excess cardiovascular disease mortality seen for all cohorts of radiologists tended to argue against radiation effects. On the other hand, survival data showed that the increased mortality from circulatory disease occurred after age 55, as did the increased mortality from cancer [M3], and this was thought to suggest a common factor, such as radiation, for both cancer and cardiovascular disease. These facts clearly illustrate the limitations of the "ecological" nature of both the United States and the United Kingdom radiologist data, owing to the lack of data on individual doses, and emphasize the need for caution in inferring a causal association.

93. Mortality data from a cohort of United States radiologic technologists showed an overall SMR of less than unity for circulatory disease for the entire cohort [M14]. More detailed analyses of ischaemic heart disease and cerebrovascular disease risks by work history were carried out in a subset of this cohort for which data on work history were available from the mail survey conducted in the mid-1980s [H3]. Relative risks of mortality from circulatory-system diseases increased significantly among the technologists who started working in earlier years, when radiation exposure was higher. For both ischaemic heart disease and cerebrovascular disease, the relative risks (adjusted for confounding variables) increased significantly with decreasing calendar year in which the subjects started working as technologists (table 10). There was no association with the cumulative number of years worked for either ischaemic or cerebrovascular disease, but the relative risk of circulatory system diseases and the subset of cerebrovascular disease increased significantly with increasing number of years worked before 1950. In this analysis, the underlying risk was estimated internally using stratified models. Since the year first worked correlated with attained age and calendar year, which also correlated with the underlying rates of circulatory disease, this can induce intrinsic confounding leading to collinearity in extreme situations. This possibility was considered unlikely since similar results were obtained when external rates were used to estimate the underlying rate. The strength of this study is the analysis based on internal comparison, taking into account confounding effects of smoking, alcohol consumption and socio-economic variables. Surrogate measures of radiation exposure based on work history and calendar year of employment are limitations.

94. In the 1946–1974 follow-up study of a smaller cohort of United States Army radiologic technologists, a non-significantly higher frequency of arteriosclerotic and degenerative heart disease was reported among the technologists (4.31%) than among the controls (3.90%) (table 10) [J1]. The 1946–1963 follow-up data of the same cohort had shown a significantly higher than expected number of deaths from respiratory cancer (17 observed versus 10.5 expected), while there was no significant excess of any other cancer, including leukaemia [M4].

## Table 10 Radiologists and radiologic technologists

| *Cohort* | *Cohort description* | *Type of disease* | | | |
|---|---|---|---|---|---|
| United Kingdom radiologists [B4] | 2 698 male radiologists registered from 1897 to 1979 | **Circulatory disease** | | | |
| | | Year of first registration: | SMR | | |
| | | | (i) | (ii) | (iii) |
| | | 1897–1920 | 1.03 | 0.94 | 0.79** |
| | | 1921–1935 | 0.96 | 0.96 | 0.83* |
| | | 1936–1954 | 0.82** | 1.03 | 0.98 |
| | | 1955–1979 | 0.41*** | 0.60*** | 0.59*** |
| | | Expected deaths using rate for: (i) all men in England and Wales; (ii) all Social Class I males; and (iii) all male medical practitioners. *$p < 0.05$; *$p < 0.01$; ***$p < 0.001$ | | | |
| United States radiologists [M2, M3] | 6 500 male radiologists and 3 cohorts of other physician specialists | **Atherosclerotic heart disease** | | | |
| | | 1920–1939: | SMR | | |
| | | RSNA (radiologists) | 1.15 | | |
| | | ACP (physicians) | 1.00 | | |
| | | AAOO (ophthalmologists and otolaryngologists) | 0.91 | | |
| | | 1940–1969: | | | |
| | | RSNA | 1.15 | | |
| | | ACP | 0.95 | | |
| | | AAOO (otolaryngologists) | 1.06 | | |
| | | AAOO (ophthalmologists) | 0.93 | | |
| United States radiologic technologists [H3] | 90 284 radiologic technologists (predominantly female) | **Ischaemic heart disease** | | | |
| | | Year of first work: | Relative risk[a] (number of deaths) | | |
| | | <1940 | 1.22 (116) | | |
| | | 1940–1949 | 1.00 (214) | | |
| | | 1950–1959 | 0.98 (157) | | |
| | | 1960+ | 1.00 (111) | | |
| | | **Cerebrovascular disease** | | | |
| | | Year of first work: | Relative risk[a] (number of deaths) | | |
| | | <1940 | 2.40 (52) | | |
| | | 1940–1949 | 1.54 (54) | | |
| | | 1950–1959 | 0.90 (27) | | |
| | | 1960+ | 1.00 (32) | | |
| United States Army technologists [J1] | 6 560 male X-ray technologists during Second World War and 6 826 controls | **Arteriosclerotic and degenerative heart disease** | | | |
| | | X-ray technologists | 283 (4.3%) | | |
| | | Controls | 266 (3.9%) | | |
| | | **Vascular lesions of the central nervous system** | | | |
| | | X-ray technologists | 37 (0.6%) | | |
| | | Controls | 42 (0.6%) | | |

[a] Age- and time-adjusted.

95. There are three other cohorts of medical radiation workers that have been followed: 27,000 diagnostic X-ray workers in China [W2], 4,100 persons who worked in radiotherapy departments in Denmark [A5] and 12,000 male radiologic technologists in Japan [Y2]. There have been no published data on non-cancer disease from these studies.

### D. Radiation workers

96. Studies of nuclear workers and other populations exposed at low doses can provide valuable information on risks of non-cancer disease at levels of dose less than 0.5 Gy. However, there are important limitations. At low doses, the disease risk attributable to radiation may be so small relative to the underlying risk that it may be undetectable. Furthermore, because the underlying disease rates vary by amounts that are greater than the risk related to low-dose exposure, it will be extremely difficult to reject the possibility that any observed difference arises from biases or other factors related to the disease of interest, even in a population large enough for a small risk to be detected. These limitations are well recognized in assessing the risk of cancer at low doses, but they become even more serious in assessing the risk of circulatory diseases. This is because the relative risk of non-cancer disease associated with radiation exposure is expected to be much smaller than the risk of cancer, and because underlying rates of circulatory disease are influenced by numerous lifestyle and socio-economic factors.

97. In the three-country study of combined cohorts of nuclear industry workers from Canada (Atomic Energy of Canada Limited (AECL)), the United Kingdom (Atomic Weapons Establishment (AWE), United Kingdom Atomic Energy Authority (UKAEA) and Sellafield) and the United States (Hanford, ORNL and Rocky Flats), a positive association was found between mortality from circulatory disease and radiation dose (table 11) in the range 0–≥0.4 Gy [C6]. The analysis was adjusted for socio-economic status within the facility as well as for age and other demographic variables. The association with mortality from circulatory disease was observed in three cohorts (AECL, Rocky Flats and Sellafield). Since the information on socio-economic status available for these three cohorts was less detailed than that for the other cohorts in this study, the authors suspected residual confounding by lifestyle factors for which the measure used for socio-economic status was an inadequate proxy. Only limited information was available on smoking and other lifestyle factors for workers in this study, but there was little evidence for an association between cumulative dose and mortality from smoking-related cancers, respiratory disease or liver cirrhosis.

98. Data from the United Kingdom NRRW demonstrated an inverse, though not significant, association between radiation dose (with the dose range comparable to that in the above three-country study) and smoking-related non-malignant diseases, which included coronary heart disease, aortic aneurysm, emphysema and chronic obstructive pulmonary disease (table 11) [M5]. A non-significant inverse association was also found for circulatory diseases not related to smoking.

99. The radiation workers of British Nuclear Fuels Limited (BNFL) plants were included in the NRRW analyses [M5], but mortality and morbidity data for the Sellafield workers, including plutonium workers, were analysed in a separate study [O1]. Compared with the mortality rates for England and Wales, there was significantly higher than expected mortality from ischaemic heart disease among all workers (1,354 observed versus 1,217.7 expected), but the excess was not apparent when compared with the Cumbrian mortality rates. Rate ratios (radiation-exposed to non-exposed) based on internal comparison showed a significant excess mortality from cerebrovascular disease (rate ratio = 1.28), though not from ischaemic heart disease (rate ratio = 0.96), for radiation workers compared with non-radiation workers (table 11). Analysis of mortality data against cumulative external dose showed a significant external-dose-related trend for ischaemic heart disease, but data were not presented. Plutonium workers also had higher mortality from cerebrovascular disease (rate ratio = 1.27), but not from ischaemic heart disease (rate ratio = 1.01), than did non-radiation workers (rate ratio = 1.27). Another separate analysis of mortality data among 470 male Sellafield employees who were involved in the 1957 Windscale accident showed a higher than expected mortality from circulatory disease (SMR = 1.21) and ischaemic heart disease (SMR = 1.28) when compared against the national rates, though not when compared against the Cumbrian rates [M8]. The elevated mortality for circulatory disease and ischaemic heart disease occurred among the workers involved in managing the fire, but was also evident for those not involved. No dose–response analysis was performed.

100. Among the other BNFL sites, analysis of the mortality data of about 14,000 workers at the Springfields uranium production facility demonstrated a significant dose-related trend for cerebrovascular disease when the cumulative external dose was lagged by 10, 15 or 20 years, but not for ischaemic heart disease (table 11). Studies of about 3,200 workers at the Capenhurst uranium enrichment facility and 2,600 workers at the Chapelcross plant showed no significant trends for mortality from ischaemic heart disease or cerebrovascular disease (table 11).

101. Large values for the excess relative risk per unit dose, apparently incompatible with the data from the survivors of the atomic bombings, have been reported for the Canadian National Dose Registry and for Chernobyl recovery operations workers (see table 11). The estimates of ERR for circulatory disease from the Canadian National Dose Registry are 2.3 (90% CI: 0.9, 3.7) $Gy^{-1}$ for males and 12.1 (90% CI: –0.4, 24.6) $Gy^{-1}$ for females [A2]. The authors indicated several sources of uncertainty, including dose estimation and record linkage errors for follow-up. In particular, underestimation of lifetime dose may have occurred

because of the manner in which dosimeter data under a reporting threshold were treated and because of incomplete dose records. It has also been noted that the ERR estimates for "all causes" (ERR = 2.5 $Gy^{-1}$ for males and 5.5 $Gy^{-1}$ for females) were as high as for "all cancer" (ERR = 3.0 $Gy^{-1}$ for males and 1.5 $Gy^{-1}$ for females) and that the ERRs for accidents were strikingly high (ERR = 8.8 $Gy^{-1}$ and 6.1 $Gy^{-1}$ for males and females, respectively). These results, together with the very low standardized mortality ratio for all causes (0.59 $Gy^{-1}$ in males and 0.58 $Gy^{-1}$ in females), raise the possibility of some bias, perhaps related to the ascertainment of deaths [G2].

102. An analysis by Gilbert et al. [G6] of mortality data for workers at the Hanford site, ORNL and Rocky Flats involved a total of about 45,000 monitored workers with mean cumulative doses of 22–41 mGy (table 11). No significant effects of radiation on circulatory disease were found in the combined mortality data. A separate analysis of the mortality data for workers at the Hanford site also found no significant association of radiation dose with circulatory disease [G7]. Two other studies, of workers at the Mound facility and at Rocketdyne/Atomics International, reported only SMRs for circulatory disease [R13, W6] (table 11).

103. More recently, Howe et al. analysed mortality data of United States nuclear power industry workers [H13]. This cohort of 53,698 individuals employed in 15 nuclear utilities in the United States was followed for up to 18 years between 1979 and 1997. Cumulative dose from whole-body radiation was estimated from dose records available at the facilities, supplemented by the dose information maintained by the United States Nuclear Regulatory Commission and the United States Department of Energy. While the analysis using dose categories revealed no significant trends for circulatory disease (table 11) or arteriosclerotic heart disease, linear analysis indicated a strong significant association between radiation dose and circulatory disease, which was driven primarily by the association for arteriosclerotic heart disease. The ERR was 8.32 (95% CI: 2.30, 18.2) $Gy^{-1}$ for circulatory disease and 8.78 (95% CI: 2.10, 20) $Gy^{-1}$ for ischaemic heart disease. These estimates were higher than those from the LSS data, although the ERR estimates for leukaemia and solid cancer from this cohort were comparable to the LSS data. The authors pointed out that an artificially high or low ERR estimate may have resulted from outliers, and emphasized that caution is needed when interpreting the results.

104. Incidence data from the first 11-year follow-up (1986–1996) of the Chernobyl liquidators showed large risks for some non-cancer disease categories [I1]. The ERRs were not significantly elevated for diseases of the circulatory system, hypertensive disease or ischaemic heart disease. However, significantly elevated relative risks were found for essential hypertension (ERR = 0.52; 95% CI: 0.07, 0.98 $Gy^{-1}$) and cerebrovascular disease (ERR = 1.17; 95% CI: 0.45, 1.88 $Gy^{-1}$). Furthermore, significantly increased ERRs were observed for many other disease categories, including endocrine and metabolic diseases (ERR = 0.58 $Gy^{-1}$), mental disorders (ERR = 0.40 $Gy^{-1}$) and diseases of the nervous system and sensory organs (ERR = 0.24 $Gy^{-1}$). Incidence data derived from health examinations are liable to potential bias. The authors also noted that psychological and emotional stress immediately after the accident was especially strong among these liquidators. The exceedingly large risks for many different disease categories are consistent with the possible presence of bias and confounding effects. Without consideration of lifestyle and other factors, the causal nature of the apparent excess risks is currently unclear. Cardiovascular and cerebrovascular data were recently updated up to the end of 2000 [I5]. ERR estimates were 0.41 $Gy^{-1}$ for ischaemic heart disease, 0.45 $Gy^{-1}$ for cerebrovascular disease and 0.36 $Gy^{-1}$ for essential hypertension. These risk estimates were not adjusted for smoking, alcohol consumption, weight and other risk factors.

105. About 9000 male workers employed at the Mayak radiochemical plant during 1948–1972 were followed to the end of 1991 for cardiovascular disease mortality [B12]. The age-adjusted mortality rates for the male workers were lower than the general population rates ("controls" in table 11), possibly reflecting the healthy worker effect. Among the Mayak workers, the age-adjusted rates for those exposed to gamma irradiation of greater than 1 Gy were not significantly different from the rates for those with less than 1 Gy (table 11).

106. Although doses from inhaled radon and radon decay products to cardiovascular organs are very low, data from a study of miners in Newfoundland, Canada, showed an association between mortality from coronary heart disease and radon exposure [V2]. This involved 1,772 underground miners and 352 surface workers employed at two fluorspar companies. The relative risk of coronary heart disease mortality adjusted for smoking habits increased with cumulative radon exposure (table 11), but the trend test was of borderline significance ($p = 0.09$). The coronary heart disease risk also decreased with increasing duration of exposure (employment), suggesting the possible influence of the healthy worker effect. Results from other miner populations with radon exposure are also mixed. No associations with radon exposure were found for circulatory disease in the French or Czech miners [T4, T5]. The joint effects of radon and arsenic exposures on circulatory disease mortality found in Chinese tin miners were difficult to interpret, since radon exposure tended to increase the risk while arsenic exposure tended to decrease the risk. In a large cohort study of 59,000 miners employed between 1946 and 1989 at a uranium mine in Wismut, Germany, 5,417 deaths from circulatory disease (3,719 from heart disease and 1,297 from cerebrovascular disease) were identified in a follow-up to the end of 1998 [K9]. Exposure to radon and its progeny, external exposure to gamma radiation and long-lived alpha emitters were estimated by a job–exposure matrix. No significant trend was found in the mortality risk of all circulatory diseases in relation to cumulative exposure to radon, external gamma radiation or long-lived radionuclides.

**Table 11 Findings on circulatory diseases in studies of radiation workers**

| *Study* | *Cohort* | *Exposure characteristics* | *Follow-up duration (years)* | *Radiation dose or exposure* | *Circulatory disease statistic (number of cases)* | *Comments* |
|---|---|---|---|---|---|---|
| Nuclear workers in Canada, the United Kingdom and the United States [C6] | 95 673 workers (AECL, Sellafield, UKAEA, AWE, Hanford; Rocky Flats, ORNL) | Recorded exposures to external radiation: mean cumulative dose, 0.04 Gy | 23.7 (mean) | Cumulative dose (mGy)<br><10<br>10–<20<br>20–<50<br>50–<100<br>100–<200<br>200–<400<br>≥400 | Circulatory disease O/E (deaths):<br>1.01 (4 689)<br>0.93 (908)<br>0.97 (954)<br>0.96 (487)<br>1.01 (372)<br>1.11 (313)<br>1.07 (132)<br>Trend $p = 0.045$ | Positive association observed in Rocky Flats, Sellafield and AECL cohorts where information on socio-economic status was least detailed; suggestion of residual confounding, but little evidence of smoking and alcohol strongly associated with cumulative dose |
| NRRW, United Kingdom [M5] | 124 743 monitored workers exposed in nuclear power plants and in fuel processing and research facilities (AWE, BNFL, CLRC, MOD, MRC-RBU, NRPB, Nuclear Electric, Magnox Generation, Nycomed Amersham, PMS, RRA, Scottish Nuclear, UKAEA) | Recorded exposures to external radiation: mean cumulative dose, 0.03 Gy | | Cumulative dose (mGy)<br><10<br>10–<20<br>20–<50<br>50–<100<br>100–<200<br>200–<400<br>≥400 | Smoking-related non-malignant diseases — heart disease, aortic aneurysm, respiratory disease<br>O/E (deaths):<br>1.00 (1 888)<br>0.99 (477)<br>0.99 (698)<br>1.00 (431)<br>0.93 (288)<br>1.15 (244)<br>0.90 (102)<br>Trend: NS | |
| Sellafield [O1] | 10 382 monitored workers employed during 1947–1975 | Recorded exposures to external radiation | 29.0 | | Rate ratio: radiation-exposed versus non-exposed (deaths), trend:<br>IHD: 0.96 (371), NS<br>CVD: 1.28 (111), $p < 0.05$ | Significant positive trend with external cumulative dose for IHD (data not published) |
| Sellafield plutonium workers [O1] | 5 203 workers monitored for plutonium exposure | Monitored for plutonium by urine samples | | | SMR (deaths), trend:<br>IHD: 110 (498), $p < 0.05$;<br>CVD: 127 (137), $p < 0.01$ | |

| *Study* | *Cohort* | *Exposure characteristics* | *Follow-up duration (years)* | *Radiation dose or exposure* | *Circulatory disease statistic (number of cases)* | | *Comments* |
|---|---|---|---|---|---|---|---|
| Chapelcross [M11] | 2 628 monitored workers employed during 1955–1995 | Recorded exposures to external radiation: mean cumulative dose, 0.0836 Gy | 24.3 | Cumulative external dose (mGy) | O/E (deaths): | | ERR (95% CI) estimates:<br>IHD: 0.51 (-0.81, 2.54) $Gy^{-1}$<br>CVD: -0.96 (<-2.95, 2.34) $Gy^{-1}$ |
| | | | | | IHD | CVD | |
| | | | | <10 | 0.99 (27) | 0.75 (6) | |
| | | | | 10–<20 | 1.25 (20) | 1.23 (4) | |
| | | | | 20–<50 | 1.11 (35) | 1.57 (11) | |
| | | | | 50–<100 | 1.07 (38) | 0.97 (8) | |
| | | | | 100–<200 | 0.70 (23) | 1.04 (9) | |
| | | | | 200–<400 | 1.03 (33) | 0.72 (6) | |
| | | | | ≥400 | 0.86 (5) | 0.71 (1) | |
| | | | | | Trend: NS | Trend: NS | |
| Springfields uranium production [M12] | 13 960 monitored workers employed during 1946–1995 | Recorded exposures to external radiation: mean external cumulative dose, 0.0228 Gy | 24.6 | Cumulative external dose (mGy) | O/E (deaths): | | |
| | | | | | IHD | CVD | |
| | | | | <10 | 1.02 (513) | 1.08 (144) | |
| | | | | 10–<20 | 1.01 (207) | 1.06 (62) | |
| | | | | 20–<50 | 0.96 (273) | 0.85 (71) | |
| | | | | 50–<100 | 0.98 (136) | 0.80 (30) | |
| | | | | 100–<200 | 1.10 (58) | 1.23 (16) | |
| | | | | 200–<400 | 0.77 (4) | 1.94 (2) | |
| | | | | ≥400 | 0.00 (0) | 8.00 (2) | |
| | | | | | Trend: NS | $p < 0.05$ | |
| | | | | | (10-, 15- and 20-year lag) | | |
| Capenhurst uranium enrichment [M7] | 3 244 monitored workers employed during 1971–1991 | Recorded exposures to external radiation: mean external cumulative dose, 0.0098 Gy | 26.7 | Cumulative external dose (mGy) | O/E (deaths): | | |
| | | | | | IHD | CVD | |
| | | | | <10 | 0.98 (143) | 0.87 (23) | |
| | | | | 10–<20 | 1.22 (32) | 1.45 (7) | |
| | | | | 20–<50 | 1.10 (31) | 1.27 (5) | |
| | | | | 50–<100 | 0.57 (5) | 0.76 (1) | |
| | | | | 100–<200 | 0.35 (1) | 3.70 (1) | |
| | | | | 200–<400 | 1.15 (1) | 0.00 (0) | |
| | | | | ≥400 | 0.00 (0) | 0.00 (0) | |
| | | | | | Trend: NS | NS | |

| *Study* | *Cohort* | *Exposure characteristics* | *Follow-up duration (years)* | *Radiation dose or exposure* | *Circulatory disease statistic (number of cases)* | *Comments* |
|---|---|---|---|---|---|---|
| Canadian National Dose Registry [A2] | 206 620 monitored workers, including dental, medical, industrial and nuclear power plant workers | Recorded exposures to external radiation: mean cumulative dose, 0.06 Gy | 13.8 (mean) | | Circulatory disease O/E (deaths): Male: 0.61 (1 708), NS; Female: 0.49 (243), NS | ERR (% for 10 mGy) for circulatory disease: Male: 2.3 (95% CI: 0.9, 3.7) Female: 12.1 (95% CI: -0.4, 24.6) |
| Hanford, ORNL and Rocky Flats [G6] | 44 943 monitored workers: Hanford: 32 643 ORNL: 6 348 Rocky Flats: 5 952 | Recorded exposures to external radiation: mean cumulative dose, Hanford: 0.026 Gy ORNL: 0.022 Gy Rocky Flats: 0.041 Gy | | Cumulative external dose (mGy)<br><10<br>10–<50<br>50–<100<br>100–<200<br>200–<400<br>≥400 | Circulatory disease O/E (deaths):<br>1.03 (2 719)<br>0.92 (846)<br>0.92 (143)<br>0.93 (99)<br>1.02 (78)<br>1.53 (22)<br>Trend: NS | |
| Hanford [G7] | 37 971 monitored workers employed during 1944–1978 | Recorded exposures to external radiation: mean cumulative dose, 0.0233 Gy | | Cumulative external dose (mGy)<br><10<br>10–<50<br>50–<100<br>100–<200<br>≥200 | Circulatory disease O/E (deaths):<br>1.03 (2 193)<br>0.92 (642)<br>0.91 (102)<br>0.91 (76)<br>1.05 (81)<br>Trend: NS | |
| Mound facility [W6] | 3 229 monitored workers | Recorded exposures to external radiation: mean cumulative dose, 0.0297 Gy | | | SMR for circulatory disease (deaths), trend: 0.82 (149), NS | |
| Rocketdyne/Atomics International [R13] | 4 563 monitored workers | Recorded exposures to external radiation: cumulative doses, 0–0.2 Gy | | | SMR (deaths), trend: Circulatory disease: 0.63 (356), NS; ASHD: 0.56 (223), NS; Vascular lesions of CNS: 0.57 (33), NS | |

| *Study* | *Cohort* | *Exposure characteristics* | *Follow-up duration (years)* | *Radiation dose or exposure* | *Circulatory disease statistic (number of cases)* | *Comments* |
|---|---|---|---|---|---|---|
| Nuclear power utilities, United States [H13] | 53 698 workers in 15 nuclear power utilities | Recorded exposures to external radiation: mean cumulative dose, 0.0257 Gy | 13 (mean) | Dose (mGy)<br><1<br>1–<50<br>50–<100<br>≥100 | Relative risk (deaths):<br>ASHD / CNS lesions<br>1.00 (141) / 1.00 (9)<br>0.70 (72) / 1.89 (4)<br>1.76 (20) / 3.27 (0)<br>1.65 (15)<br>Trend: NS / Trend: NS | ERR (95% CI):<br>circulatory disease: 8.32 (2.30, 18.2) $Gy^{-1}$;<br>ASHD: 8.78 (2.10, 20.0) $Gy^{-1}$;<br>vascular lesions of CNS:<br>-2.05 (<-2.06, 353) $Gy^{-1}$ |
| Chernobyl recovery operations workers, Russian Federation [I1, I5] | 61 017 workers participating in clean-up work after the Chernobyl accident | Assessed external radiation doses, 0.109 Gy (mean) | 14 | | IHD (10 942);<br>CVD (12 832) | ERR (95% CI):<br>IHD: 0.41 (0.05, 0.78) $Gy^{-1}$;<br>CVD: 0.45 (0.11, 0.80) $Gy^{-1}$ |
| Mayak workers [B12] | 15 601 persons monitored for external radiation | Recorded doses for external radiation: lung, 3.8–35 Gy | | Total external gamma irradiation (mGy):<br>0 (controls)<br>>0–<1 000<br>≥1 000 | CVD mortality (age-adjusted):<br>513.3 ± 36.1<br>497.4 ± 18.0<br>504 ± 25.7 | |
| Fluorspar miners, Newfoundland, Canada [V2] | 1 772 underground and 352 surface workers employed at fluorspar companies between 1933 and 1960; cumulative exposure, 379 WLM | Internal exposure to inhaled radon and its decay products | To 1985 | Cumulative radon exposure (WLM)<br>0<br>>0–<250<br>250–<500<br>500–<1 000<br>≥1 000 | CHD relative risk<br>1.0<br>0.90<br>1.12<br>1.57<br>1.46<br>Trend $p = 0.09$ | |
| Uranium miners, France [T4] | 1 785 uranium miners with underground mining experience between 1946 and 1972 | Internal exposure to inhaled radon and its decay products | To 1985 | Total cohort<br>First exposure 1946–1955<br>First exposure 1956–1972 | Circulatory disease SMR (number of deaths)<br>0.85 (69)<br>0.87 (40)<br>0.82 (29) | |
| Uranium miners, Czech Republic [T5] | 4 320 male uranium miners, West Bohemia | Internal exposure to inhaled radon and its decay products | 25 (mean) | | 779 deaths from circulatory disease other than rheumatic heart disease; O/E = 1.16 | No significant trend with cumulative radon exposure |

| *Study* | *Cohort* | *Exposure characteristics* | *Follow-up duration (years)* | *Radiation dose or exposure* | *Circulatory disease statistic (number of cases)* | *Comments* |
|---|---|---|---|---|---|---|
| Tin miners, China [X1] | 17 143 tin miners | Internal exposure to inhaled radon and its decay products | NA | | CHD (47 deaths); CVD (302 deaths) | Significant joint effects of radon and arsenic exposure |
| | | | | Radon exposure | CHD relative risk | |
| | | | | Low (referent group) | 1.0 | |
| | | | | Medium | 0.8 | |
| | | | | High | 1.7 | |
| | | | | Radon exposure | CVD relative risk | |
| | | | | Low (referent group) | 1.0 | |
| | | | | Medium | 1.1 | |
| | | | | High | 1.3 | |
| Uranium miners, Wismut, Germany [K9] | 59 001 male uranium miners, employed between 1946 and 1989 | Cumulative exposure to radon, external exposure to gamma radiation and long-lived alpha particle emitters estimated by a job–exposure matrix | 30.5 (mean) | | Circulatory disease (5 417 deaths) | |
| | | | | Radon exposure (WLM) | All circulatory disease relative risk | ERR for 100 WLM = 0.0006 (95% CI: -0.004, 0.006) |
| | | | | 0 | 1.00 | |
| | | | | >0–100 | 0.96 | |
| | | | | >100–400 | 0.93 | |
| | | | | >400–800 | 0.98 | |
| | | | | >800–1 600 | 0.92 | |
| | | | | ≥1 600 | 1.11 | |
| | | | | Exposure to long-lived radionuclides (kBq·h/m$^3$) | All circulatory disease relative risk | ERR for 100 kBq·h/m$^3$ = -0.02 (95% CI: -0.5, 0.06) |
| | | | | 0 | 1.00 | |
| | | | | >0–<1.0 | 0.98 | |
| | | | | 1.0–<3.0 | 1.02 | |
| | | | | 3.0–<10.0 | 0.91 | |
| | | | | ≥10.0 | 0.94 | |
| | | | | Exposure to gamma radiation (mSv) | All circulatory disease relative risk | ERR = -0.26 (95% CI: -0.6, 0.05) Sv$^{-1}$ |
| | | | | 0 | 1.00 | |
| | | | | >0–<50 | 0.97 | |
| | | | | 50–<100 | 0.92 | |
| | | | | 100–<300 | 0.95 | |
| | | | | ≥300 | 0.85 | |

*Note*: ASHD: arteriosclerotic heart disease; CHD: coronary heart disease; CNS: central nervous system; CVD: cerebrovascular disease; IHD: ischaemic heart disease; NA: not available; WLM: working level month.

## E. Survivors of the atomic bombings in Japan

### 1. Mortality (Life Span Study)

107. In the latest LSS report [P4], deaths from heart disease and stroke together accounted for 58% (8,431) of the 14,459 deaths from all non-cancer diseases (except for diseases of the blood and blood-forming organs) that occurred during the period 1968–1997. The analysis of mortality data from 1968 or later indicated significant linear dose responses for heart disease and stroke. The ERR was 0.17 (90% CI: 0.08, 0.26) $Sv^{-1}$ for heart disease and 0.12 (95% CI: 0.02, 0.22) $Sv^{-1}$ for stroke. Estimated numbers of radiation-related deaths were 101 (2.2%) of the 4,477 deaths from heart disease and 64 (1.6%) of the 3,954 deaths from stroke during the above follow-up period. As described earlier in this annex, detailed analyses of the dose–response curve and the modifying effects of age, sex and time were performed for non-cancer disease mortality as a group [P4, S1] and also specifically for stroke and coronary heart disease [L10] (see section II).

### 2. Incidence and morbidity data (Adult Health Study)

108. The AHS is a long-term clinical follow-up investigation of a subset of the LSS cohort. This subset consists of 20,000 subjects who have been undergoing biennial health examinations since 1958. Morbidity data and longitudinal clinical data from this study are useful for studies of specific non-cancer diseases and related clinical end points.

109. An increased prevalence of coronary heart disease in proximally exposed survivors was first noted in 1958–1960 [Y1] but was not confirmed by subsequent studies of incidence of stroke and coronary heart disease in the first years (1958–1964) of the AHS follow-up [J2]. Cases were few and radiation doses were not available at that time. The studies of stroke and coronary heart disease continued and the data were updated several times, i.e. to 1974 [R6], to 1978 [K4] and to 1990 (or later) in the latest study, which is currently under way. The latest AHS incidence data from biennial health examination records show a significant quadratic dose–response relationship for myocardial infarction among those exposed at age ≤40 years, with a relative risk of 1.25 (95% CI: 1.00, 1.69) at 1 Sv, although the linear dose response for overall myocardial infarction was not significant [W5, Y3]. It should be noted that the morbidity data described above are based on biennial health examinations and thus may have missed some of the interim events, especially fatal events. Date from surviving cases may have been biased.

110. In an attempt to ascertain all incident cases of cardiovascular disease, additional efforts have been made to identify cases from a variety of AHS and other sources (i.e. self-reported diagnoses, electrocardiograms, death certificates and autopsy reports) and to apply standardized diagnostic criteria. Cardiologists review records to identify cases on the basis of standardized criteria. [R6]. Cases of coronary heart disease were defined as those with evidence of angina pectoris, myocardial infarction or death from coronary heart disease [R6]. The analysis of 288 incident cases of myocardial infarction (163 male and 125 female) that had been ascertained up to the end of 1990 by this intensive search [K5] showed a significant dose response. The relative risk at 1 Sv was estimated to be 1.17 (95% CI: 1.01, 1.36). The association between myocardial infarction and radiation dose remained significant after adjusting for blood pressure and serum cholesterol levels as well as age and sex.

### 3. Subclinical changes

111. While morbidity or incidence data on clinically overt disease from routine health examinations are prone to potential selection bias, subclinical (asymptomatic) end points or clinical laboratory data are less likely to be affected by selection bias. A number of subclinical cardiovascular changes or precursor lesions have been studied in the AHS cohort. Growth curve models were applied to the analysis of repeated longitudinal cholesterol measurement data among 9800 AHS subjects for the period 1958–1986 [W1]. The growth curves of individual subjects are assumed to vary randomly about a population growth curve, and are appropriate for assessing a radiation effect, taking into account the changing serum cholesterol levels in the Japanese population. For each sex, temporal trends of cholesterol levels were characterized with respect to age, body mass index, city and birth year, and the question was examined as to whether the temporal trends differed by radiation dose. The mean growth curve of cholesterol levels was significantly higher in exposed than in non-exposed subjects. There was no difference in dose response between Hiroshima and Nagasaki, and cigarette smoking did not alter the dose–response relationship.

112. Using similar growth models, Sasaki et al. [S17] found that systolic and diastolic blood pressure levels increased with radiation dose in subjects exposed at young ages (≤16 years), but this trend was reversed in older subjects. A significant quadratic, but not linear, dose response was also found for hypertension diagnosed at the AHS clinical examinations [Y3]. Other end points studied in the AHS cohort include the prevalence of aortic arch calcification [K6], isolated systolic hypertension [K7] and pulse wave velocity [U16], all of which have been found to be associated with radiation.

113. The AHS findings regarding the radiation effects on hypercholesterolaemia and other cardiovascular end points, which are well correlated with each other, offer little insight into a possible role of radiation in the process of atherogenesis, but they are consistent with the possibility of accelerated atherogenesis associated with radiation exposure.

114. A statistically significant association between radiation dose and increased inflammatory responses, as

measured by leukocytosis, accelerated erythrocyte sedimentation rates or acute phase proteins, has been noted in this population for some time [N3, S7]. This association has been re-examined with updated clinical data using various inflammatory response markers. Among 7,463 subjects examined during 1988–1992, the relationship between radiation dose and a series of inflammatory tests (including leukocyte counts, neutrophil counts, erythrocyte sedimentation rate (ESR), α-1 globulin, α-2 globulin and sialic acid) was examined [N4]. ESR is influenced by a variety of serum components, including acute phase proteins, which comprise α-1 globulin and α-2 globulin. Sialic acid is a glycoprotein component related to the surface membrane in the inflammatory process. After allowing for the effect of covariates such as city, age, sex and smoking, radiation dose was found to be associated with increased leukocyte counts per unit bone marrow dose (71.0 $mm^{-1}$ $Gy^{-1}$), ESR (1.58 mm $h^{-1}$ $Gy^{-1}$), corrected ESR (1.14 mm $h^{-1}$ $Gy^{-1}$), α-1 globulin level (0.0057 g $dL^{-1}$ $Gy^{-1}$), α-2 globulin level (0.0128 g $dL^{-1}$ $Gy^{-1}$) and sialic acid level (1.2711 mg $dL^{-1}$ $Gy^{-1}$), though not with neutrophil counts. No confounding effects of the presence of dose-related inflammatory diseases, i.e. clinically detectable chronic thyroiditis or chronic liver disease, were found.

115. Blood samples from 453 Hiroshima study participants between 1995 and 1997, excluding those with a history of cancer or an inflammatory disease, were studied by Hayashi et al. [H6]. C-reactive protein (CRP) levels were associated with age, sex, body mass index and a history of myocardial infarction. After adjusting for these factors, CRP levels increased significantly with bone marrow dose (an increase of about 28% at 1 Gy), as did IL-6 levels, by 9.3% at 1 Gy. CRP is an acute phase reactant that increases during an inflammatory response, and recent epidemiological evidence indicates increased CRP levels as an independent risk predictor for cardiovascular disease [R8, R9]. IL-6, a primary inducer of CRP, has also been found to be a predictor of myocardial infarction.

## F. Mechanistic models

### 1. Microvasculature theory

116. High-dose irradiation is capable of damaging all structures of the heart, including the pericardium, myocardium, valves, conduction system and coronary arteries, as reviewed by Adams et al. [A3]. Histologically, radiation-induced tissue damage is characterized by marked diffuse fibrosis, especially of the pericardium and myocardium [A3, B7, F4, S9]. In an autopsy study of 16 young patients (aged 15 to 33 years) with heart disease who received over 35 Gy and 10 controls, the arterial plaques in patients treated with radiotherapy were largely composed of fibrous tissues, with the media more frequently replaced by fibrous tissues and more focal thickening of the intramural coronary arteries, than in the controls. Radiation-induced microvascular injuries can contribute to late damage of normal tissue. Capillaries are the most radiosensitive component of the vasculature [T2]. In a classic study of experimental radiation-induced heart disease in rabbits by Stewart [S10], electron microscopy studies of changes taking place during the latent stage of disease development indicated changes in endothelial cells of the myocardial capillaries with progressive obstruction of the lumen, resulting in formation of thrombi.

117. The dose–volume histogram and normal tissue complication models described in section IV.A.5 above [B7, S9] are used to describe the pathophysiology for heart disease induced by direct tissue damage from irradiation. These models are primarily applicable to damage from high-dose exposures. On the basis of data from patients treated for Hodgkin's lymphoma, a fractionated dose of 40 Gy was previously considered as a threshold for clinical radiation-induced heart disease [F3, S16]. The extent to which these models can explain heart disease, especially atherosclerotic coronary heart disease induced by low-dose irradiation, is not clear [T2]. It has been suggested [B7, J4] that damage to coronary artery endothelial cells may be a primary event in the pathogenesis of coronary heart disease. Irradiation may cause fibrointimal hyperplasia, which leads to thrombus formation and potentially to lipid deposition. Subtle changes to the blood vessels, such as abnormal vascular permeability, can occur at lower doses (down to 5 Gy) ([U8] p. 626, para. 496).

### 2. Inflammation theory

118. There have been a number of hypotheses for the pathogenesis of atherosclerosis, which underlies the development of ischaemic heart disease and cerebrovascular disease. Recent evidence suggests that atherosclerotic plaques arise from endothelial injury or dysfunction induced by cardiovascular risk factors and develop through a series of highly specific cellular and molecular responses, which can best be described as an inflammatory process [L3, L6, R10]. Initial endothelial injury may be induced by endotoxins, hypoxia, infection or other agents, but it is generally thought that haemodynamic disturbances and the adverse effects of hyperlipidemia are most important. Among the processes involving lipids in atherogenesis is their oxidative modification by free radicals, yielding oxidized low-density lipoprotein (LDL). Oxidized LDL is taken up by macrophages, contributes to monocyte recruitment and leads to foam cell formation. Fibrous plaques then develop as a growing mass of extracellular lipid with accumulating extracellular matrices derived from smooth muscle cells. Cytokines and growth factors secreted by macrophages and T-cells play multiple roles in this process.

119. Infection by cytomegalovirus and other viruses has recently been linked to atherosclerosis. Infectious organisms may incite a chronic inflammatory process. Another

plausible mechanism is stimulation of smooth muscle cell migration by the virus-coded chemoine receptor [L6]. It has been speculated that radiation-induced genomic instability and/or bystander effects may set off inflammatory responses that may persist for many years [H6, L5, N4].

### 3. Monoclonal theory

120. It was some 20 years ago that the monoclonal origin of the atherosclerotic lesion was proposed. In studies using the X-linked enzyme glucose-6-phophatase dehydrogenase (G6PD) to determine X chromosome inactivation patterns, aortic media were found to contain a mixed pattern of G6PD expression, whereas most atherosclerotic plaques contained a single isoform of G6PD [B8]. This was interpreted as providing evidence that atherosclerotic plaques arise from single progenitor cells. However, it has not been clear when monoclonal expansion occurs and what cell types give rise to the clone, owing in part to limitations in the G6PD methods [M9]. It was originally suggested that the monoclonal patchiness of atherosclerotic lesions may involve a transformation of smooth muscle cells [L6]. However, recent data indicated that the monoclonal populations result from patches of pre-existing clones of cells [M9, S8]. There is some evidence, however, consistent with oncogene activation, of loss of heterozygosity and microsatellite instability in human lesions [L6].

# V. SUMMARY

121. Until recently, the effects of ionizing radiation on diseases other than cancer (non-cancer diseases) had been regarded as having a threshold in the dose response. Threshold doses vary by tissues and other factors, but are below a few grays for clinically evident diseases of the circulatory, digestive and respiratory systems following radiotherapy. Recent data from the follow-up of the LSS cohort of atomic bombing survivors indicated that excess risk of mortality from non-cancer diseases occurs at a level below these threshold doses. The excess risk of fatal non-cancer disease in the LSS was not explained by confounding, selection bias or disease misclassification, to the extent that these factors were evaluated. The effects on several specific non-cancer diseases were also supported in part by morbidity and clinical data from the AHS subset of the LSS population. The primary purpose of this annex was to evaluate epidemiological data on various fatal non-cancer disease outcomes from radiation-exposed populations. The annex specifically focuses on circulatory diseases, as these are among the most common non-cancer causes of disability and mortality in many populations.

122. Although non-cancer diseases have not been the subject of primary interest in major epidemiological studies of populations exposed to radiation at low doses, many of the existing cohort studies are potential sources of data on non-cancer risk. A review of the literature, however, indicated that non-cancer disease data are currently available for only a portion of these cohorts. However, data on circulatory disease mortality are the most frequently reported and are the most informative non-cancer data currently available for assessing the association with radiation exposure. Epidemiological data on other fatal non-cancer diseases are limited. Generally, published non-cancer findings are variable and inconsistent, and interpretation of the results is problematic because of the possible selection of data published, differences in analytical methods used, differences in data quality and, in several studies, the difficulty in dealing with the effects of potential confounders.

123. Radiation-induced heart disease after high-dose radiotherapy for cancer has long been recognized as a medical sequela. It can involve all parts and structures of the heart. Long-term follow-up and randomized trials of patients receiving radiotherapy for Hodgkin's lymphoma or for breast cancer have demonstrated an increased risk of heart disease, including coronary heart disease. Increased risk of heart disease has been linked to mediastinal doses in excess of 40 Gy from early radiotherapy for Hodgkin's lymphoma, but few data exist regarding the risk from the lower-dose radiotherapy currently in use (30–35 Gy for adults and 15–25 Gy for children). Increased risk of heart disease has been linked to breast tumour doses of 40–50 Gy from an early series of post-mastectomy radiotherapy. More recent radiotherapy used for early-stage breast cancer typically exposes up to 5% of the left ventricle to about 25 Gy. Studies show a diminished risk of heart disease associated with modern adjuvant radiotherapy for breast cancer, but longer follow-up is needed because of the persistence of the risk, possibly lasting for more than 3–4 decades, suggested by previous studies. Additional information on the risk for heart disease after low-dose radiotherapy may be expected from studies of patients irradiated for other cancers.

124. Some useful insights into factors that affect radiation-related heart disease risk have also been obtained from high-dose radiotherapy studies. Among the most prominent is the persistence of excess heart disease risk that may span over 3–4 decades, and this is consistent with the data on the atomic bombing survivors. The effects of partial organ irradiation differ from those of whole-organ irradiation, and there may be heterogeneity in response to radiation in different locations of the heart. The radiation-related heart disease risk is strongly related to age at irradiation and is especially high when exposure occurs during childhood or adolescence. Little is known about the possible effects of smoking and other risk factors on the radiation-related risk of heart disease.

125. Patients irradiated for treatment of benign diseases or for diagnostic purposes received much lower doses than cancer patients. In the ankylosing spondylitis patients, who received an estimated mean cardiac dose of 2.5 Gy, the observed numbers of deaths from cerebrovascular and other circulatory diseases were higher than expected from the general population, but the relative risks compared with a separate group of non-irradiated spondylitis patients were not elevated. Detailed dose–response characterization was reported from the follow-up study of patients irradiated for peptic ulcer disease. Coronary heart disease mortality risk adjusted for possible confounders among 10-year survivors increased with increasing cardiac dose ranging from 1.6 to 3.9 Gy (volume-weighted cardiac organ) and from 7.6 to 18.4 Gy (5% of the heart). The elevated risk associated with about 13 Gy to 5% of the heart indicates that excess coronary heart disease risk can occur at doses lower than the 30–40 Gy received from earlier radiotherapy for Hodgkin's lymphoma or breast cancer. A combined study of tuberculosis patients who received multiple fluoroscopic exposures

is of interest as there was a mean cumulative lung (surrogate cardiac) dose of about 1 Gy and the follow-up was for up to 50 years. Circulatory disease (including both cardiovascular and cerebrovascular disease) mortality was not elevated in the irradiated group compared with non-irradiated tuberculosis patients or the general population. No dose–response analysis was performed.

126. Radiologists and other medical radiation workers from the early half of the twentieth century received excessive doses of radiation. Cohort studies of radiologists provide conflicting evidence regarding the radiation effects on mortality due to circulatory disease (including heart and/or cerebrovascular disease). The results from the United States radiologic technologists using work history (e.g. calendar periods or length of employment) as a surrogate measure of exposure provide only indirect evidence regarding radiation effects. The lack of individual dose estimates in these cohorts is a common weakness.

127. Several major studies of occupationally exposed workers at nuclear facilities provide little evidence for increased risk of cardiovascular or cerebrovascular disease related to radiation exposure. Few of the occupational studies have sufficiently controlled for possible confounding effects.

128. Biological mechanisms by which low-dose radiation exposure might increase circulatory disease risks are currently unclear. Although several plausible biological models have been suggested, more research is needed to explore possible mechanisms.

# VI. CONCLUSIONS

129. There is an increased risk of circulatory disease associated with high doses to the heart that may be incurred with radiotherapy, but newer treatment techniques resulting in lower cardiac doses have reduced the risk substantially. To date, the evidence for an association between fatal cardiovascular disease and radiation doses in the range of less than 1–2 Gy comes only from the analysis of the data on the survivors of the atomic bombings in Japan. Other studies have provided no clear or consistent evidence of a fatal cardiovascular disease risk at radiation doses of less than 1–2 Gy. It is the judgement of the Committee that, given the inconsistent epidemiological data and the lack of a biologically plausible mechanism, the present scientific data are not sufficient to establish a causal relationship between ionizing radiation and cardiovascular disease at doses of less than about 1–2 Gy. There also are insufficient epidemiological data for constructing appropriate risk models relative to these end points.

130. Circulatory diseases, which are multifactorial and heterogeneous in nature, occur commonly in non-exposed populations. Numerous risk factors, including tobacco use, genetics and cholesterol level, need to be taken into account when attempting to assess the risk associated with radiation. Given the relatively small increase in risk associated with radiation at doses of less than 1–2 Gy, it is uncertain whether epidemiological studies of mortality alone will be able to make a significant contribution to understanding the potential for and the nature of any relationship between circulatory diseases and radiation at these levels of dose.

131. For mortality from diseases other than circulatory diseases and cancer, evidence for an association with radiation at doses of less than about 1–2 Gy also comes only from the atomic bombing survivor data. Studies of other radiation-exposed populations linking other fatal non-cancer diseases to radiation at doses of less than about 1–2 Gy have yielded even less evidence than that which exists for circulatory diseases. For other non-cancer diseases, much less epidemiological information is available than for circulatory diseases, and the evaluation of the causal association is more difficult, owing to the greater heterogeneity in disease aetiology and pathology and the more numerous risk factors involved.

# VII. FUTURE RESEARCH

132. Further studies of other irradiated populations are needed. A clear conclusion derived from this epidemiological review is that, apart from the studies of the survivors of the atomic bombings in Japan, there is a lack of data, in terms of both quality and quantity, on non-cancer disease risk. Not only are there few data on non-cancer disease outcomes reported from potentially informative cohorts, but also the disease outcomes addressed by published data are disparate and mostly based on varying methods and analyses not relevant for risk assessment. Individual investigators should be encouraged to revisit non-cancer data available in existing radiation cohorts and to conduct detailed dose–response analysis. A combined analysis pooling non-cancer data from a large number of exposed populations would also be desirable.

133. In future, reporting of epidemiological studies of non-cancer disease end points should include clear descriptions of any limitations of the statistical methods used. Underlying rates for non-cancer disease entities that can be used for risk estimation are quite high, and the indications are that the proportional increase (excess relative risk) per unit dose is low in comparison with that for solid cancers. This reduces the power to detect effects and limits the usefulness and credibility of exposed versus unexposed or external comparisons, because confounding factors are more likely (than for cancer) to distort inference. Vague statements about potential and unspecified confounding factors or bias should be avoided. If an argument is made that an observed association arises because of confounding, it would be useful to provide some indication of the nature and extent of the confounding that could give rise to such an association. The effects of potential bias should be evaluated. Confounding is less likely to markedly bias results from dose–response analyses than from exposed versus unexposed comparisons. Thus, to the extent possible, analyses should make use of doses or dose surrogates, with attention to the effects of uncertainty in these dose estimates on the risk estimates.

134. Mortality data are generally inadequate as the measure of the risk of non-cancer diseases, because of variable case fatality. Incidence or morbidity data are preferred, provided that systematic ascertainment of morbidity data is possible. When using mortality data, consideration should also be given to addressing the effect of disease misclassification on risk estimates. More attention should be given to results for other disease entities, such as digestive or respiratory diseases, in addition to circulatory diseases.

135. To the extent possible, future epidemiological studies should be designed to assess clinical and subclinical end points as well as biomarkers, since this information is more likely to lead to insights useful for developing mechanistic models than simple epidemiological data limited to case counts and rates. Mechanistic leads suggested by the studies of the atomic bombing survivors and others should be tested in other irradiated populations, and radiation-related subclinical changes suggested from therapy experience should be investigated in larger epidemiological cohorts. Laboratory and clinical scientists should be consulted to generate alternative and novel mechanistic hypotheses that can be tested in epidemiological studies.

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