

SOURCES, EFFECTS AND RISKS OF IONIZING RADIATION

# UNSCEAR **2017 Report**

## Report to the General Assembly

SCIENTIFIC ANNEXES A and B





# SOURCES, EFFECTS AND RISKS OF IONIZING RADIATION

United Nations Scientific Committee on the  
Effects of Atomic Radiation

UNSCEAR 2017  
Report to the General Assembly,  
with Scientific Annexes



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New York, 2018

#### NOTE

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

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## Chapter I

### Introduction

1. Since the establishment of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) by the General Assembly in its resolution 913 (X) of 3 December 1955, the mandate of the Committee has been to undertake broad assessments of the sources of ionizing radiation and its effects on human health and the environment.<sup>1</sup> In pursuit of its mandate, the Committee thoroughly reviews and evaluates global and regional exposures to radiation. The Committee also evaluates evidence of radiation-induced health effects in exposed groups and advances in the understanding of the biological mechanisms by which radiation-induced effects on human health or on non-human biota can occur. Those assessments provide the scientific foundation used, inter alia, by the relevant agencies of the United Nations system in formulating international standards for the protection of the general public, patients and workers against ionizing radiation;<sup>2</sup> those standards, in turn, are linked to important legal and regulatory instruments.

2. Exposure to ionizing radiation arises from naturally occurring sources (such as radiation from outer space and radon gas emanating from rocks in the Earth) and from sources with an artificial origin (such as medical diagnostic and therapeutic procedures; radioactive material resulting from nuclear weapons testing; energy generation, including by means of nuclear power; unplanned events such as the nuclear power plant accident at Chernobyl in 1986 and that following the great east-Japan earthquake and tsunami of March 2011; and workplaces where there may be increased exposure to artificial or naturally occurring sources of radiation).

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<sup>1</sup> 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). The Committee was originally composed of the following Member States: Argentina, Australia, Belgium, Brazil, Canada, Czechoslovakia (later succeeded by Slovakia), Egypt, France, India, Japan, Mexico, Sweden, Union of Soviet Socialist Republics (later succeeded by the Russian Federation), 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 (later succeeded by 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. In its resolution 66/70 of 9 December 2011, the Assembly further enlarged the membership of the Committee to 27 and invited Belarus, Finland, Pakistan, the Republic of Korea, Spain and Ukraine to become members.

<sup>2</sup> For example, the international basic safety standards for radiation protection and safety of radiation sources, currently co-sponsored by the European Commission, the Food and Agriculture Organization of the United Nations, the International Atomic Energy Agency (IAEA), the International Labour Organization, the Nuclear Energy Agency of the Organization for Economic Cooperation and Development, the Pan American Health Organization, the United Nations Environment Programme and the World Health Organization.

## Chapter II

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

3. The Committee held its sixty-fourth session in Vienna from 29 May to 2 June 2017.<sup>3</sup> The following served as officers of the Committee: Hans Vanmarcke (Belgium) as Chair; Patsy Thompson (Canada), Peter Jacob (Germany) and Michael Waligórski (Poland) as Vice-Chairs; and Gillian Hirth (Australia) as Rapporteur.

4. The Committee took note of General Assembly resolution 71/89 on the effects of atomic radiation, in which the Assembly requested the Committee to report to the Assembly at its seventy-second session on its important activities to increase knowledge of the levels, effects and risks of ionizing radiation from all sources.

#### A. Completed evaluations

5. At its sixty-third session, the Committee had discussed progress on an evaluation of epidemiological studies of cancer incidence from low-dose-rate exposures due to environmental sources of radiation. It had welcomed the development of an appendix on quality criteria for the Committee's reviews of epidemiological studies, and requested that the scientific review and the quality criteria be brought into accordance with each other. It also had requested that the appendix be finalized for publication as an independent annex because of its wider application. In addition, it had also requested the secretariat to prepare a short paper on the scientific view of the Committee on the dose and dose rate effectiveness factor.

6. The Committee discussed in detail the two revised scientific annexes to the present report (see ch. III below) and the short paper (see para 5 above), agreed on the scientific report of their findings, and decided that the annex on the evaluation of epidemiological studies of cancer incidence from low-dose-rate exposures should incorporate relevant material from the paper. It requested that the two annexes then be published in the usual manner, subject to modifications agreed upon.

7. At its sixty-third session, the Committee had also requested the secretariat to prepare an evaluation of data on thyroid cancer in regions affected by the Chernobyl accident. The Committee discussed a paper that recapitulated the Committee's previous findings on this matter, reported the latest data provided by the three most affected countries (Belarus, Russian Federation and Ukraine), summarized key literature of the past several years, and made an assessment of the fraction of the observed thyroid cancer incidence that could be deemed attributable to radiation exposure of the thyroid:

(a) Both the total number of cases and crude incidence rate (number of cases per 100,000 person-years) basically increased monotonically over the period 2006-2015. The total number of cases of thyroid cancer registered in the period 1991-2015 in males and females who were under 18 in 1986 (for the whole of Belarus and Ukraine, and for the four most contaminated oblasts of the Russian Federation) approached 20,000. This number is almost three times higher than the number of thyroid cancer cases registered in the same cohort in the period 1991-2005;<sup>4</sup>

(b) However, the observed increase in the incidence of thyroid cancer is not all attributable to radiation exposure. It is influenced by various factors: increased

<sup>3</sup> The sixty-fourth session was also attended by observers for IAEA, the International Agency for Research on Cancer, the European Union, the International Commission on Radiological Protection and the International Commission on Radiation Units and Measurements.

<sup>4</sup> *Sources and Effects of Ionizing Radiation: United Nations Scientific Committee on the Effects of Atomic Radiation 2008 Report to the General Assembly*, vol. II, annex D (United Nations publication, Sales No. E.11.IX.3).

spontaneous incidence rate with adulthood, radiation effect, and improvement of diagnostic methods. Discerning the effect of exposure to ionizing radiation contributing to this complicated situation requires both careful epidemiological analysis and basic research of processes in molecular biology;

(c) The Committee estimated that the fraction of the incidence of thyroid cancer attributable to radiation exposure among non-evacuated residents of Belarus, Ukraine and the four most contaminated oblasts of the Russian Federation who were children or adolescents at the time of the accident, is of the order of 0.25. The uncertainty in the estimated attributable fraction ranges at least from 0.07 to 0.5.

8. The Committee requested that the evaluation of thyroid cancer data in regions affected by the Chernobyl accident be issued electronically on its website as a non-sales publication in English, subject to modifications agreed upon.

## **B. Present programme of work**

### **1. Developments since the 2013 report on the levels and effects of radiation exposure due to the nuclear accident following the great east-Japan earthquake and tsunami: review of 2016 scientific literature**

9. The Committee recalled its assessment of the exposures and effects due to the nuclear accident after the 2011 great east-Japan earthquake and tsunami, as presented in its report to the sixty-eighth General Assembly in 2013<sup>5</sup> and the supporting detailed scientific annex.<sup>6</sup> It had concluded in that report that, in general, doses were low and that therefore associated risks were also expected to be low. A discernible increase in cancer incidence in the adult population of Fukushima Prefecture that could be attributed to radiation exposure from the accident was not expected. Nevertheless, the report noted a possibility that an increased risk of thyroid cancer among those children most exposed to radiation could be theoretically inferred, although the occurrence of a large number of radiation-induced thyroid cancers in Fukushima Prefecture — such as occurred after the Chernobyl accident — could be discounted because absorbed doses to the thyroid after the accident at Fukushima were substantially lower. It had also concluded that no discernible changes in birth defects and hereditary diseases were expected and that any increased incidence of cancer among workers due to their exposure was expected to be indiscernible because of the difficulty of confirming a small increase against the normal statistical fluctuations in cancer incidence. The effects on terrestrial and marine ecosystems were expected to have been transient and localized.

10. Following its assessment, the Committee put in place arrangements for follow-up activities to enable it to remain abreast of additional relevant information as it was published. The Committee's reports of the sixty-second and sixty-third sessions to the seventieth and seventy-first sessions of the General Assembly, respectively, included the Committee's findings from its follow-up activities up to the relevant time in each case.

11. The Committee has continued to identify further information that had become available up to the end of 2016, and systematically appraised relevant new publications to assess their implications for the Committee's 2013 report. A large proportion of these new publications have again confirmed the main assumptions and findings of the Committee's 2013 report. None of the publications have materially affected the main findings in, or challenged the major assumptions of, the Committee's 2013 report. A few have been identified for which further analysis or more conclusive evidence from additional research is needed. On the basis of the

<sup>5</sup> *Official Records of the General Assembly, Sixty-eighth session, Supplement No. 46 and corrigendum (A/68/46 and Corr.1).*

<sup>6</sup> *Sources, Effects and Risks of Ionizing Radiation: United Nations Scientific Committee on the Effects of Atomic Radiation 2013 Report to the General Assembly, vol. I, annex A (United Nations publication, Sales No. E.14.IX.1).*

material reviewed, the Committee sees no need, at the current time, to make any change to its assessment or its conclusions. However, several of the research needs identified by the Committee have yet to be addressed fully by the scientific community.

12. The Committee has requested that the findings be issued electronically on its website as a non-sales publication in English and that, subject to available resources, its publication be fostered in Japanese.

## **2. Selected evaluations of health effects and of risk inference due to radiation exposure**

13. The UNSCEAR 2012 report, annex B, entitled “Uncertainties in risk estimates for radiation-induced cancer”, summarized the current methodologies to estimate health risks from exposure to ionizing radiation including their uncertainties.<sup>7</sup> A key outcome was the need to go beyond purely statistical uncertainties and take into account other sources of uncertainty, for example those due to dose estimates or the model chosen for analysing epidemiological data.

14. At its sixty-second session, the Committee agreed to start work on evaluations of selected health effects and the inference of risk. Five scenarios have been developed for risk evaluation, based on literature reviews: leukaemia after medical computed tomography scans during childhood or adolescence; leukaemia after occupational exposure; solid cancer risk after acute and protracted exposure; thyroid cancer risk after exposure during childhood or adolescence; and risk of circulatory diseases after acute and protracted exposure. In the draft presented by the expert group the authors considered some of the uncertainties involved in the estimation of health effects and of risk inference. The Committee noted that it needed more time to fully express and analyse these and other uncertainties for each scenario, as well as to ensure that the process was in line with the newly completed annex on principles and criteria for ensuring the quality of the Committee’s reviews of epidemiological studies of radiation exposure (see section III.A below). It expected to discuss a draft scientific annex addressing these issues at its sixty-fifth session.

## **3. Lung cancer from exposure to radon and to penetrating radiation**

15. The Committee considered the effects of exposure to radon (and thoron) in homes and workplaces in 2006,<sup>8</sup> when it concluded that inhalation of radon and its decay products was carcinogenic mainly for the lungs. Since that last comprehensive evaluation there have been many scientific publications concerning radiation exposure and lung cancer, including those related to epidemiological studies of lung cancer in exposed populations from both internal exposure to radon and external exposure to penetrating radiation (typically gamma), as well as many relevant publications on dosimetry.

16. At its sixty-third session, held from 27 June to 1 July 2016, the Committee agreed to thoroughly assess the recent literature with a view to clarifying and assessing recent developments in risk estimates for lung cancer from exposure to radon and thoron compared to the lung cancer risk from external exposure to penetrating radiation, and to convey an up-to-date picture of radon dosimetry.

17. An expert group has started a systematic review of the literature and the Committee envisages that a draft scientific annex can be discussed at its sixty-fifth session, thereby allowing the Committee to consider how it would assign dose values for its own evaluations of exposure to radon.

<sup>7</sup> *Sources, Effects and Risks of Ionizing Radiation: United Nations Scientific Committee on the Effects of Atomic Radiation 2012 Report to the General Assembly*, annex B (United Nations publication, Sales No. E.16.IX.1).

<sup>8</sup> *Effects of Ionizing Radiation: United Nations Scientific Committee on the Effects of Atomic Radiation 2006 Report to the General Assembly*, vol. II, annex E (United Nations publication, Sales No. E.09.IX.5).

#### **4. Biological mechanisms influencing health effects from low-dose radiation exposure**

18. At its sixty-third session, the Committee decided to develop an up-to-date picture of the current knowledge on biological mechanisms of radiation actions relevant to disease development, particularly at low incremental doses and dose rates, their implications for the dose-response relationship for health effects at low doses, and thus their relevance for estimation of associated risks to health.

19. The specific objective will be to address the following questions: (a) for which biological mechanisms is there evidence that indicates they can affect the frequency of health effects following exposure to ionizing radiation, including at low doses and dose rates? What are the differences in utilization and/or activation of those pathways and mechanisms at low doses compared with moderate doses? What dose-response relationships are available as evidence for these mechanisms? (b) considering such mechanisms, can any conclusions be drawn as to their overall influence on the dose-response relationship between health effects of radiation exposure at low doses compared with moderate doses? (c) are there ways to link information on the biological processes and mechanisms found to be relevant to human health effects to existing epidemiological data on incidence of disease in exposed populations? (d) is there evidence for tissue-specific variation in the mechanisms of response to ionizing radiation that relate to the differing sensitivity of tissues to radiogenic cancer? (e) are the mechanisms that operate similar for low- and high-linear-energy-transfer exposures?

20. An important aspect of this work is to constrain the range of biological endpoints and/or phenomena under consideration to those that are known or reasonably expected to play a role in radiogenic disease. The Committee decided that work should be focused on carcinogenesis.

21. For the coming year, the Committee expects that formal literature searches will be conducted for publications relevant to addressing each detailed objective and identified subsidiary issues. Moreover, it expects to review at its sixty-fifth session a draft document that will focus on reporting what has changed significantly since 2006 that might be relevant for the dose-response at low doses.

#### **5. Assessments of human exposure to ionizing radiation**

22. The Committee took note of a progress report by the secretariat on the collection, analysis and dissemination of data on radiation exposures of the public, patients and workers. The Committee welcomed the fact that the General Assembly, in its resolution 71/89, had encouraged Member States to nominate a national contact person to facilitate coordination of the collection and submission of data on human exposure. However, as of May 2017, only 60 countries had nominated national contact persons, 27 countries had submitted data for the UNSCEAR Global Survey on Medical Exposure and 3 countries for the UNSCEAR Global Survey of Occupational Radiation Exposures. The Committee requested the secretariat to once again request States Members of the United Nations to nominate national contact persons to coordinate data collection at the national level, and extended its deadline for submission of data until June 2018.

##### **(a) Exposures of the public to ionizing radiation**

23. Exposures from natural sources constitute the largest component of human exposure, though they remain relatively stable over time, in contrast to artificial sources of patient, occupational and public exposure. Exposures of the public from artificial sources in the environment are usually the smallest component (excluding accidents), and yet they are of considerable interest to Governments and civil society. The most significant database in this regard is the Database on Discharges of Radionuclides to the Atmosphere and the Aquatic Environment (DIRATA), developed by the International Atomic Energy Agency (IAEA). It centralizes official records on radioactive discharges to the terrestrial and aquatic environment worldwide. DIRATA

includes data on atmospheric and aquatic discharges of radionuclides from nuclear and non-nuclear facilities where available and has interfaces for the entry, editing, interrogation and reporting of data. With regard to any future UNSCEAR assessment of public exposure from such discharges, the Committee noted that the secretariat has held preliminary discussions with IAEA to explore the best methods to update and use the relevant datasets.

**(b) Exposures of patients to ionizing radiation**

24. Given that radiation exposures of patients worldwide are the main artificial source of human exposure to ionizing radiation, that there is a continuing upward trend in population doses, and that the pace of technological development in this field continues to accelerate, the Committee's regular evaluations of population doses and trends continue to be important. The scope of the Committee's past evaluations has included assessing the annual frequency of procedures undertaken and the evaluation of radiation doses for each type of procedure. There are four general categories of medical practice involving exposure to ionizing radiation: diagnostic radiology, image-guided interventional radiology, nuclear medicine and radiation therapy. Doses from radiation therapy have not been included in the global estimates of population doses, but have been considered in trend analyses.

25. The Committee's evaluation relies on data submitted by Member States, supplemented by information published in the scientific literature. Since 2010, when the Committee agreed on a long-term strategy for improving data collection, analysis and dissemination, the following steps have been taken: (a) the questionnaires for the UNSCEAR Global Survey of Medical Exposure have been revised; (b) collaboration with international and intergovernmental organizations has been enhanced, including arrangements with the World Health Organization and the European Union; (c) an online platform has been developed for data collection; (d) a network of national contact persons has been instituted; and (e) an expert group has been established to prepare the evaluation of literature and data using a standard methodology.

26. The General Assembly had previously encouraged Member States to submit data. However, as of May 2017, only 27 countries had submitted data concerning diagnostic and interventional radiology, 25 countries for nuclear medicine and 22 countries for radiotherapy. All submissions currently available related to countries with high levels of health care, yet the quality of the data submitted was quite variable and were insufficient to allow any worthwhile assessment of global practice. Thus, the Committee decided to extend data collection until June 2018 and to circulate a simplified questionnaire requesting information on the total number of diagnostic radiology examinations (including and excluding dental examinations), interventional radiological procedures, and the total numbers of nuclear medicine procedures and radiotherapy treatments. The aim of this very much simplified approach was to obtain more submissions from countries with lower health-care levels, as such submissions were needed for a valid assessment of global practice.

27. The expert group on patient exposure has started the systematic review of more than 250 relevant new publications identified by literature search since the Committee's last evaluation of medical exposure, in 2005. Moreover, it has reviewed and developed the model for assessing population exposures based on data collected in the survey, as well as an approach to quantifying uncertainties. However, it is clear that literature dealing with medical exposure in Africa, Asia and Latin America is limited. The Committee recommends encouraging States Members of the United Nations to submit relevant national reports or evaluations to the secretariat, ideally including a short summary of the publication in English or another official language of the United Nations.

**(c) Exposures of workers to ionizing radiation**

28. The Committee conducts evaluations of the worldwide occupational exposure to provide information relevant for policy and decisions regarding the use and

management of radiation, in particular: (a) to provide a reliable and comprehensive estimate of worldwide dose distributions and trends so that they may be placed in context; (b) to provide insight into the main sources of exposure, the most significant exposure situations and the main factors influencing dose distributions and trends, reflecting as appropriate high-level concerns of the United Nations such as those related to environment, security, human rights and gender issues; (c) to facilitate the evaluation of the impact of new techniques or technologies, of regulatory changes and of risk management programmes; (d) to identify emerging issues and opportunities for improvement that may warrant more attention and scrutiny; (e) to provide authoritative information that can be used for communicating, formulating or underpinning policy and decisions, and for investigative work; and (f) to provide insight into the reliability of the evaluations and identify areas for future research.

29. The Committee has conducted its evaluations of worldwide occupational exposure and trends based on two sources: (a) data from the UNSCEAR Global Survey of Occupational Radiation Exposures; and (b) reviews of analyses conducted and published by others. With respect to the first source, the secretariat has developed an online platform for data submission and in August 2016 launched a survey.<sup>9</sup>

30. Since 2010, when the Committee agreed on a long-term strategy for improving data collection, analysis and dissemination, the following steps have been taken: (a) the questionnaires for the UNSCEAR Global Survey of Radiation Occupational Exposures have been revised; (b) collaboration with international and intergovernmental organizations has been enhanced, including arrangements with IAEA and the International Labour Organization; (c) an online platform has been developed for data collection; (d) a network of national contact persons has been instituted; and (e) an expert group has been established to prepare the evaluation of literature and data using a standard methodology. In the same way as with data on medical exposure, the Committee has decided to extend data collection until June 2018.

31. The expert group on occupational exposure has also started the systematic review of more than 450 relevant new publications identified by literature search since the Committee's last evaluation of occupational exposure, in 2002. Moreover it has reviewed and developed the model for assessing population exposures based on data collected in the survey, as well as an approach to quantifying uncertainties. As was the case for the assessment of patient exposure, it is clear that literature dealing with occupational exposure in Africa, Asia and Latin America is limited. The Committee recommended encouraging States Members of the United Nations to submit relevant national reports or evaluations to the secretariat, ideally including a short summary of the publication in English or another official language of the United Nations.

## **6. Implementation of the Committee's strategy on public information and outreach strategy**

32. The Committee took note of a progress report by the secretariat on outreach activities, and acknowledged in particular the work done in Japan to disseminate the Committee's 2013 report on the levels and effects of radiation exposure due to the accident at the Fukushima Daiichi nuclear power station,<sup>6</sup> and the subsequent white papers of 2015 and 2016 on developments since that report. The progress included outreach events in Fukushima Prefecture and preparation and dissemination of information material in Japanese. The Committee noted that while the General Assembly had encouraged the secretariat to continue to disseminate the findings to the public, and that activities conducted by the secretariat had had a demonstrable impact in that regard, this and other outreach activities would henceforth have to be curtailed because of a lack of personnel in the secretariat and associated financial resources. The Committee also welcomed the online publication by the United Nations Environment Programme (UNEP) of the updated booklet entitled "Radiation:

<sup>9</sup> Available at <http://www.survey.unscear.org>.

effects and sources”. The booklet was intended as a guide for the public and appeared in the official languages of the United Nations. Further efforts were being made to make it available in other languages as well. The Committee noted with appreciation the timely launch of the UNSCEAR 2016 report,<sup>10</sup> the secretariat’s outreach efforts to engage with other audiences such as the diplomatic community in Vienna, academia, students and tour groups visiting the Vienna International Centre, and the use of other media such as United Nations Radio and social media, to further raise awareness of the Committee and its work. It also noted that the UNSCEAR homepage<sup>11</sup> had been updated to indicate that the Committee’s work was relevant to achieving the Sustainable Development Goals.<sup>12</sup>

### C. Implementation of the Committee’s long-term strategic directions

33. The Committee recalled that at its sixty-third session it had considered its long-term strategic directions beyond the period covered by its present strategic plan (2014-2019), and had envisaged to direct its future work in specific scientific areas. It also recalled the possible need to implement a range of strategies that would support its efforts to serve the scientific community as well as wider audiences. It was foreseen that these strategies would include:

(a) Establishing standing working groups focused on areas such as sources and exposure, or health and environmental effects;

(b) Inviting, on an ad hoc basis, scientists from other States Members of the United Nations to participate in evaluations regarding the above areas;

(c) Increasing the Committee’s efforts to present its evaluations, and summaries thereof, in a manner that attracts readers without compromising scientific rigour and integrity;

(d) While maintaining its lead in providing authoritative scientific evaluations to the General Assembly, liaising closely with other relevant international bodies to avoid duplication of efforts to the extent possible.

34. The Committee also recalled that, in its resolution 71/89, the General Assembly had encouraged the Committee, over its coming sessions, to work towards implementing such strategies.

35. Although it recognized that these strategies were intended for beyond 2019, the Committee nevertheless began preliminary discussions on concepts of operations for standing working groups in two areas — exposures and effects — to scrutinize technical work and to monitor scientific developments in those areas. The Committee requested the Bureau to develop the concept of operations, assessing the associated roles, responsibilities and resource implications, for discussion at the sixty-fifth session.

36. The Committee noted that the secretariat and the Bureau had already taken steps to involve scientists from other States Members of the United Nations in supporting the secretariat in conducting ongoing evaluations.

37. The Committee also noted that the secretariat continued to liaise with other relevant organizations, in particular IAEA, the International Labour Organization, and the World Health Organization for matters directly related to its programme of work. Through the Inter-Agency Committee on Radiation Safety the Committee liaised with the same organizations as well as with other relevant international

<sup>10</sup> *Sources, Effects and Risks of Ionizing Radiation: United Nations Scientific Committee on the Effects of Atomic Radiation 2016 Report to the General Assembly* (United Nations publication, Sales No. E.17.IX.1).

<sup>11</sup> Available at <http://www.unscear.org>. The work of UNSCEAR is linked to achieving Sustainable Development Goals 3, 14 and 15.

<sup>12</sup> See General Assembly resolution 70/1.

governmental and non-governmental organizations collectively to avoid duplication of efforts to the extent possible.<sup>13</sup>

#### **D. Future programme of work**

38. The Committee discussed plans for two new projects, one on second primary cancers after radiotherapy and another on epidemiological studies of radiation and cancer. It also considered two new proposals for future work, namely a revision of the 2013 UNSCEAR report on the levels and effects of radiation exposure due to the 2011 Fukushima accident and a re-evaluation of exposure to natural sources of radiation. Having considered the current work programme, the capacity of both the Committee and its secretariat, and the foreseeable voluntary contributions to the general trust fund established by the Executive Director of UNEP, the Committee requested the Bureau to foster the development and implementation of project plans on second primary cancers after radiotherapy and on epidemiological studies of radiation and cancer in line with the guiding principles of UNSCEAR and the processes to ensure quality evaluations. The Committee further requested that a project plan be developed for consideration at the sixty-fifth session to update the Committee's 2013 report on the levels and effects of exposure due to the Fukushima accident. The proposal to re-evaluate human exposures to natural radiation sources was received positively. However, the Committee decided to postpone project initiation until its report on lung cancer from exposure to radon and to penetrating radiation was completed, and more extensive data on human exposures from natural sources in different parts of the world became available.

#### **E. Administrative issues**

39. The Committee noted that its current scientific secretary had, in January 2017, tendered his resignation with effect from November 2017. The Committee also noted that the general trust fund was currently depleted, which would result in the departure of two additional secretariat staff in June and November 2017, respectively. Consequently, the capacity of the secretariat would be severely limited until a suitable replacement for the scientific secretary could be found. The Committee expressed its highest appreciation of the work of its outgoing secretary, noting its concern that, apparently, UNEP had not yet initiated the procedure of selecting a suitable replacement. The Committee also noted that the roles and responsibilities of the secretariat of UNSCEAR, of UNEP and of staff at United Nations Headquarters, the United Nations Office at Nairobi, and the United Nations Office at Vienna needed clarification.

40. The Committee recognized that, because of the need to maintain the intensity of its work — particularly its work to develop exposure databases and to improve the dissemination of its findings to the public — regular pledges to make voluntary contributions to the general trust fund would be pivotal. In particular, considering the encouragement expressed by the General Assembly in its resolution 71/89, the Committee recognized that the secretariat would require additional professional personnel support to meet the implementation goals set forth, i.e. to further enhance the dissemination of the findings of the Committee. The Committee suggested that the General Assembly urge Member States to consider making regular pledges of

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<sup>13</sup> The Inter-Agency Committee on Radiation Safety (IACRS) was formed in 1990 to facilitate collaboration between international organizations in matters of radiation safety. It provides a forum for the exchange of information between member agencies and organizations on their activities with a view to harmonizing to the extent possible their plans and activities related to radiation safety and avoid duplication of radiation safety standards and recommendations. As and when appropriate, IACRS considers proposals for and facilitates the review and revision of the International Basic Safety Standards for Protection against Ionizing Radiation and for the Safety of Radiation Sources. IACRS functions without prejudice to the roles and responsibilities of the member organizations and agencies (see <http://www.iacrs-rp.org/>).

voluntary contributions to the general trust fund for those purposes or to make contributions in kind.

41. The Committee agreed to hold its sixty-fifth session in Vienna from 23 to 27 April 2018.

## Chapter III

### Scientific report

42. Two scientific annexes provide the rationale for the findings set out below.

#### **A. Principles and criteria for ensuring the quality of the Committee's reviews of epidemiological studies of radiation exposure**

43. Evidence from epidemiological studies of radiation exposure forms an important part of the scientific evaluation of radiation effects regularly conducted and reported by the Committee. Epidemiological studies are evaluated by the Committee to assess the health risks of radiation exposure. Methods to synthesize evidence have evolved considerably during recent decades, particularly in evidence-based medicine and health risk assessment. The current preferred methods of evidence synthesis are systematic reviews, meta-analyses and pooled analyses, which are regarded as the state-of-the-art scientific standards for pooling research data and are deemed superior to traditional narrative reviews.

44. The Committee discussed principles and criteria for ensuring the quality of its reviews of epidemiological studies of radiation exposure that take into account these scientific developments. The specific nature and scientific contents of such studies do not allow for a mechanistic application of generic quality assurance criteria. Therefore, the Committee has developed an approach to assess the quality of such studies and to synthesize the findings from many studies into its evaluations of radiation effects. The Committee's approach provides for increased methodological rigour, which is expected to further enhance the degree of coherence, transparency and objectivity in its evaluations.

45. A focus on the quality of the various studies and the assessment of their strengths and limitations are long-standing features of the Committee's work. The Committee will systematically apply the principles and approach described in this annex for its evaluations of epidemiological studies of radiation exposure, wherever applicable. Ideally, similar principles and approaches should be applied to the selection and inclusion of literature from other sciences, such as radiobiology, radiation dosimetry and radiation physics, into future reviews and evaluations of the Committee.

#### **B. Epidemiological studies of cancer risk due to low-dose-rate radiation from environmental sources**

46. In recent years, the Committee has been evaluating epidemiological studies analysing cancer risk on the basis of individual doses due to exposure at low dose rates from environmental sources. The overall results of those studies do not provide evidence of a risk of cancer per unit dose higher than that derived from studies of high radiation doses. There is considerable uncertainty in the estimates owing to both limited statistical power and limitations in other aspects such as residual confounding and inaccuracies in exposure assessment. Hence, the bounds of uncertainty do not rule out a lower risk per unit dose than that observed in studies of higher doses.

47. Environmental radiation exposure at low dose rates typically results in low and moderate doses, and therefore potential excess cancer risks are expected to be small. The estimation of such small incremental risks of cancer from protracted exposures could easily be affected by confounding due to other cancer risk factors. This may contribute to the differences between study results, because the existence of confounders and their association with radiation exposure can vary. An analysis accounting for the effects of confounders also sets requirements for sample size in a study. Precise estimates of health effects and their frequencies need sufficient follow-up, case ascertainment through high-quality cancer registry systems and accurate

information on risk factors other than radiation exposure. This emphasizes the need for prospective long-term studies with high-quality dosimetry, as well as comprehensive and accurate outcome data and information on cancer risk factors other than radiation exposure.

48. The Committee recognizes that studies of low-dose-rate exposure from environmental sources can potentially contribute to a better understanding of the risks of radiation-induced cancer. Direct evidence from such studies would be important because the general population is exposed to radiation primarily at low dose rates. However, improvements would be needed to overcome the key limitations of the studies, including low statistical power, dosimetric uncertainties and imperfections in control of confounding.

49. At its sixty-fourth session, the Committee discussed the relevance of the dose and the dose rate effectiveness factor, a radiation protection concept, in the context of scientific evaluations of epidemiological studies of cancer risk from low-dose-rate exposure.<sup>14</sup> It concluded that the dose response relationships depend on a large number of factors such that the scientific evidence regarding a possible reduction in the radiation-induced effects per unit dose at low doses and low dose rates relative to acute exposures with moderate or high doses cannot be expressed by a single value. The Committee is evaluating separately the influence of dose and dose rate by cancer type, and continues to review the developments in epidemiological, biological and statistical analyses that contribute to improved inference and estimation of low-dose and low-dose-rate health effects.

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<sup>14</sup> Introduced in *Sources and Effects of Ionizing Radiation: United Nations Scientific Committee on the Effects of Atomic Radiation 1993 Report to the General Assembly with Scientific Annexes*, annex F (United Nations publication, Sales No. E.94.IX.2).

## Appendix I

### Members of national delegations attending the sixty-second to sixty-fourth sessions of the United Nations Scientific Committee on the Effects of Atomic Radiation

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Australia	G. Hirth (Representative), M. Grzechnik, C.-M. Larsson (Representative), C. Lawrence
Belarus	A. Stazharau (Representative), A. Nikalayenka, A. Rozhko, V. Ternov, N. Vlasova
Belgium	H. Vanmarcke (Representative), S. Baatout, H. Bosmans, H. Engels, F. Jamar, L. Mullenders, H. Slaper, P. Smeesters, A. Wambersie, P. Willems
Brazil	L. Vasconcellos de Sá (Representative), J. G. Hunt (Representative), D. de Souza Santos
Canada	P. Thompson (Representative), J. Chen, P. Demers, C. Lavoie, E. Waller, R. Wilkins
China	Z. Pan (Representative), L. Dong, T. Fang, D. Huang, Y. Li, X. Lin, J. Liu, L. Liu, S. Liu, J. Mao, S. Pan, G. Song, Q. Sun, F. Yang, H. Yang, X. Wu, P. Zhou
Egypt	W. M. Badawy (Representative), T. Morsi
Finland	S. Salomaa (Representative), A. Auvinen, E. Salminen
France	J.-R. Jourdain (Representative), E. Ansoborlo, J.-M. Bordy, I. Clairand, I. Dublineau-Naud, L. Lebaron-Jacobs (Representative), K. Leuraud, F. Ménétrier, A. Rannou, M. Tirmarche
Germany	P. Jacob (Representative), S. Baechler, A. Böttger, A. A. Friedl, K. Gehrcke, T. Jung, J. Kopp, R. Michel, W.-U. Müller, W. Rühm, W. Weiss, H. Zeeb
India	K. S. Pradeepkumar (Representative), R. A. Badwe (Representative), B. Das, A. Ghosh
Indonesia	E. Hiswara (Representative), Z. Alatas (Representative)
Japan	M. Akashi (Representative), K. Akahane, S. Akiba, N. Ban, H. Fujita, R. Kanda, I. Kawaguchi, K. Kodama, M. Kowatari, M. Nakano, S. Saigusa, K. Sakai, H. Yasuda, Y. Yonekura (Representative)
Mexico	J. Aguirre Gómez (Representative)
Pakistan	R. A. Khan (Representative), Z. A. Baig (Representative), M. Ali (Representative)
Peru	A. Lachos Dávila (Representative), B. M. García Gutiérrez
Poland	M. Waligórski (Representative), L. Dobrzyński, M. Janiak, M. Kruszewski
Republic of Korea	B. S. Lee (Representative), K.-W. Cho (Representative), M. Baek, M.-S. Jeong, J. K. Kang, J.-I. Kim, K. P. Kim, S. H. Kim, D.-K. Keum, J. K. Lee, J. E. Lee, S. W. Seo, K. M. Seong

Russian Federation	A. Akleyev (Representative), R. Alexakhin, T. Azizova, S. Geraskin, D. Ilyasov, V. Ivanov, L. Karpikova, A. Koterov, A. Kryshev, S. Mikheenko, A. Rachkov, S. Romanov, A. Samoylov, A. Sazhin, S. Shinkarev, V. Uyba, V. Usoltsev
Slovakia	L. Auxtová (Representative), M. Berčíková, A. Ďurecová, V. Jurina, K. Petrová, L. Tomášek
Spain	M. J. Muñoz González (Representative), M. T. Macías Domínguez, J. C. Mora Cañadas, B. Robles Atienza, E. Vañó Carruana
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Ukraine	D. Bazyka (Representative)
United Kingdom of Great Britain and Northern Ireland	S. Bouffler (Representative), A. Bexon, J. Harrison (Representative), R. Wakeford, W. Zhang
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## **Appendix II**

### **Scientific staff and consultants cooperating with the United Nations Scientific Committee on the Effects of Atomic Radiation in the preparation of its scientific report for 2017**

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### **Secretariat of the United Nations Scientific Committee on the Effects of Atomic Radiation**

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# ANNEX A

## PRINCIPLES AND CRITERIA FOR ENSURING THE QUALITY OF THE COMMITTEE'S REVIEWS OF EPIDEMIOLOGICAL STUDIES OF RADIATION EXPOSURE

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## I. INTRODUCTION

1. Evidence from radiation epidemiology studies forms an important part of the scientific evaluation of radiation effects regularly conducted and reported by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). In many UNSCEAR evaluations, epidemiological studies are reviewed and their results used to assess health risks of radiation. As for any field of research, epidemiological studies have strengths and limitations, and each study requires careful and systematic assessment to gauge its contribution to the issue being addressed. Already in the UNSCEAR 1994 Report, it was stated that “Studies of disease in human populations must adhere strictly to epidemiological principles in order to achieve valid quantitative results. These include sound case ascertainment, an appropriate comparison group, sufficient follow-up, an accounting for confounding factors<sup>\*1</sup> and well-characterized dosimetry.” [U1]. In epidemiological studies of radiation effects, the key concerns are typically limitations in exposure assessment as well as the general issues for epidemiological studies, including study size, statistical power and chance, information bias\* (comparability of information on health outcomes), selection bias\* (potential selective inclusion or exclusion of subjects in relation to exposure or outcome) and control of confounding influences (impact of other determinants of disease risk than radiation). Many studies in radiation epidemiology deal with exposure at low doses\* and low dose rates.\* This makes the assessment of exposure-outcome associations, including the evaluation of dose responses, particularly challenging. Examples of such studies are used for illustration in this scientific annex. More examples are presented in more detail in annex B on the evaluation of epidemiological studies of cancer risk due to low-dose-rate radiation from environmental sources.

2. The Committee’s evaluations commonly need to cover a broad array of epidemiological studies, often with widely differing objectives, designs and results. Clear and transparent criteria that define the processes and decisions for the inclusion or exclusion of individual studies are essential to ensure that its evaluations meet the key scientific norm of objectivity, i.e. to use sound evidence in an undistorted manner, regardless of the composition of the group of experts conducting the evaluation for UNSCEAR’s scrutiny, with assessment unaffected by non-pertinent features of studies.

3. The Committee agreed at its sixty-second session (1–5 June 2015) that the use of epidemiological evidence to evaluate risks to the public and to workers from radiation exposure at low doses and low dose rates is a methodological challenge, and expressed the need for quality criteria to evaluate epidemiological studies in line with the UNSCEAR 2006 Report (annex A) [U3] and the UNSCEAR 2012 Report (annex A) [U7].

4. The key principles of systematic reviews are very clearly applicable and fundamental for the Committee’s evaluations. Compiling, summarizing and comparing the results from all relevant and sound evidence is essential for achieving the goal of the Committee in producing high quality evaluations. As pointed out above, this requires that a question to be addressed is clearly defined, a search of all evidence is carried out, relevant studies fulfilling the inclusion criteria are identified, their results compiled and conclusions drawn from the evidence.

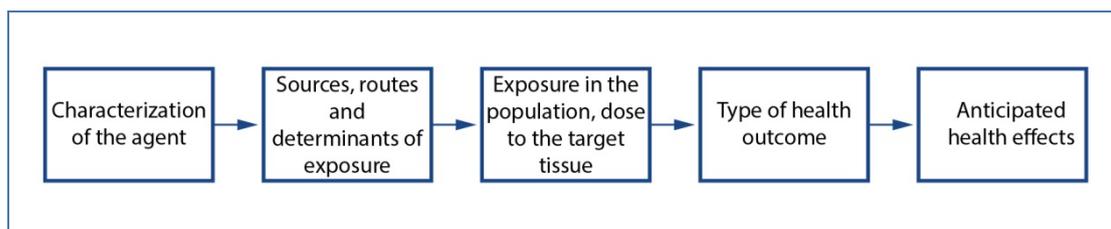
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<sup>1</sup> Technical terms are explained in a detailed glossary, and are marked with an asterisk (\*) the first time that they appear.

5. Systematic reviews have emerged as a key tool for providing guidelines in medicine, largely due to the evidence-based medicine (EBM) movement since the 1990s [E1, S1]. EBM offers broad principles for translating research into policies and practice. The need for it arose largely from conflicting guidelines prepared by professional societies and other bodies, and also from the explosion in the number of scientific literature available. A key tenet of EBM is the requirement that practice of medicine should be based on the best available scientific evidence. The concept of science-based medicine was not first introduced with EBM, but it emphasizes that the evidence must be directly applicable, i.e. based on real patients and outcomes of treatment. For health effects\* of radiation exposure, this would translate into underscoring the importance of human studies.

6. Another parallel development has been the evolution of health risk assessment, combining several lines of evidence from toxicology, epidemiology and other disciplines for estimating the health impact of exposure to potentially harmful substances. In general, health risk assessment is a process consisting of hazard\* identification, exposure assessment, dose-response assessment and risk characterization [I5] and it provides the basis for risk management and risk communication (figure I). Health risk assessment has been widely applied by expert committees mainly for chemical agents [I4]. Across the world, systematic reviews are increasingly becoming the basis for these assessments [F1].

Figure I. Health risk assessment [I5]



7. To satisfy the criteria of comprehensiveness and transparency, a thorough search for the relevant evidence must be performed as the basis for a systematic assessment of health risks. Scanning reference lists from studies, conducting dedicated hand/Internet searches, and actively contacting study authors and relevant organizations may additionally prove useful. Personal paper collections of experts in a working group can be a very good starting point on specific topics, but should be augmented by systematic searches. For example, key terms from identified key studies can be used in further searches to identify additional studies of relevance for the topic.

8. In critical appraisal of evidence derived from individual studies, evaluation criteria include relevance, validity\* and precision. Relevance means that a study can provide information pertinent to the aims of the report. Validity means lack of bias (i.e. systematic error\*) and capturing the essential features of study quality for epidemiological research. Validity can also be conceptualized as the degree to which a study reaches a correct conclusion. Precision refers to statistical power and amount of information, or limited presence of random and shared error.\*

9. The Committee's evaluations synthesize studies of effects of radiation exposure on humans and the environment to guide decision-making, assist in preparing regulations and inform the scientific community and the public. Its reports comprise evidence summaries and aim to be comprehensive and systematic in order to conduct a balanced and exhaustive evaluation of the current scientific knowledge and provide evidence-based conclusions. However, the Committee has previously stated, in its UNSCEAR 2012 Report, that a balanced evaluation involves avoiding unjustified causal associations (false positives) and also unjustified dismissal of real health effects (false negatives) [U7]. The overall approach entails several sequential steps:

- (a) Clearly define the topic and objectives of the specific evaluation;
- (b) Perform a search that allows identification of all studies with potential to contribute to the evaluation and its defined objectives;
- (c) Apply a uniform approach to scrutinizing the quality of the studies;
- (d) Synthesize the available evidence from the studies by summarizing their results from those studies meeting criteria for inclusion (providing relevant, high-quality evidence);
- (e) Develop overall conclusions drawn from the systematically retrieved, assessed and summarized studies.

10. This annex reconfirms and expands upon prior UNSCEAR Reports including guidelines to judge the quality of epidemiological studies [U2, U3]. Further, it aims to recommend procedures for assessing radiation epidemiological studies and criteria for conducting scientific reviews of epidemiological studies for the Committee's evaluations. These criteria make use of the experience of development of EBM, within Cochrane Collaboration and other settings, and of the extensive expertise specifically for radiation epidemiology available within the Committee. Furthermore, this annex also re-iterates the importance of adhering to the Governing Principles<sup>2</sup> of the Committee, notably to its process in the selection of experts according to defined terms of reference, qualifications and competence, and the declarations of potential conflicts of interest are essential steps in securing quality and scientific excellence of the Committee's evaluations. All conflict of interest statements collected in the framework of the Committee's work are available at the secretariat.

## II. OVERVIEW OF EPIDEMIOLOGICAL STUDY TYPES

11. A commonly cited definition for epidemiology is “the study of distribution and determinants of disease in human populations” [M1], with some expansions of the definition more recently [P2]. Epidemiology has also been characterized as “occurrence research in medicine” [M3] and as the science of understanding the causes and distributions of population health with a view to intervening for disease prevention and health promotion [K2]. Its key features include a population perspective on human health and disease, with disease occurrence perceived as a stochastic\* process and analysed with statistical tools. Epidemiology is largely an observational (i.e. non-experimental) science. Randomized, experimental or intervention designs can sometimes be used in epidemiology, for example screening or prevention trials, or post-intervention follow-up of persons included in a clinical trial, but generally cannot be applied to evaluations of radiation risk. A typical sequence of radiation risk evaluation using population-based epidemiological methods includes (a) assessment of radiation exposure, (b) assessment of presence or absence of a health effect of radiation, (c) determining the magnitude of the effect (if present), (d) studying dose-response patterns and variation of observed patterns in different populations/subgroups and (e) review the overall evidence with regard to causation\* (e.g. by using Hill's considerations for the assessment of causality [H5]). The drawing of conclusions from scientific observations in the presence of uncertainty\*—such as those obtained from well-designed studies of radiation epidemiology—is called inference. The two principal approaches—outlined in detail in the UNSCEAR 2012 Report (annex A) [U7]—are the frequentist inference\* and the Bayesian inference.\*

<sup>2</sup> [http://www.unscear.org/unscear/en/about\\_us/governingprinciples.html](http://www.unscear.org/unscear/en/about_us/governingprinciples.html)

12. Unlike experimental studies (e.g. randomized controlled clinical trials), observational studies rely on data generated by the uncontrolled conditions of everyday life, i.e. research opportunities created by variations in exposure conditions within and between populations (sometimes slightly misleadingly called “natural experiments”). This exposure variation in the study population is the fundamental requirement that needs to be fulfilled for observational studies with the objective of evaluating radiation risks. Such settings rarely provide highly comparable study populations, and the effects of extraneous factors make interpretation of epidemiological results challenging despite the apparently straightforward data they produce, with temptingly oversimplified conclusions to be derived. However, as epidemiological findings relate directly to humans, the results are not (or are much less) affected by the limitations of generalizability that apply to extrapolations of the findings of experimental studies (e.g. using laboratory animals) to humans, where simplified and often highly specific model\* settings do not represent real human disease, heterogeneity of susceptibility in the population, or variations in co-exposure.

13. Any epidemiological study has a defined scope, specified by the research questions to address one or several specific end points, or health outcomes. Descriptive studies provide estimates on features such as mortality or incidence rates\* in populations and subgroups thereof and may be useful to generate hypotheses about possible associations based on the frequency\* distributions observed. Studies that focus on risk factors/determinants such as ionizing radiation and their effect on health outcomes are generally termed analytical studies and tend to rely on individual, not aggregate data. In analytical studies the determinant (generically termed “exposure” in epidemiology), the effect of which is studied, has to be defined conceptually and operationally. Observational epidemiological studies, including cohort, case-control, cross-sectional and geographical/temporal correlation (“ecological”) studies are non-experimental and thus, in addition to ever-present statistical uncertainties, always prone to bias or confounding, which can lead to spurious results.

14. High-quality epidemiological studies minimize bias and confounding and provide strong empirical evidence about health outcomes in human populations. This requires careful selection of study participants, valid and accurate assessment of exposure and outcome, and data on potential confounders, all of which have to be described in detail in a study protocol that also specifies in advance the study questions and statistical analyses to be conducted. Statistical power, i.e. the probability to detect an effect or association of a given strength if it really exists, can also be a major issue as only studies with sufficient data (e.g. number of subjects, length of follow-up) allow precise estimation of effects. The Committee summarized the concept of statistical power in its 2000 Report [U2] and further expanded it in its 2006 Report [U3].

15. Calculation of sample size and statistical power in the planning stage is a feature of good quality epidemiological studies. When the sample is determined beforehand, for example by the inclusion of all exposed persons, sample size calculation is superfluous, but an estimate of statistical power—or, more generally, precision—of the study given the available study population is still informative. Sample size calculations are particularly relevant at the planning stage of studies with extensive and costly exposure and/or end point assessments, in order to achieve the optimum balance between scientific value and financial costs. The statistical power is, however, always estimated using simplifying assumptions such as no measurement error\* and a particular underlying excess risk\* and does not usually reflect other sources of uncertainty beyond random error\* [P5]. Therefore, it is an imperfect measure of information that can be obtained in a study as a small high-quality study can provide more useful information than a large study with major systematic error.

16. The measure of effect for many epidemiological studies is some form of relative risk\* (RR), such as the odds ratio\* (OR) in case-control studies. The focus in most radiation epidemiology studies is on magnitude and precision of the central effect estimate of interest, often expressed as excess relative risk (ERR)\* or excess absolute risk (EAR)\* and usually accompanied by a confidence interval\* as a

measure of statistical precision. Statistical methods that provide an estimate of the expected confidence interval (i.e. precision) are explained in Goodman and Berlin [G3]. Several realistic statistical power scenarios using the best available insight into the expected average dose or the dose distribution should be applied, if possible including uncertainty considerations as explained in the UNSCEAR 2012 Report (annex B) [U7]. As cohort studies commonly allow for the investigation of multiple end points, one or a few primary end points should be specified for which these calculations are done. The other health outcomes studied are then considered as secondary end points, which require particular caution in reporting and interpretation as they are not the primary focus of the study, and their statistical power may be too limited for them to be addressed. Guidelines on good epidemiological practice (GEP) such as those developed by the International Epidemiological Association (IEA) give further guidance on planning, conducting and interpretation of epidemiological studies [I1].

17. For the Committee's evaluations, in general, epidemiological studies are considered to be useful that address one of the following key study questions:

- (a) Is there an increased frequency of disease (individual entities or disease groups) associated with radiation exposure?
- (b) What is the magnitude of the effect associated with radiation exposure?
- (c) What is the time-, sex- and age dependency and the shape of the dose-response curve?

It should be noted that the most valuable epidemiological studies on health effects of radiation exposure are those with quantitative dose-response results. This implies that the quality of quantitative exposure and disease data is central to the value of a given study.

18. Besides the overall effect, variation in effect due to factors that modify the exposure-disease associations such as age at exposure and time since exposure may be relevant for the Committee's evaluations. In epidemiological terms, the study of the existence of a causal effect (also called hazard identification in risk assessment) corresponds to hypothesis testing, the assessment of magnitude of effect to risk estimation, and the study of differences in risk within the study population refers to effect modification. The UNSCEAR 2006 Report (annex A) [U3] provides an overview of common epidemiological study types, and denotes two main types, both of which are based on individual data:

- Cohort studies collect data on exposure and other factors for a defined group—the cohort—before the outcome event such as cancer diagnosis or death. Cohort studies are useful for the study of rare exposure and allow investigation of multiple outcomes. The temporal relationship between exposure and outcome can be identified; exposure, outcome and confounders can be measured repeatedly over time. They are less useful for rare diseases, and in many instances time-consuming and relatively expensive. If—after baseline data for the cohort have been collected—further follow-up is conducted in the future (relative to the baseline), this is called a prospective cohort study. A prominent example of a prospective cohort study in radiation epidemiology is the life span study of the atomic bombing survivors, where individuals from Hiroshima and Nagasaki with individual exposure estimates have been followed-up over more than 60 years since the study began in 1950 [O1]. Historical (sometimes called retrospective) cohort studies are often used in studies of occupational exposure, but may also be used for population-wide exposure. Their particular feature is the fact that the study period is extended to the past, for instance, if occupational radiation exposure of employees first occurred decades before the data collection for the study was started [R1]. Thus, the cohort is defined and study entry occurs at a past date, while the conduct of the study, i.e. data collection on study subjects, exposure and outcomes takes place well after that date. All information on study

subjects needs to be reconstructed/retrieved without information bias, as well as without selection bias. Availability of historical exposure information is a core feature of these studies. The retrospective data collection necessary for these studies also frequently means that dose estimates have a higher uncertainty, for example, because exposure measurements from decades ago are likely to be fewer and less accurate than for more recent periods. For example, in European cohort studies of uranium miners [K3, V1] exposure assessment in the early years of mining was less accurate than in later years, leading to a higher degree of uncertainty. Similarly, reliable outcome information (e.g. from disease registries) may be available only for more recent periods. Thus, there are no or very limited outcome data for early time windows in cohort follow-up such that health effects in these early periods cannot be studied.

- Case-control studies collect retrospective exposure and other data for cases with the disease of interest and controls that do not have the disease under study and are representative of the underlying population from which the cases derive. Case-control studies are useful for rare diseases, and they allow investigation of multiple past exposures. They are often less time-consuming than cohort studies and, thus, require fewer resources. However, the case-control design is not suitable for the study of rare exposure, and it is vulnerable to numerous biases. The core difference from cohort studies is the fact that disease or, in certain cases, death has already occurred and thus defines case status whereas in prospective cohort studies, individuals from a defined group are followed up to determine whether disease or death occurs within a defined period (in historical cohort studies, the follow-up period starts in the past). For example, case-control studies have been used to investigate lung cancer and indoor radon. For cases with lung cancer and appropriately selected control persons without lung cancer, exposure histories based on residential radon measurements were constructed and compared, and individual information on other important risk factors, such as smoking history and occupational exposure, were used in the analysis. Case-control studies from different countries were later pooled to obtain more statistical power [D1, K4]. Other examples include case-control studies of thyroid cancer after the Chernobyl accident [A3, K1]. Case-control studies can also be nested within cohorts: detailed data on exposure and other relevant factors are collected on a subset of all cohort participants (e.g. all cases of a particular type of cancer, and a set of control persons drawn from the cohort), which enhances efficiency as detailed information is collected only for a small subset of the cohort members. Thus, well-conducted nested case-control studies can be of similar value to that of cohort studies, and often there is only a moderate loss of statistical power. For example, Schubauer-Berigan et al. [S4] conducted a case-control study focused on leukaemia deaths in a larger cohort of nuclear shipyard workers. Information on benzene exposure as potential confounder was retrieved for all cases and the respective controls (but not for the whole cohort). Thus, the authors were able to include benzene as a confounder in their case-control analysis.

19. Other and related study designs include the following:

- Randomized trials use similar follow-up procedures to those of prospective cohort studies but form the groups (called trial arms) by randomization at baseline with one arm receiving an intervention and the control arm receiving another procedure (commonly no intervention except placebo/sham or, in treatment trials, the routine treatment). All individuals in both groups are then followed up for the outcome(s) under study as in cohort studies. In randomized controlled trials (RCTs), the intervention is administered by the researchers and these trials are experimental studies. Randomized trials are regarded as the gold standard for the study of effectiveness of medical interventions, including disease treatment, screening and prevention. This is so because the fundamental requirement of randomization is designed to remove or minimize bias and confounding, which is not possible in observational studies. It should be

noted that this study design is generally not feasible for the study of harmful exposure such as ionizing radiation in human populations, except in a therapeutic context or for radiation protection (where primarily the beneficial effects are assessed). For example, an RCT design can be used to assess the efficacy of occupational radiation protection measures [A2].

- In cross-sectional studies both exposure and outcome of interest are assessed at the same time. This study type is commonly used in health surveys, including the Fukushima Health Management Survey (FHMS), conducted among residents of Fukushima prefecture in Japan after the nuclear power plant accident [Y2]. Cross-sectional studies can serve as baseline investigation for a subsequent cohort follow-up (this is the case in the FHMS), but do not themselves allow inference about the cause and effect sequence. There are instances when a study that collects clinical/laboratory information on persons with previous radiation exposure is also described as cross-sectional. This type of study is conceptually closer to a cohort design and can provide evidence on cause-effect relationships or dose response if well conducted, with appropriate comparison groups. The thyroid disease survey of residents in eight villages near the Semipalatinsk Test Site in north-eastern Kazakhstan [L1] is an example of this approach. Individually reconstructed thyroid doses were used for the analysis of thyroid abnormalities detected by ultrasonographic screening and subsequent cytopathological examination of suspicious findings.
- Geographical/temporal correlation studies (at times called “ecological studies” in epidemiology) and time-series studies rely only on group-level (aggregated) data on exposure and outcome, without individual data. Therefore, they cannot show whether the exposure and outcome occur in the same subjects. The groups compared may also differ with regard to other relevant factors, for example lifestyle, occupation, medical care, which impairs comparability and can induce confounding factors. Studies comparing incidence or prevalence of disease between geographical areas related to distance from a nuclear power plant [H3, J1], to natural background radiation [N1] and to fallout from atmospheric nuclear weapon testing [D3] are examples for this study type. The potential bias of such studies has been detailed elsewhere [G5, P1].

20. It is not uncommon for epidemiological studies to involve some aggregate-level element, as some extent of grouping is commonly used in estimating exposure even in analytical studies such as those with a historical cohort design. For instance, typical exposure levels may be assigned for all subjects with a similar job title. This is distinct from ecological studies in that imputed exposure and health outcomes are being studied for individuals; in this case, the use of aggregate exposure data falls under the category of “grouped” or “Berkson”\* measurement error, also called assignment error\* [H2].

21. When assessing exposure-disease associations, cross-sectional and correlational studies generally provide evidence of markedly lower quality than cohort and case-control studies, and are considered to be hypothesis-generating or exploratory rather than answering questions of cause and effect.

22. Further epidemiological non-experimental (observational) study designs include the case-cohort, the case-only or further, less frequently used designs. Case-cohort studies are a variant of nested case-control studies with random selection of controls from the overall cohort at baseline. For example, Auvinen et al. [A4] studied the association of radon in drinking water with stomach cancer, using this design. All stomach cancer cases in a sample of the base cohort of people not connected to the municipal tap water system were compared with a set of controls defined from the same cohort at baseline, with focus on radon and other radionuclides in the drinking water of the study groups. No risk increases associated with ingestion of radon or other radionuclides were found. Case only studies compare subsets of cases in relation to a potential determinant. These simply provide an overview of all or a subset of cases reported, for example to a specific hospital or department. They are not usually

regarded as epidemiological studies and, more specifically, cannot provide information on exposure-disease relationships.

23. For many of the study designs mentioned here, mortality or disease registries, including cancer registries, are a major source of information for outcomes. Population registers are also an important source of information, as epidemiological studies require definition and enumeration of the population from which the cases arise, and there is a need to accrue information about vital status and place of residence in their study populations.

24. Of particular relevance for evidence synthesis are systematic literature reviews, with or without quantitative meta-analysis.\* Systematic reviews are a key component of EBM. Well-conducted meta-analyses of randomized trials, if available, form the highest level of evidence in EBM or public health [S12]. Meta-analyses of non-randomized studies may also provide strong contributions to an overall evidence assessment and constitute the main method of pooling quantitative evidence for risk assessment. Comprehensive overviews of the scientific literature are also a cornerstone of many of the Committee's historical evaluations while meta-analyses of quantitative data have rarely been performed specifically in this regard. A systematic and comprehensive quality-oriented process of research synthesis is described in more detail in chapter IV.

### III. MAIN FEATURES AFFECTING THE QUALITY OF EPIDEMIOLOGICAL STUDIES

25. Scientific assessment of research evidence needs to consider the quality of studies available. This chapter discusses the core features influencing study quality. All these issues are relevant when reviewing study quality, and should not be viewed separately. For studies of radiation health effects, however, radiation exposure assessment—i.e. a scientifically sound and validated approach to dosimetry—is a crucial issue when establishing how informative a single study is.

26. *Definition of study population.* Populations included in epidemiological studies (and also any exclusion criteria) need to be clearly defined with regard to age, sex, period of observation, exposure and other characteristics relevant for the particular study. For cohort studies, the data consists of person-years of observation and events (disease cases). Hence, the accumulated duration of follow-up is important, particularly as minimum latency\* between radiation exposure and effect (onset of risk elevation) is typically several years.

27. *Exposure assessment.* Exposure assessment is a critical component of any epidemiological study. For radiation epidemiology, absorbed dose\* to the relevant organ or tissue (“organ dose”) is often considered the gold standard as an exposure indicator, in particular when exposure to an individual is a mixture of external and internal exposure. However, the choice of the most suitable exposure metric depends on the study question. For example, in cases where exposure measured by an instrument or device can be directly used for public health purposes, such as in radon decay products in homes, this exposure measure (e.g. long-term average  $\text{Bq m}^{-3}$  in air) may be the preferred indicator for epidemiological studies. The actual lung dose reconstruction requires information on breathing rate, equilibrium factor between radon and its decay products, inhaled particle size, deposition fraction, target cell location and other factors that may vary by individual and working conditions as well as over time. In practice, there are numerous constraints to the precise estimation of organ doses in the context of epidemiological studies including the fact that physical dose is not evenly distributed over large

organs/tissues such as lungs or skin. Nevertheless, useful and high quality exposure assessments can be conducted for epidemiological studies.

28. Dosimetry systems such as that developed for the Techa River cohort study provide organ dose estimates for external and internal doses, integrating information from different exposure situations and time dimensions and applying conversion factors, as described in detail in annex B. The equivalent dose to an organ or tissue is a radiation protection quantity and accounts for different radiation quality in terms of biological effectiveness. It is calculated using predefined factors for different types of radiation and thus represents a radiation-weighted absorbed dose. The radiation weighting factors used to calculate the quantity are not necessarily those to be used in a scientific study. This quantity cannot be measured directly [M2], which is the case also for other dose quantities—for example, for the absorbed dose received within the body from intakes of radionuclides. Effective dose, a derived dose quantity with application of predefined radiation and organ/tissue risk weighting factors, is not the preferred quantity for risk estimation. It is not a direct measure of dose, but a construct developed for radiation protection purposes [M2]. Further, changes over time, for example with regard to the tissue weighting factors, may limit the comparability of effective dose values from different periods.

29. Whole-body dose can be useful when the outcome is incidence of all cancers and the dose within the body is relatively uniform. Alternatively, colon or stomach dose has been used as an indicator of typical organ dose for several parts of the body, with the understanding that colon or stomach doses are representative of doses received deep within the body.

30. Epidemiological studies should be based on highly detailed and accurate dose data. Quantitative estimates of radiation doses are required because simple classification of the study population into exposed and non-exposed is inadequate for quantitative risk estimation. Ideally, radiation exposure should be assessed by measuring or recording the physical quantities at individual level, such as personal dosimetry of radiation workers or patient dosimetry [S9]. Regarding external irradiation, this is for example done using personal dosimetry of radiation workers or patient dosimetry. For environmental studies, because the individuals exposed are not expected to wear dosimeters during the period of exposure, external doses at individual or group level are derived from other measurements, when available, such as ambient dose rates\* at the locations of exposure in the Karunagappally and in the Yangjiang studies of natural background radiation [M6, N2], or deposition densities of  $^{137}\text{Cs}$  and other radionuclides in the localities contaminated as a result of the Chernobyl accident [M4]. When radiation measurements are not available during the period of exposure, reconstruction of the source term is used in the LSS studies to estimate ambient dose rates [C7] or environmental concentrations of radionuclides in the locations of interest affected by the early releases of  $^{131}\text{I}$  at Hanford [N4]. With respect to internal exposures, ideal situations, in which empirical data are available at the individual level, usually occur in occupational studies and medical studies of patients, but are rare in environmental studies, with notable exceptions such as the thyroid scans performed on all subjects of the studies of thyroid disease in Belarus and Ukraine [D8] or  $^{90}\text{Sr}$  body-burden measurements or in-vivo measurements of surface activity of anterior teeth in the Techa River study [D5].

31. Individual-based radiation measurements are not sufficient to determine the doses to specific organs and tissues. The steps involved in the derivation of the organ doses from the individual-based measurements vary according to the type of study and to the information available. Detailed information and reviews for a range of studies is provided in [T3]. Only two specific examples will be given in this annex. In the first example, related to personal dosimetry of radiation workers, care must first be taken that the recorded doses are available for each subject for the entire period of exposure and that the undetected and unmonitored doses are estimated in an appropriate manner. Undetected dose is defined as the dose received that was not measured by the dosimeter, because it fell below the minimum detectable response of the dosimeter. Since the undetected dose may in reality range from

zero to the minimum detectable, it is customary to assign some fraction of the minimum detectable dose (or some other clearly stated value) for each monitoring period in which the dosimeter read zero (i.e. less than the minimum detectable), although zeroes were customary in some historical occupational data. Unmonitored dose is that assumed to be received when a personal dosimeter was not worn, and often may be reconstructed from information about workplace activities or from co-worker data when others in the same location did wear dosimeters. Attention must also be paid to the fact that changes in technology may have affected the recorded dose values. Additional complications are: (a) the recorded doses may include a mixture of radiation types (e.g. photons and neutrons) or may have measured some radiation types poorly; (b) organs or tissues may be only partially irradiated, for example when medical personnel wear lead aprons; and (c) recorded doses must be collected from all facilities where the worker was exposed during her/his career. The main effort then consists in defining the exposure scenarios for the various tasks carried out by the workers in order to determine the irradiation geometry and the energy spectrum of the incident photons on the body. It is important to note that the relative geometrical relationship between the dosimeter's placement on the worker, the incident source direction, and the organ or tissue is needed to derive an organ dose from the recorded dose in a manner that is suitable for epidemiological purposes [B4].

32. In environmental studies, very different steps are taken to derive internal organ doses from individual-based measurements. In this second example, related to the derivation of internal thyroid doses derived from thyroid scans performed in Belarus following the Chernobyl accident, the exposure rate obtained from the radiation detector was first processed to subtract the background due to the contamination of body and clothes from the signal in order to obtain the exposure rate due to the  $^{131}\text{I}$  activity in the thyroid at the time of measurement. The variation of the thyroidal  $^{131}\text{I}$  activity before and after the measurement was then estimated using environmental transport models adjusted according to information on lifestyle and dietary habits provided by the subjects during a personal interview. The thyroidal  $^{131}\text{I}$  activity was integrated over the time of exposure and divided by the age- and region-dependent thyroid mass of the subject to yield the integrated  $^{131}\text{I}$  concentration in the thyroid, which is proportional to the thyroid dose [D8].

33. Owing to the fact that the exposure assessment is limited to quantities that are only indirect (proxy) indicators of the true dose\* causing the effect, some uncertainty inevitably arises. When exposure is determined using ambient exposure measurement, but also in cases where a dosimeter is not placed close to the target organ or measurements from one person's dosimeter are extrapolated to a group, the magnitude of this uncertainty increases. Some examples of such situations include dosimeters worn on the chest for assessing eye lens doses [C2] and the epidemiological study of Chernobyl clean-up workers for whom shared dosimeters were used for exposure assessment [I6]. This error (called Berkson-type error) may result in too narrow confidence intervals of the dose-response relationship if standard statistical methodology is used. Epidemiological studies frequently need to reconstruct doses retrospectively, carefully identifying and evaluating all available dose exposure information. An example of such an approach is provided by nuclear worker studies where external doses in particular were reconstructed from dose monitoring registries and many other information sources. This approach is more difficult and less precise for neutrons and internal exposure occurring in some settings, and even the estimation of photon doses in early years was problematic in times [T2].

34. A crucial requirement is that to avoid information bias, the exposure assessment should be applied in a similar fashion regardless of outcome, i.e. whether a study participant develops the disease(s) of interest in the course of the study or not. For that reason, a standard algorithm applicable across exposure settings is preferred. Also, for combining data from several studies, comparability needs to be evaluated to ensure consistency as a requirement for meaningful pooling. Another requirement is to add the doses from external and internal irradiation, and to capture all sources of exposure, such as those from natural background and medical sources, particularly in low-dose studies.

35. The quality of the data is the main determinant of the precision and validity of the results. For instance, imprecise and non-specific data for exposure estimation result in inaccurate and uncertain dose estimates. Exposure measurement errors can bias dose-response relationships and the extent of bias depends on the amount of measurement error. Classical\* non-differential random error in exposure estimation tends to dilute the dose response (bias towards null). However, if individual values are replaced with group means (Berkson-type error), no bias is expected (if the group means are unbiased) though precision is lost as the loss of information reduces statistical power. Good quality studies in radiation epidemiology include a scientifically sound and transparent scientific approach to dosimetry or dose estimation, preferably at the level of the individual study participant. Examining possible systematic measurement errors in dosimetry (e.g. with regard to occupational doses over time) is needed in analysis of uncertainties. Uncertainty due to measurement or estimation error should be considered in the main analysis or in sensitivity analyses [U7]. The effect of measurement error (or uncertainty) can be dealt with by using statistical error mitigation tools such as regression calibration,\* Bayesian methods and simulations. Several such examples have been published [K5, L2, L6, S13]. Uncertainties are further discussed below.

36. Biodosimetry\* and electron paramagnetic resonance (EPR) dosimetry can be used to validate dosimetric information but, at present, it generally applies to individual exposure at dose levels above about 0.1 Gy. However, there are reports of lower detection limits for unstable chromosomal aberrations related to doses from low dose gamma rays of around 0.02 Gy [I8]. For EPR, a detection limit of around 0.03 Gy has been described [S10]. Unstable chromosomal aberrations (dicentric in lymphocytes detected in metaphase scoring) are likely to be the most sensitive such indicators and also reasonably specific for radiation exposure but they are eliminated relatively soon after exposure (with a half-life of around three years). Stable chromosomal aberrations (translocations that are retained in cell division) are, therefore, more useful for longer-term exposure in the past. However, the detection threshold of this technique is limited by the variation in the background levels, which are dependent on age, sex and lifestyle factors. Furthermore, stable translocations are not radiation specific and can be affected by other environmental agents that can cause chromosome damage (mutagenic agents or clastogens). As indicated above, a limitation of these methods of biodosimetry is the rather high detection threshold, roughly 0.1 Gy [E2, L4, S14, T1]. However, efforts to validate the dose estimates using biodosimetry or other techniques is encouraged, whenever feasible. An example is the use of personal thermoluminescent dosimeters in the Karunagappally and the Yangjiang studies of natural background radiation to validate ambient dose rates [M6, N2].

37. *Outcome definition.* The health outcome (or disease end point) under study should be defined and described very clearly, with explicit diagnostic criteria and coding with international standards (e.g. international statistical classification of diseases and related health problems (ICD)) [W1]. Large groupings of disease entities (all cancer, all cardiovascular disease) may be used to provide an overview on average effect for a group of diseases but generally information on more specific disease entities is preferred. Otherwise, the results indicate that the average effect (weighted by frequency of outcomes) and the possibly different effect on specific diseases are difficult to disentangle. Causes of death are the most widely available outcome data for assessment of health effects although incidence data are preferable, particularly for chronic diseases such as cancer. However, the accuracy of death certificates is likely to vary between different diseases and can also be affected by other factors such as time period. According to the ICD coding guidelines, the underlying cause of death should be distinguished from immediate and contributory causes.

38. Adjudicating the various diseases that may be involved in the process leading to death may be complicated and error-prone, particularly when no autopsy has been carried out. A potential source of misclassification\* is a change in assigning and coding practices over time and, in some cases, across regions or institutions. In several industrialized countries, cancer registries provide comprehensive

high-quality incidence data on neoplastic disease. Quality parameters for cancer registries include the estimated completeness of ascertainment (e.g. Nordic countries: close to 100%), the percentage of cancer detected only retrospectively by death certificate (<2%), the percentage of cancer with unknown primary site (<5%), and the percentage with microscopic verification (>95%) [E6]. However, completeness varies between registries and, in some instances, over time or by type of malignancy (commonly less comprehensive for haematological malignancies). Medical records are a less ideal source of information as they are indicators of health-care use (not only disease risk), and often involve some variation in diagnostic criteria over time or between institutions and levels of health care. Medical examinations conducted systematically for research purposes can provide more standardized outcome data than medical records. For example, in the Adult Health Study such examinations were conducted periodically on the atomic bombing survivors in Japan [Y1]. Biomarkers of radiation effect are sometimes used in epidemiological studies. An example is thyroid nodules, which are correlated with radiation dose and are not a meaningful disease entity in themselves, but only when progressing to malignancy [A1].

39. *Bias*. As described in the UNSCEAR 2006 Report (annex A) [U3], bias is any process at any stage of study design and conduct that tends to produce results or conclusions that differ systematically from the true exposure-disease association. There are numerous types of bias, the major categories being selection and information bias. Publication bias is of particular relevance for evidence synthesis.

40. Selection bias occurs when the actual study group differs from the intended target group in a fashion that affects the results, i.e. study subjects differ from the target group in terms of exposure, disease risk or both. Different length of follow-up in cohort study can also result in selection bias. In case-control studies, participation among controls is often lower than among cases, and subjects who agree to participate as controls tend to be more motivated than non-participants—due to their interest in either the exposure or the outcome (being affected by these usually increases willingness to participate)—or, more generally, to have a higher level of education. Therefore, they may differ from the non-participating controls in terms of exposure or other determinants of disease risk. Particular care needs to be taken when controls are recruited in hospitals as they may represent a selected group with disease risk and exposure probabilities that differ from the general population.

41. In studies of occupational exposure, the exposed group is defined by a certain occupation, employer or tasks performed. Therefore, study participants have to be employed to be included in the exposed group. If the comparison group represents the entire population, including those outside employment due to existing health conditions, mortality rates tend to be lower in the employed group. This “healthy worker effect”, often observed in studies with standardized mortality ratio (SMR: observed mortality in the exposed group compared with expected mortality estimated from the entire source population) as the effect measure, is a classic example of selection bias. As employed persons tend to be healthier than those who are outside the workforce (the latter include those who are unable to work for health reasons), their mortality rate is generally lower than that in the entire population. Furthermore, long duration of employment, including extended work with radiation, requires that the good health status is retained for long periods. Such additional selection may result in selection effects for the subgroup of workers with highest cumulative doses. This means that the disease incidence or mortality rates in the population are not appropriate indicators of the expected rate in the exposed group (do not represent what would have happened among them in the absence of exposure). Hence, the healthy worker effect typically underestimates risks in the exposed population, i.e. causes a downward bias in results.

42. Information bias occurs if there are systematic differences in information between the groups being compared. Perhaps the most classic example of information bias is recall bias in case-control studies, which is due to the fact that the cases are generally more motivated to provide full exposure information and therefore provide different, more complete exposure histories (and sometimes even over-report it), while controls do not have a similar interest and are more likely to under-report their exposure. For example, this may at least partly explain the reportedly increased risk of meningioma associated with dental X-rays (despite very low doses) [C3]. For instance, more comprehensive ascertainment and recording of disease may occur for a group with known radiation exposure. If completeness of coverage of cancer registries is different in high background radiation areas and reference areas (control population), this would result in distortion of results due to information bias (cancer rates would differ between the areas even if the true cancer risks were identical). Chernobyl liquidators are an example of an exposed population that has received special medical examinations because of a specific exposure. This may improve diagnosis and registration of any disease detected and the group is, thus, difficult to compare with the general population not undergoing such checks.

43. As a further example, thyroid screening with ultrasound is likely to increase detection of small thyroid carcinomas [E5, I7, J2]. This will result in earlier diagnosis of asymptomatic disease and some cases might not have developed into a symptomatic stage, but have remained latent or even regressed and, hence, can be regarded as over-diagnosis. This can result in information bias if screening is more intense in groups with higher exposure. Examples of bias due to thyroid screening were discussed in the UNSCEAR 2008 Report (annex D) [U4]. To ensure uniform and comparable assessment, blinding can be used to avoid the effect of exposure outcome assessment that involves any subjective component (i.e. any degree of subjective judgement or interpretation of information). Also, to ensure comparability and minimize the effect of variability\* between different assessors, the same people should conduct assessments in all study groups (with similar proportion of subjects in various exposure groups assigned to each assessor). Likewise, performing the assessments during the same period may be essential to avoid bias due to drift, i.e. change over time in assessment due to changes in equipment, calibration, reagents or procedures. Capturing records, for example by photography, may be a valuable approach to allow a standardized and systematic review at a later stage.

44. A specific type of bias related not to study design but to reporting of results is publication bias. It is a bias resulting from preferable publication of significant results. It can occur within a study with only positive results being reported. Publication bias can also affect the entire body of evidence, with results ending up completely unpublished, or only in the grey literature (e.g. conference abstracts). If an exploratory analysis is conducted, but only the significant findings are published, proper interpretation of the results is challenging as multiple testing can produce chance findings distorting statistical significance\* unless all other (negative) test results are also revealed. It distorts the published evidence as null or non-significant results remain unreported and thus not retrievable even by systematic literature search. A related issue is “winner’s curse” due to very striking initial observations turning out much more modest in further research [I3].

45. *Confounding*. Confounding occurs when a third factor is associated with the exposure under study and also affects the outcome of interest, which leads to bias in the results pertaining to the exposure-disease association [U3]. Hence, it reflects the inability of the study to disentangle the effects of the exposure studied from the other determinants of disease risk. In principle, all known risk factors of the health outcome studied are potential confounders. They become actual confounders if they are also associated with the exposure of interest. This means that they can distort a radiation-disease association unless their effect is taken into account. An example of confounding in studies of high background radiation could be differences between high exposure and comparison areas in lifestyle, occupational or other environmental factors that affect the cancer risk. In such situations, the expected cancer rates

would not be similar between the areas even if background radiation levels were identical due to differences in other cancer risk factors. As a further example, smoking was considered a strong confounder in studies of nuclear workers as it is related both to cumulative radiation exposure and to cancer as the health outcome of interest [C1]. Confounding needs to be differentiated from effect modification where the effect of the exposure under study on an outcome varies by the level of the modifying factor.

46. Several methods can be used to control confounding. At the design stage, matching (e.g. selecting similar controls for cases in terms of age, sex or other potential confounders) or restriction (only including a strictly selected subgroup, such as never-smokers, for better comparability) address confounding to some extent. However, matching may also induce bias and is now regarded as an approach mainly to increase study efficiency. The basic concept of confounder control at the analysis stage is stratification\* by the confounder. Beyond simple stratified analysis, adjustment\* in multivariate analysis is one of the most widely used methods. However, collection of information on confounders is needed to control for their effects, which makes it equally important to obtain such data as to obtain information on the exposure and outcome. Some confounders may not be known at all, so control is not possible in an observational design. If information on confounders is incomplete or inaccurate, adjustment does not necessarily remove all confounding, but some of it may remain (known as residual confounding). Such inaccuracies arise when the confounder is assessed imperfectly, with measurement error or missing data (which is always the case to some extent). This implies that only some of the effect of the confounder(s) is actually removed, but some of it remains in the results. If the outcome under study is a broad group of diseases (such as all cancers or cardiovascular diseases), then various confounders show different effects in subtypes of disease. This means that effective control of confounding is challenging.

47. In order to illustrate the effect of confounding by a confounding factor, a simple example is shown in table 1. The dose distribution in this table is constructed so that it is similar to that of the Karunagappally cohort study of cancer risk in a high natural background radiation area in India [N2] (for more details see annex B). An important risk factor for cancers of the upper digestive tract is smokeless tobacco (in India predominantly tobacco chewing), and it may act as confounder when analysing the radiation-related cancer risk. The RR for the potential confounder with regard to solid cancer is assumed to be 3 for this example. The prevalence of tobacco chewers in the 50 mGy and 200 mGy groups is given as 40%. However, in the lowest dose group, the prevalence is set to be 20%, i.e. half of that in the higher dose groups. For the total sample, the ERR estimate is 0.1438 per 100 mGy. When stratifying the total sample by the confounder tobacco chewing, the ERR estimate is 0.05 per 100 mGy among both tobacco chewers and non-chewers. In other words, tobacco chewing positively confounded the ERR estimate per unit dose in this example by a factor of almost 3, since the overall ERR per unit dose was much higher than the ERR in the individual strata of smokeless tobacco use. As shown in this example, confounding can be caused irrespective of whether the radiation dose is linearly related to the prevalence of a confounder or not.

48. *Analysis.* An appropriate analysis is based on an a priori study plan. A clear and transparent data description is necessary, and a comprehensible choice of effect measures. To improve transparency of research findings, making the original non-identifiable data publicly available is encouraged for example by the open science framework and medical journal editors. Confidentiality requirements have to be kept in mind when making study data available to the scientific community.

Table 1. Illustration of confounding by tobacco chewing

ERRs estimated on theoretical cohort data, using model-based calculation software

Mean dose (mGy)	Person-years	Cancer cases	Cancer incidence per 10 <sup>5</sup>	RR
0	100 000	140	140	1.0 (referent)
50	400 000	738	184.5	1.32
200	100 000	198	198	1.36
			ERR=0.1438 per 100 mGy	
WITH TOBACCO CHEWING				
0	20 000	60	300	1 (referent)
50	160 000	492	307.5	1.025
200	40 000	132	330	1.1
			ERR=0.05 per 100 mGy	
WITHOUT TOBACCO CHEWING				
0	80 000	80	100	1 (referent)
50	240 000	246	102.5	1.025
200	60 000	66	110	1.1
			ERR=0.05 per 100 mGy	

49. In radiation epidemiology, the main purpose of the analysis is usually estimation of shape and slope of the dose response (particularly if the outcome is cancer), typically expressed as ERR per dose unit (sometimes as EAR per dose unit). As for cancer studies, for health effects of radiation other than cancer a quantitative risk estimate is desirable (besides statistical significance for hypothesis testing) as an obvious concern for application of well-established risks is radiation protection, including setting exposure limits. The confidence interval is a key feature reported beside the point estimate\* and indicates comparability with other risk estimates, precision of the estimation procedure and assessment of consistency with previous results. Typically, 95% confidence intervals are estimated when presenting epidemiological results, but 99% and 90% confidence intervals are also reported in the literature, representing either broader or narrower coverage probabilities with respect to the true effect size. Ideally, the confidence interval should also incorporate uncertainties associated with the dose measurement errors, which are further discussed later on in this section, but it usually accounts only for statistical errors. Also, biologically based or mechanistic models have been developed to integrate epidemiological data with the understanding of disease mechanisms. They can supplement traditional risk models and provide information about consistency between biological understanding and disease occurrence in humans [E5].

50. The main and supplementary analyses should be clearly specified. The main analysis should generally cover all or a very extensive section of the study subjects. Sometimes, a subset with the most valid data can be defined as the primary analysis, but this should be specified a priori. The cut-point defining the categorizations also needs to be selected a priori; not on the basis of results obtained. Otherwise, the reported analysis can be seriously biased. Sensitivity analyses involving different cut-points can be informative for the interpretation of study results.

51. Several temporal factors are relevant for analysis. Radiation effect may vary in relation to time since exposure. Adequate latency needs to be considered and is often dealt with by lagging exposure in analyses. Age at exposure and age at observation (age attained) may modify the risk.

52. Additional sensitivity analyses (sometimes called analyses of influence) are often used to evaluate the robustness of the results, i.e. the impact of sources of error or choices made in the analysis plan (assumptions or definitions). Such analyses model the impact of changes in some or all factors contributing to the final results. Their results may help to strengthen and differentiate the results of the primary analysis. An example of a study with such sensitivity analysis is the recent INWORKS report [R1] where different lag times for cumulative doses, a restriction to lower dose ranges and the exclusion of women and workers with suspected or documented internal contamination were assessed in sensitivity analyses.

53. Adjustment for well-established risk factors to minimize confounding can be easily justified, but adjustment for factors not known as risk factors for the disease under study can also induce bias (adjustment does not always and necessarily reduce bias) [S3]. If several alternative measures or groupings of exposure/outcome are used, findings may arise just by chance. Multiple comparisons are sometimes dealt with by using significance level adjusted for the number of tests performed. It is preferable, however, to specify the main analyses beforehand.

54. Subgroup analyses can be used to address heterogeneity of effect (effect modification or effect measure modification) such as differences in risk by age at exposure or other features of specific subgroups. It is important to note that the criterion for presence of effect modification is the statistical significance of the interaction term. Such differences in effect may reflect susceptibility and subgroup analyses are then a secondary outcome worth evaluating and reporting, provided that the statistical power is sufficient. Other research questions involving effect modification include, for instance, joint effects of radiation and other exposure. Research focusing on joint effects is challenging as detailed information of good quality on all exposure considered in the respective analyses is necessary, and subgroups jointly exposed may be small. Nevertheless, evidence on joint effects may be highly informative for risk assessment and as guidance for future targeted studies.

55. *Dealing with uncertainties.* The evaluation of uncertainties begins by identifying the sources of uncertainty that are likely to have substantial impacts on conclusions of a single study or a systematic review. This depends on the topic and objective of the study/review as the following two examples illustrate:

(a) Certain types of shared dosimetry errors such as those resulting from uncertainty in a source term, could result in substantial bias in estimates of excess cancer risk associated with radiation, but would have no effect on calculations for testing whether the excess risk equals 0;

(b) Model uncertainty\* regarding the choice and functional form used for effect modifiers is important regarding estimates of excess rates for parameter values outside the centre of the data, for example for doses lower than the average dose, specific age groups above or below the average age of the cohort, shorter or longer times after exposure than the average cohort value.

56. The various sources and types of uncertainties for observational studies were discussed in the UNSCEAR 2012 Report (annex B) [U7]. These include sources or uncertainty that result in random and/or systematic error in estimates of relative or excess risk:

(a) Random error is a major issue especially for small studies (particularly those with a limited number of cases by dose range) and studies of low doses. Two measures of the amount of information in a study that is affected by random error are statistical power and the precision of

relevant estimates of risk. Statistical power can be defined as the probability of the study being able to detect an association or effect of a given size if one exists [P2]. Precision is closely related and refers to how close an estimate might be expected to be to the target quantity if potential sources of systematic error could be properly adjusted for, and is indicated, for example by the width of confidence intervals. For cohort studies, both power and precision depend on the number of cases of the disease of interest, the functional relationship between the proportion of excess cancer cases (ERR) and dose, and the distribution of dose within the study population. The number of background (unexposed) cases is, of course, the product of the cancer background rate and the person-years at risk, which is closely related to the years of follow-up. For a linear dose response, the required study size to attain adequate statistical power is roughly inversely proportional to both (i) the square of the slope of the dose response, and (ii) the variance of the dose distribution. For simple comparisons between a large unexposed group and an exposed group, the required sample size to detect an effect in an exposed group is inversely proportional to the square of the mean effect. If the ERR is proportional to dose, it follows that the sample size will also be inversely proportional to the square of the mean dose. For example, it has been pointed out that, assuming an ERR proportional to dose, the sample size needed to detect an effect for a population-mean organ dose of 50 mGy would be about 16 times greater than that needed to detect an effect for 200 mGy [N3].

(b) Selection bias, information bias, confounding, the healthy worker effect, survivor bias,\* diagnostic inaccuracy, follow-up losses, and some types of dosimetry error are among the potential sources of epidemiologic uncertainties that may lead to systematic error or bias in estimates of excess risk. Methods for adjusting estimates of excess risk for some potential sources of bias, such as classical non-differential dosimetry error for relatively simple situations, are well-developed. However, systematic error in effect estimates arising from many sources of uncertainties are especially difficult to quantify. Examples include biases associated with (i) residual confounding; (ii) differential dosimetry error in occupational studies where measurements may not have been performed in accordance with protocols (e.g. misplaced badge dosimeters); (iii) shared dosimetry error for exposure from internal emitters based on complicated biokinetic models of uncertain functional form, unrecorded intakes, and sparse bioassay data; and (iv) motivated personal recall bias in dose reconstructions for case-control studies. Furthermore, the amount and existence of bias depends on the risk metric used. Nevertheless, approaches have been proposed for estimating the bias in effect estimates. Typically, these involve a series of sensitivity analyses applied serially for each source of bias (as described by Lash et al. [L3]). A problem with this approach is that it does not account for the joint effect of multiple sources of bias. More complex methods are based on an expansion of models for the data likelihood\* to include parameters that explicitly account for sources of bias. An example of this is a multiple-bias modelling approach outlined by Greenland [G6], which incorporates ideas from Bayesian inference. However, the underlying methodology requires a high degree of statistical sophistication to be properly implemented, and concerns have been raised about its applicability.

57. Special care is warranted when making inferences from small underpowered studies. In such studies, there is a high probability that even sizeable radiogenic health effects will not be detected, and negative results are at best weak indicators of null or negligible effects. Risk estimates associated with positive findings from small studies can also be misleading. Such estimates are likely to be gross overestimates of risk, as explained by the following example adapted from a recent NCRP report [N3]: suppose there are several underpowered studies, for which the expected ERR associated with the mean dose is about 0.2. However, suppose for each study, a statistically significant finding would require an estimate of ERR of at least 2. If there are enough such studies, one is likely to yield a significant result, based on an estimate of ERR which is at least 10 times greater than the “true” value.

58. Even large studies are often underpowered for making inferences about risks for specific categories of health effects or population subgroups. For example, a recent analysis by Ozasa et al. [O1] of solid cancer mortality in the Life Span Study (LSS) of the Japanese atomic bombing survivors yielded an estimate of 0.42 with 95% confidence interval for the sex-averaged ERR per Gy of (0.32, 0.53) at age 70 years and age at exposure 30 years. For specific cancers, random error is greater, and confidence intervals are noticeably wider, for example (0.21, 3.8) for bladder cancer, for which a relatively small number of 183 deaths had been observed and random error is especially large. For this cancer, the LSS is effectively a small study and the central (maximum likelihood) estimate of ERR per Gy of 1.5 is potentially a large overestimate of the “true” ERR, in addition to the lack of precision of the estimate noted above. Sample size requirements are, in general, even greater for making reliable inferences on how site-specific risks depend on effect modifiers such as age, sex and other factors such as tobacco use.

59. Measurement error in exposure assessment is an important source of both random and systematic error for estimates of dose and ultimately excess risk. Such error stems from both inaccuracies in measures of the specific exposure and doses received from other sources (e.g. environmental and medical exposure). Measurement error is often classified as differential (varying between groups) or non-differential (not varying), shared or unshared, and Berkson-type or classical. For some types of non-differential measurement error, standard methods for testing hypotheses of no effect are still valid and methods for adjusting for bias in estimates of excess risk are well established. However, differential dosimetry error is a major concern in epidemiological studies. While it may be possible to assess whether dose estimates have been underestimated—or overestimated—as a consequence of differential errors, quantifying the impact on the dose response is almost impossible without a detailed understanding of the structure and magnitude of such errors [U7]. Comprehensive data on all sources of radiation exposure is rarely available for epidemiological studies. Ignoring some sources of exposure causes non-differential misclassification if it is not correlated with the exposure of interest, or differential misclassification and bias if it differs between groups that are compared (e.g. across dose levels). The impact of dosimetry uncertainties on dose-response analyses is discussed by Gilbert [G2].

60. Some studies include complex correction approaches for non-differential measurement error that build on plausible assumptions about the distribution of the error. In the pooled European study of lung cancer and indoor radon [D2], such an approach was applied, leading to a substantial increase in the estimated lung cancer risk per 100 Bq m<sup>-3</sup>. Medical doses were not included in the exposure estimation in this study but they were not likely to play a substantial role for lung doses. As described in annex B, studies in high background natural radiation areas such as the Karunagappally study [N2] do not include any information on medical exposure, and it is not easy to determine if this leads to differential or non-differential misclassification of exposure.

61. Assessment of outcome is also prone to measurement error, as in cohort studies there is typically some loss to follow-up (information on possible outcomes is not available due to emigration or other factors). Censoring (exit from follow-up) also occurs through death or withdrawal from study by persons originally included (loss to follow-up). Informative censoring indicates death (the deceased are no longer at risk of outcome), while non-informative censoring refers to loss to follow-up since the subjects remain at risk of the outcome but information on its occurrence is not available anymore. If the exposure studied is associated with the risk of other causes of death than the outcome of interest, such competing risks may need to be taken into account in the analysis. Misclassification of the type of outcome (exact diagnosis or cause of death) also has effects on study results similar to measurement error. As mentioned earlier, such measurement error adds to uncertainty in the results, as do missing data on the outcomes, exposure or confounder. Selective loss from follow-up (attrition) or selective participation (e.g. in medical examination or autopsy for establishing a diagnosis) can also cause bias.

62. Model uncertainty refers to the fact that models are approximations to reality based on assumptions on how dose and other factors impact risk. In general, model uncertainty can be reduced in well-designed studies with sufficiently rich information to evaluate underlying assumptions. For analysis of dose response, the exposure distribution is crucial: the dose response can be estimated only within the dose range covered with sufficient amount of observations. More information can be obtained from studies with a wide and even dose distribution (with subjects and cases along a range of exposure, though typically most study populations are skewed towards low exposure). An even distribution will facilitate, for example, evaluation as to whether a linear or linear-quadratic function provides an adequate description of the true dose response. Similarly, model assumptions for effect modifiers such as age-at-exposure can be evaluated only within ranges sufficiently covered by the data. Errors in the dose measurement (or other independent variables) also affect the modelling and can lead to biased results or confidence intervals that are too narrow. Model uncertainty is, in general, difficult to quantify although methods such as multimodel inference\* have been developed [U7].

63. Evaluations of uncertainties should consider how results from individual studies might be incorporated within the review. For example, pitfalls in making inferences from a small study (with large sampling errors) might be mitigated if results from the study and others can be combined through a meta-analysis of published data from different studies or if original data from the study and others could be combined for a pooled analysis\* (see also the section on synthesis of studies).

64. *Reporting.* While a study may have been conducted with great accuracy and care, the written report may not necessarily be of the same quality due to using selective reports or omitting details of the study plan and procedures). Reporting standards for observational studies in epidemiology (STROBE), systematic reviews (PRISMA) and non-randomized evaluations of interventions (TREND) provide guidelines for this stage of research [E8]. Most of the 22 items of the STROBE checklist are common to cohort, case-control and cross-sectional studies, while some are study design-specific. Improved study reporting following STROBE can facilitate critical appraisal and interpretation of studies.

65. The key items in STROBE include proper description of the setting, eligibility criteria, defining exposure, outcome and confounding variables, sources of information and methods of assessment, and also description of statistical methods and ways the investigators dealt with any missing information. Furthermore, the study subjects (including non-participants) and their key characteristics, and also numbers of outcome events should be described. The results section should cover the effects of adjustments and any subgroup and sensitivity analyses besides the main results. In the interpretation of the findings, the limitations of the study (such as biases and imprecision), and also generalizability and previous findings should be adequately reflected.

66. Similarly, PRISMA guidelines support transparent and comprehensive reporting of systematic reviews and meta-analyses. While the focus of PRISMA is on healthcare interventions, the checklist items can be applied with minor adaptation to systematic reviews of observational epidemiological studies [M5].

67. TREND guidelines promote transparent reporting of evaluations of behavioural and public health intervention studies with non-randomized designs. Similar to STROBE, the guideline includes 22 items in a checklist for standardized reporting [D6].

68. Beyond reporting, separate guidance has been developed to focus on the methodological quality of systematic reviews. For example, the AMSTAR checklist consists of a valid and reliable eleven-item scale for methodological quality assessment of systematic reviews [S6, S7].

## IV. PROCESS OF SYNTHESIS OF RESEARCH RESULTS

69. For radiation risk assessment (as for other risks), epidemiological studies are instrumental as they provide the most directly applicable evidence, i.e. quantitative evidence on frequencies and determinants of disease and effects of interventions for human populations in real-life conditions. For traditional narrative reviews, no rigorous methodological standards have been established. They aim to provide assessment of weight or strength of evidence, i.e. judgement of value or contribution of studies commonly reporting (seemingly) contradictory results. However, the degree of credibility assigned to each study and formulation of summary measures does not tend to follow formal procedures. Hence, the appraisal of the balance of evidence is heuristic<sup>3</sup> and generally based on ad hoc criteria. This methodological “softness” makes such reviews susceptible to judgemental bias, however not intentionally.

70. For literature synthesis and evidence assessment, which are both essential components for the Committee’s evaluation of epidemiological studies, appraising their quality of evidence is a key task. Two levels of quality are to be considered. The first is the quality of any individual study used for the topic at hand. As outlined in chapter III, several core aspects affect the quality of observational studies in radiation epidemiology: notably appropriate measurement of exposure and of outcomes, confounder control, and other design and analysis issues. Quality limitations influence the risk of bias, which may differ for the various outcomes considered. Guidelines for assessing risk of bias have been developed, focusing mainly on randomized controlled studies on treatment and diagnosis but also applicable to some extent for other study types [H4]. Furthermore, tools and guidelines to assess non-randomized studies are available elsewhere [M7, S11]. So far, there is limited consensus on the elements and details of quality assessment guidelines for observational epidemiological studies. Nevertheless, a common set of topics requiring consideration has emerged, and these are also applicable—with some modifications—to radiation epidemiology (see section IV.C).

71. The next step in the assessment of quality pertains to the totality of the evidence, i.e. all studies used for reporting on the topic of interest for the respective evaluation by the Committee. In the overall assessment of the available evidence, low-quality studies should be assigned less weight than high-quality studies, or even excluded if the quality limitations are critical. A qualitative categorization of quality is preferred over quantitative and semi-quantitative numerical scoring approaches because the relative weighting of bias related to individual quality items requires questionable assumptions [G8].

72. For a scientific evaluation of a defined research topic according to established scientific procedures and values (thus following Governing Principles<sup>2</sup> of the Committee), a systematic approach is recommended, including the following steps:

- Step 1: Transparent and systematic collection of information, based on a protocol;
- Step 2: Abstraction of relevant data from selected studies or other sources of information;
- Step 3: Assessment of individual study quality following unambiguous and consistent standards;
- Step 4: Synthesis of information;
- Step 5: Drawing of conclusions.

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<sup>3</sup> Any approach to problem solving that uses practical methods not guaranteed to be optimal or perfect, but sufficient for the immediate goals. It is not formally derived.

73. This structured approach is being used in high-quality systematic reviews of radiation epidemiological studies. For example, the review by Little et al. [L5, L7] aimed to investigate a possible causal association between low-level ionizing radiation exposure and circulatory disease in a general unselected population. Clear descriptions of the information search and abstraction of data, quality assessment of included studies using clearly defined criteria and qualitative and quantitative synthesis in several meta-analyses led to evidence based conclusions provided in the review.

74. Well-conducted and reported studies should always form the main input into a scientific report (otherwise no informative conclusions can be drawn). Lower quality studies can and should be identified and evaluated with a transparent decision either to exclude them or to include them with a lower weight assigned to their results. Conclusions and summary quantitative risk assessments should rest primarily on the best quality studies. The low quality studies can be assessed as to whether their results are generally consistent with or strongly deviate from the summary results.

75. The different steps in the process of research synthesis, including the definition of the study question (topic), systematic evidence search, study identification, quality assessment, synthesis and derivation of conclusions have been described [C5, H4, W2]. The following sections give an overview of the overall process.

## A. Definition of the topic for which evidence is required

76. A crucial issue at the planning stage of a scientific evaluation is a clear and precise definition of the question or topic the evaluation seeks to cover. The scope of the planned work should be clearly outlined in a document plan, ideally with precise and answerable study questions organized using the population, intervention (exposure), comparison, and outcome (PICO or PECO) framework. For a review of epidemiological studies on cardiovascular diseases, such a question could be: is low dose and low-dose-rate exposure to ionizing radiation associated with increases in incidence and mortality from cardiovascular diseases in human populations? A protocol giving a clear definition and description of exposure, including dose levels of interest and further exposure details, should be produced. Likewise, the outcomes of interest need to be specified in advance, and eligible study designs and outcome measures outlined. Identification of relevant confounding factors that should be addressed in studies is also important. For example, in studies on ionizing radiation and cardiovascular risk, classical cardiovascular risk factors such as smoking, hyperlipidaemia and diabetes should be included as potential confounders, and confounder-adjusted regression analyses conducted. This preparatory work should result in a thorough and detailed work plan. Changes to the protocol and to the agreed scope/direction of the report should be avoided. Any necessary changes should be clearly documented and endorsed by the Committee or the scientific experts charged with an evaluation by the Committee.

## B. Collection of information: searching the literature

77. Systematic reviews address a clearly defined objective, use transparent and reproducible methodology and include a systematic literature search for all studies that meet predefined eligibility criteria. The systematic literature search results in a set of research reports consequently used for the overall evidence assessment and research synthesis.

78. The substantial growth of new journals, particularly those with an open-access model, over recent years has changed the scientific publishing landscape. There are many (online) journals with non-transparent quality control measures that nevertheless claim to be peer-reviewed and reputable. This development makes research synthesis more difficult and calls for even more emphasis on strict quality assessment of publications that are to be included in evidence synthesis.

79. There are many ways to find relevant literature. A systematic search of at least two electronic databases for specified key words provides a way to ensure completeness of information and extend the knowledge base, minimizing the possibility of selective inclusion of research reports. Nowadays, several databases of scientific literature are used, such as Medline/PubMed, Scopus or EMBASE. These can provide a good coverage of the published literature, but augmentation by expert databases and expert knowledge of the respective literature is often warranted particularly for very specific topics that may not be identified through keyword searches. A standard procedure is to also cover the reference lists of included publications and of related research overviews. Through its revision and discussion process, the Committee additionally ensures that further literature contained only in expert databases can be screened for relevance and inclusion. Unpublished research (“grey literature”) is more difficult to find, and while EBM systematic reviews nowadays do include unpublished research, the Committee usually does not use unpublished literature. However, reference lists of unpublished work may hint to further published research, and at times such work may be useful for hypothesis generation or for highlighting previously unconsidered facts. Even if English is the predominant language in scientific publishing, studies published in other languages can also contribute to the knowledge base and should, as a rule, be identified and evaluated. Expert groups often comprise members from several different countries and can thus potentially provide for expertise in different languages.

80. For searches in electronic databases, a translation of the review topic into the language of the database (e.g. in terms of specific keywords) is required, and also a clear and concise use of search terms for the population(s) and exposure(s) of interest, for the comparisons (e.g. disease rates according to different dose levels) and the outcomes (e.g. specific cancer types, ischaemic heart disease, lens cataract). Searches may be limited to particular designs or publication types such as cohort studies, using index terms. Spelling variants and natural language variants of text terms should be considered [E7]. Overlap between publications because of several publications deriving from the same material needs to be identified and taken into account.

81. A documentation of the literature search and selection process is needed so that the search can be repeated or updated at a later stage. Methods used for retrieval of information and data in the report should be described, including evidence abstraction (e.g. was it based on titles and abstracts, review of full texts?), criteria for inclusion, and quality assessment. This part is not necessarily to be published in an UNSCEAR report, but should be made available to reviewers upon request and archived at the secretariat. An information flow chart is recommended by PRISMA [M5] as a useful tool to provide an overview of the process, which could be included in an UNSCEAR report, as supplementary information or attachments. An example of a flow diagram from a systematic review on cataracts and low doses of ionizing radiation using an adaptation of the PRISMA template is given below in figures II and III [H1]. The Committee has applied this approach—with some modification—in its evaluation on the Fukushima accident and its follow-up white papers [U5, U6, U8]. In general, updates of systematic reviews may be necessary when new evidence and new methods become available. Frameworks for decisions on updating systematic reviews are available [G1].

Figure II. Information flow chart for systematic reviews [M5]

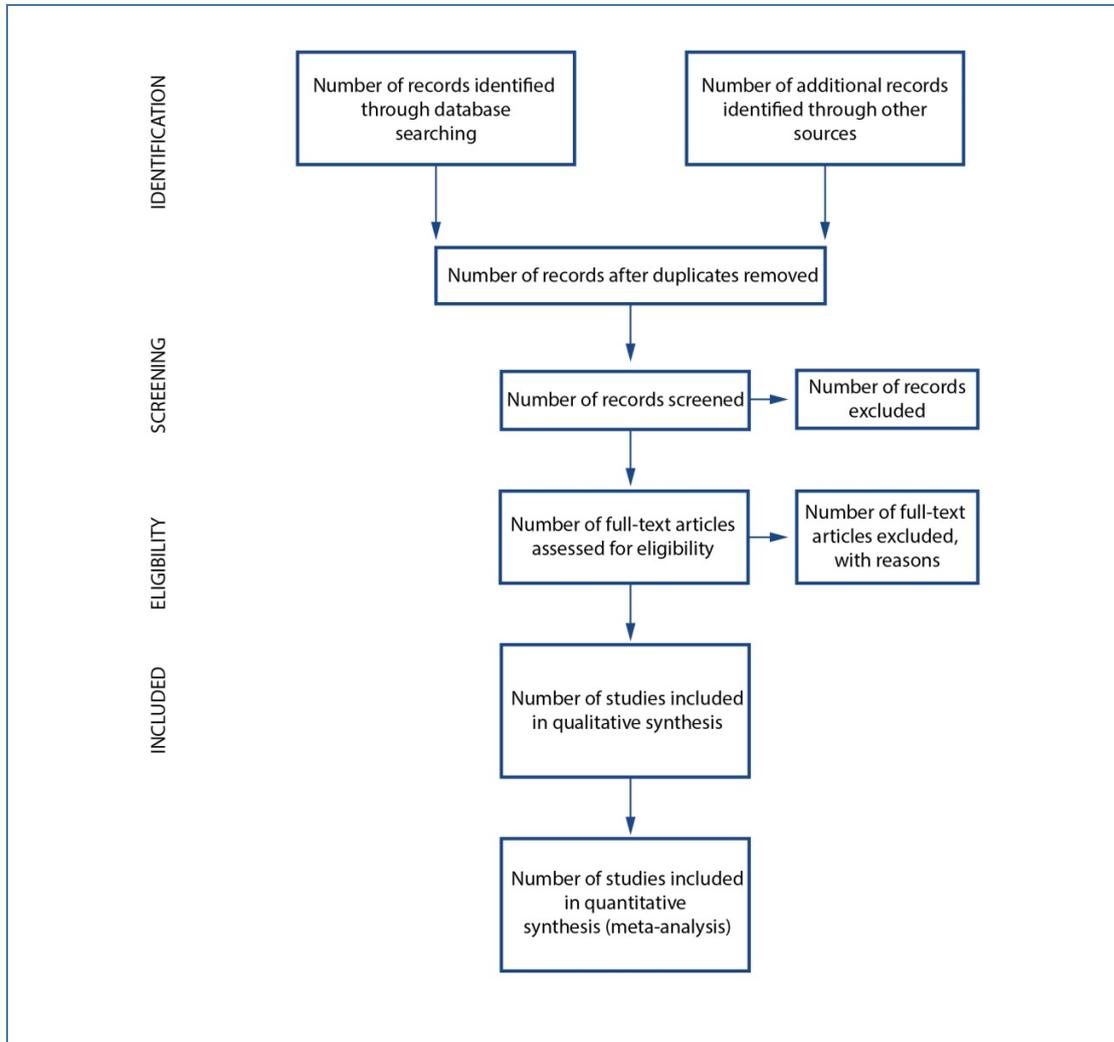
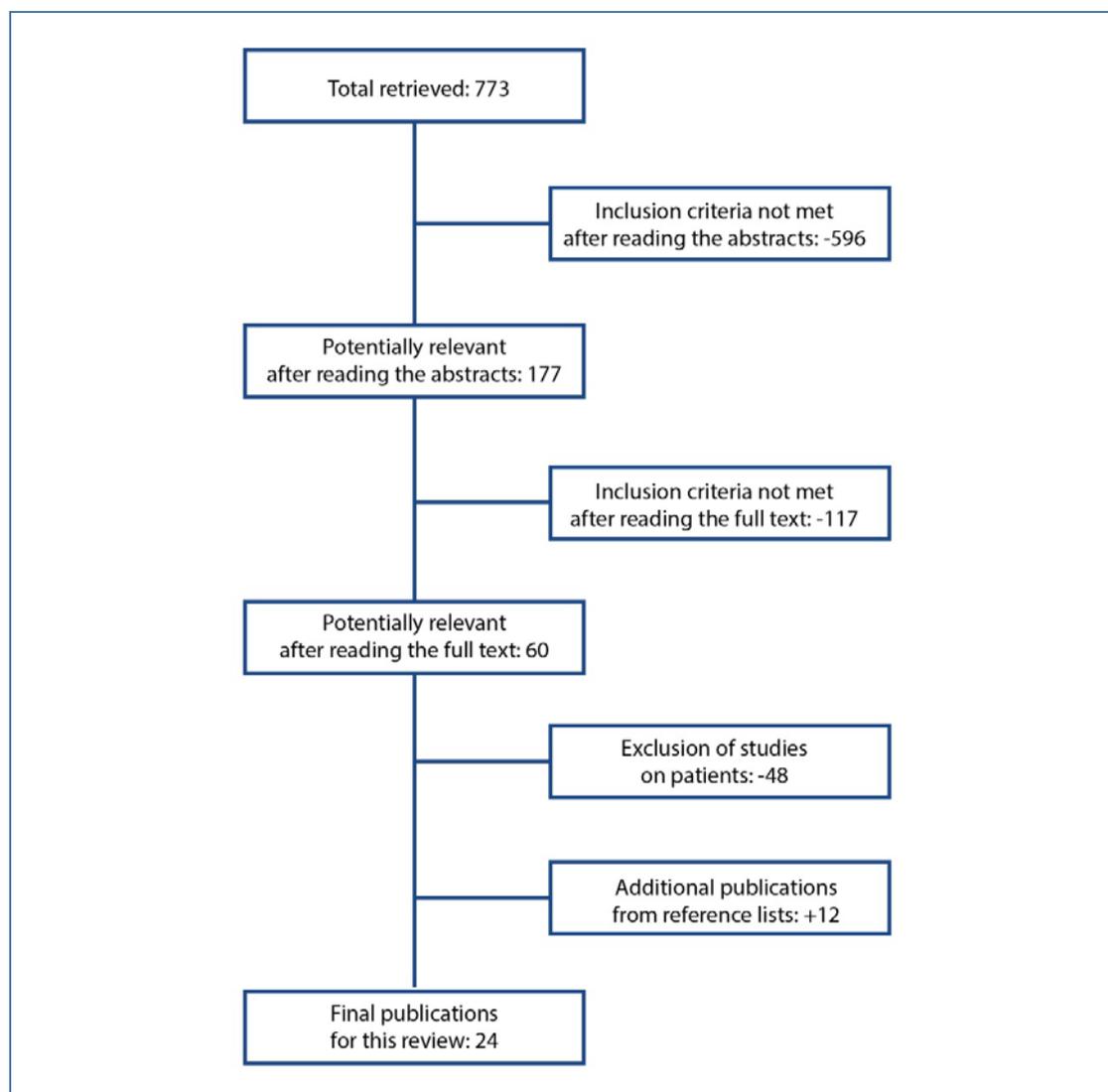


Figure III. Flow chart based on PRISMA from a systematic review on cataract development and low doses of ionizing radiation [H1]



### C. Assessment of study quality

82. Once the studies to be included have been identified, core features are abstracted for further assessment, for example in tabular form as presented in table 2. These features usually include study identifier (e.g. author, year), study design, characteristics of the population studied and duration of follow-up (for cohort studies), type of exposure, exposure assessment methods, dose distribution, core results such as ERR/unit dose or EAR/unit dose per outcome (with confidence interval), and main confounding variables included in the analysis. Further comments or details relevant to the respective study can be added. Next, study quality and relevance are assessed. Study quality assessment aims to provide a transparent judgement on the risk of bias and other methodological issues of the study at hand. Study quality assessment forms an integral part of evidence synthesis, and must be performed in a transparent and reproducible fashion. There are numerous tools available to assess individual study quality, and they are frequently designed for specific study types [S2].

83. Risk of bias or quality assessments are focused on the methodological quality of the study, and not on issues such as magnitude of effect or applicability of results. It should be noted that study size or statistical power to identify effects (if existing) are not included in the quality assessment, but need to be considered in the overall assessment of the evidence. Several core domains addressed in quality assessment have been described while for the Committee's work, the following domains should be addressed:

- (a) Method of selection of study participants;
- (b) Methods for assessing exposure;
- (c) Methods for measuring outcome;
- (d) Sources of bias specific to the study design;
- (e) Methods to control for confounding;
- (f) Statistical methods;
- (g) Study reporting;
- (h) Statement on conflict of interest of authors.

84. For the quality assessment, these domains are reviewed and appraised individually. The appraisal results in a domain being judged as having low, moderate, serious or critical risk of bias (or no information for judging risk of bias). A critical risk of bias judgement would be evident if a study is considered too problematic in the respective domain to provide any useful information. From the judgement on bias risk in the individual domains, an overall risk of bias—the overall quality assessment for the specific study—is derived, using the same categories. As indicated earlier, there is a critical discussion on the use of numerical summary scores as these involve some weighting of components and this may be not justified or applicable across studies [S2].

85. For the appraisal of these domains in radiation epidemiological studies, the following quality issues—framed as questions—are of particular importance, as explained in chapter III. To provide linkage to concepts used by the Cochrane Collaboration [H4], biases addressed using the Cochrane terminology are given in brackets. It should be noted, however, that each study requires its own critical assessment, taking account of specific study objectives, design and methods, and available data:

- (a) Study participants (selection bias)
  - For cohort studies: was the selection of participants unrelated to outcome? Do start of follow-up and start of exposure coincide for most study subjects?
  - For case-control studies: was the selection of cases and controls unrelated to exposure?
  - All study types: is there a clear description of inclusion and exclusion criteria? Is the degree of participation (response proportion) specified? How high is it?
  - All study types: are the comparison groups appropriate?
- (b) Exposure (performance bias)
  - Are individual organ doses available and used for risk estimation?
  - How extensive is the problem of missing exposure data? Were reasonable steps taken to address this problem?
  - Were temporal changes in technology, frequency of measurement, and reporting procedures of yearly doses considered while preparing the dose estimates—if applicable?
  - Were dose estimation uncertainties taken into account appropriately? Are the uncertainties substantial? How much could they affect the results?

- (c) Outcomes (detection bias)
  - Was there an objective measure of outcome, such as mortality, cancer incidence from registries or reliable medical sources?
  - How were changes in disease classification (ICD coding) handled over time?
  - Are the outcomes appropriately justified and selected, i.e. specific entities rather than large groupings of outcomes that provide only averaged overviews?
  - Were methods of outcome assessment identical across all exposure groups? Was the same effort expended on case identification in (suspected) high versus low or non-exposed groups?
  - Were there any systematic outcome measurement errors?
- (d) Design-specific bias (attrition bias, other biases)
  - Cohort study: is the follow-up reasonably complete? Is follow-up related to exposure or outcome?
  - Case-control study: does case recruitment focus on incident cases? Do controls represent the reference population, i.e. the source population from which the cases arise? Is there potential for recall bias? Is the study nested in a cohort?
- (e) Confounder control (other biases)
  - Are all important confounders assessed in the study? For example, in cancer studies are other carcinogens considered that can be associated with radiation exposure. However, some confounders may not be known.
  - How likely is residual confounding?
- (f) Statistical methods (other biases)
  - Was there a pre-specified main analysis?
  - Are the statistical methods appropriate for the available data (e.g. regression models for cohort (longitudinal) data or conditional logistic regression for matched case-control data)?
  - Are confounder-adjusted or stratified analyses available?
  - Does the study provide dose-response analyses and measures such as ERR or EAR per unit dose?
  - Are sensitivity analyses and analyses incorporating uncertainty available?
- (g) Reporting (other biases)
  - Is the reporting of the study complete and unbiased, as assessed for example via STROBE guidelines?
  - Are the reported results unlikely to be selected from different multiple outcome measures, multiple subgroups, multiple analyses?
- (h) Conflict of interest
  - Have all contributors provided conflict of interest statements in line with international recommendations?<sup>4</sup>
  - Is any potential influence of conflict of interest appropriately dealt with?

86. The Cochrane Collaboration provides a risk of bias tool for randomized clinical trials [H4] and a separate tool for non-randomized studies (ACROBAT-NRSI, now called ROBINS-I) [S11]. This later tool is being developed to provide a consistent approach for assessing risk of bias in non-randomized studies of interventions. It can also be applied to observational studies of exposure-disease associations [S11] including radiation epidemiological studies. However, given the specific issues that need to be

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<sup>4</sup> For example: International Committee of Medical Journal Editors ([www.icjme.org](http://www.icjme.org)).

taken account of in these studies, adapted tools and approaches are useful in this context. Therefore, the Committee recommends working with the study domain approach for quality assessment as outlined here, individually addressing the domains (a)–(h) (see above).

87. A risk of bias assessment of radiation epidemiological studies can also be based on quality assessment instruments, tools or approaches such as Newcastle-Ottawa Scale but they generally cover similar aspects as the ROBINS-I and the related approach applied by the Committee. Generally, assessment of bias is an area of ongoing development. Monitoring of initiatives such as the Cochrane Collaboration for assessment of the risk of bias in non-randomized studies of exposure (ROBINS-E) is recommended. A practical way to provide an overview of study quality is the use of study-specific tables noting strengths and limitations, as applied by the Committee [U3]. These tables can be organized according to the general domains described above, noting all issues that contribute to low risk of bias (i.e. high quality = strength) and moderate or (very) serious risk of bias (moderate to very low quality = limitation) [U3]. Annex B on epidemiological studies of cancer risk due to low-dose-rate radiation from environmental sources provides an overview of study quality arranged according to the study-specific domains. The specific aspects of study quality in radiation epidemiology are also summarized in table 3.

88. In addition, a setting-specific description of key quality features is provided. Some of these features for setting-specific studies can be used for the risk of bias assessment as described above. The overall assessment of study quality is then based on the quality assessment across domains, by using the quality categories:

- High;
- Moderate;
- Low;
- Very low.

89. Observational epidemiological studies can be of high quality if no or very few limitations, none of them serious, are noted in the quality assessment. Vice versa, if there are serious or very serious quality limitations in one or more domains, the overall study quality is judged as low or very low. Most studies will fall in between. A transparent domain-specific assessment and overall judgement allows for discussion and justification of further (non-) use of the study and its results.

90. The result of the quality assessment for each study is documented, and the review should then describe how the quality rating approach is used in the further steps of the review. There is little use in assessing quality without utilizing its results. Studies with critical risk of bias or no information on risk of bias from the evidence synthesis should generally be excluded. This also pertains to studies with seriously inadequate dosimetry or outcome assessment. Sensitivity analyses in quantitative meta-analyses are used to investigate results in pre-specified subgroups of studies, for example those with a similar design or those with high quality. The results of these sensitivity analyses can provide a perspective on the interpretation of the main results whether results are robust across carefully selected subgroups.

91. Applying the approach recommended by the Committee will ensure that research overviews will be more informative as they identify and summarize the best and most relevant studies on a given topic and put less or no weight on flawed or non-relevant investigations. Providing transparency in quality assessment as outlined here will form a good scientific basis for the Committee's discussions on the merits of study-specific scientific evidence used for the Committee's evaluations.

Table 2. Example of an extraction table of epidemiological studies dealing with diagnostic exposure (based on table 15, annex A [U3])

Study	Type of study, end point	Population studied		Follow-up (years)	Total person-years <sup>a</sup>	Type of exposure	Type of dosimetry	Cancers studied
		Characteristics	National origin					
EXTERNAL HIGH-DOSE-RATE EXPOSURE								
Diagnostic examinations								
TB fluoroscopy: Massachusetts [B2, S8]	Cohort, incidence	2 367 exposed women 2 427 unexposed women Age: 12–50 (26)	United States	0–>50	54 609 (11.4)	Multiple X-ray chest fluoroscopies	Individual exposure from medical records and doses from phantom measurements and computer simulations	Breast, skin
TB fluoroscopy: Massachusetts [D4]	Cohort, mortality	6 285 exposed persons 7 100 unexposed persons 49% females Age: 12–50 (26)	United States	0–>50	331 206 (24.7)	Multiple X-ray chest fluoroscopies	Individual exposure from medical records and doses from phantom measurements and computer simulations	Breast, oesophagus, lung, leukaemia
TB fluoroscopy [H6, H7]	Cohort, mortality	25 007 exposed persons 39 165 unexposed persons 50% females Age: <20–>35 (28)	Canada	0–57	1 608 491 (25.1)	Multiple X-ray chest fluoroscopies	Individual exposure from medical records and doses from phantom measurements	Lung, breast
Diagnostic X-rays (U.S. health plans) [B1]	Case-control	2 203 exposed persons 278 unexposed persons 39% females Age: 15–>50	United States	n.a.	n.a.	Diagnostic X-rays	Average dose based on number and type of procedures and estimated doses from published literature	Leukaemia, non-Hodgkin's lymphoma, multiple myeloma
Medical and dental X-rays: Los Angeles [P3]	Case-control	62% females 408 cases 408 controls	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 [P4]	Case-control	39% females 130 cases 130 controls	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

Study	Type of study, end point	Population studied		Follow-up (years)	Total person-years <sup>a</sup>	Type of exposure	Type of dosimetry	Cancers studied
		Characteristics	National origin					
Diagnostic X-rays: Sweden [I2]	Case-control 484 cases 484 controls	736 exposed persons 232 unexposed persons 77% females Age: <20–>60	Sweden	5–>50	n.a.	Diagnostic X-rays	Average dose based on number and type of procedures and estimated doses from published literature	Thyroid
Scoliosis (U.S. Scoliosis Cohort Study) [D7]	Cohort, mortality	4 822 exposed women 644 unexposed women Age: <3–≥10 (10.6)	United States	3–>60	218 976 (40.1)	Diagnostic X-rays	Average dose based on number of treatments and estimated doses from published literature	Breast

<sup>a</sup> Mean per person in parentheses.

Table 3. Overview of specific aspects of study quality in radiation epidemiology, based on selected domains

<i>Positive</i>	<i>Negative/Questionable</i>
1. STUDY POPULATION/PARTICIPANTS	
Individual level data	Only aggregate level data (ecological or geographical/temporal correlation study)
Comprehensive identification of the subjects	Poorly defined study population
Wide range of ages at exposure	Age at exposure not specified, or very narrow age-range (unless this age group is the target group, e.g. children)
In case-control studies, controls representative of exposure in source population	Inadequately-defined or absent control group; in case-control studies hospital-based controls with more potential for bias
In cohort studies, non-exposed reference group representative of disease risk in absence of exposure	Inadequately-defined, unsuitable or absent control group
In cohort studies, completeness of participant selection (or the selection sampling frame) comparable across the dose range	Indications of differential completeness of participant selection according to level of dose (e.g. higher completeness in high dose/exposure groups)
2. EXPOSURE	
Individual dosimetry, assessed for accuracy	Exposure indicator not organ dose, but indirect proxy indicator, e.g. in diagnostic exposure administered amount of activity, number of examinations
Organ doses calculated	Inaccuracy in dose estimation due to, e.g. lack of detailed information
Exposure assessment comprehensive, includes all relevant radiation exposure sources	Assessment does not cover all sources or periods of radiation exposure
Detailed dose data, e.g. for relevant organ or tissue compartment such as red bone marrow for leukaemia	Self-reported exposure data, e.g. number of X-ray examinations, food consumption data for estimating intake
Wide range of doses	Narrow and crude dose range description, e.g. high in radiotherapy, low in environmental exposure
Detailed documentation of exposure features	Only mean level of exposure assessed (e.g. from a sample of the exposed subjects)
Comprehensive, individual dose monitoring, with proper assessment and treatment of potential deficiencies	Retrospective dose reconstruction with uncertain data
Other relevant exposure sources considered, e.g. medical radiation	No or unreliable information of other radiation exposure
3. OUTCOME	
Comprehensive and uniform disease ascertainment not varying by exposure, e.g. through high-quality population-based cancer registry	Self-reported outcome through active follow-up, without verification; different outcome assessment for different exposure groups
Pathological review of cases for diagnostic verification	Abstraction of data from non-comprehensive medical records
Disease incidence, plus mortality	Mortality only
Large number of cases with specific disease	Unclear or heterogeneous diagnostic criteria

<i>Positive</i>	<i>Negative/Questionable</i>
Long-term follow-up	Potential for confounding by indication or reverse causality in diagnostic medical exposure
High percentage of histologically verified cancer diagnoses	Disease ascertainment or screening varies by exposure
<b>4. BIAS AND 5. CONFOUNDING</b>	
Detailed information on confounders	Missing data on key confounders, e.g. smoking or other behavioural factors
Attempts made to indirectly assess confounding potential, e.g. through adjustments for sociodemographic variables, job type, duration of employment	Indications of uncontrolled or residual confounding
Low likelihood of important unknown confounders	Exposure associated with other disease risk factors, e.g. both radiation and chemotherapy in studies of second cancers, co-exposure to chemical agents in occupational studies
Risk factors similar across exposure levels	Potential for recall and other information bias in exposure assessment
Systematic and unbiased exposure assessment	Low/differential participation in groups being compared
Selection bias minimized	No consideration of potential selection bias, inclusion of (highly) selected study participants; effect of migration not considered
<b>6. STATISTICAL METHODS/ANALYSIS</b>	
Sample size/power calculations presented and discussed	No consideration of study size and power
Adjustment for confounders	Comparison to disease occurrence in general population only (SMR, SIR)
Attempts to indirectly assess confounding potential, e.g. through adjustments for sociodemographic variables, job-type, duration of employment	No or very limited assessment potential for confounding through indirect approaches
Analysis of several dose-response models, including linear, linear-quadratic and quadratic, and non-parametric dose-response curves	Analysis limited to one model, or no dose-response considerations; insufficient number of categories to allow dose-response assessment
Use of pre-specified cut-points in Poisson regression	Opportunistic or post-hoc cut points
Sensitivity analyses	No sensitivity analyses reported
Pre-specified analysis plan	Unclear if analysis plan existed
<b>7. REPORTING</b>	
Complete, clear and impartial study reporting	Incomplete report, report outside range of reputable peer-reviewed journals
Conscientious search for unidentified bias or confounding, non-selective outcome reporting	Suspicion of selective reporting
Adherence to reporting guidelines, e.g. STROBE	Omission of important sections or issues in the report
<b>8. CONFLICT OF INTEREST</b>	
Statement is included	No statement
No conflict is reported	Significant conflict reported or likely

## D. Synthesis of studies: meta-analysis and narrative approaches

92. The subsequent step of the literature review process is the actual study synthesis and interpretation. Narrative synthesis involves description and summary of the core findings from the included studies of varying structure and method. This involves grouping of the studies, for example according to study design, population or outcome, and providing a verbal account of the body of evidence relevant for the review question. On the basis of focused description of the individual studies, the evidence across the different studies is summarized and jointly assessed. When few studies are available or are very diverse in terms of important characteristics, a narrative review may be more appropriate than meta-analysis of data that are not truly compatible. An example of a table describing study results in a narrative approach is given in table 4. The issues described here correspond closely to those described in table 2.

93. An important concern is the potential for publication bias, i.e. the selective reporting of studies, often those with statistically significant findings. Publication bias can seriously affect the synthesis of evidence, and several methods to detect and evaluate publication bias have been developed for use in meta-analyses [E3, J3].

94. A meta-analysis involves a formal statistical analysis of pooled results from at least two studies, yielding a joint effect estimate for the outcome. There are numerous meta-analytic techniques, and the approach chosen depends on aspects such as the study designs and the outcomes/effects to be analysed. Guidance can be found in the Cochrane handbook for systematic reviews [H4], and in textbooks for example by Borenstein et al. and Egger et al. [B3, E4]. Briefly, the minimum requirement for meta-analysis is abstraction of point estimates for the effect measures (e.g. rate ratios or hazard ratios) and their confidence intervals from each study. Study design and procedures can also contribute useful information. In pooling the results for meta-analysis, the summary estimate is generally obtained as weighted average, with inverse variance weighting. This technique assigns more weight to studies with more information, as indicated by the standard errors or confidence intervals of the effect estimates. It may be useful to examine the weight of studies as only a small number of studies may drive the overall result. Influential studies can be identified in sensitivity analyses that omit single or several studies [H4]. Meta-analyses of individual study data require that researchers obtain raw data from all studies to be included, which are subsequently analysed jointly. This approach (also called pooled analysis) allows more analytic consistency and provides flexibility for the analysis (e.g. in studying dose response across the combined data set). It is best performed as a prospectively planned pooled analysis, since retrospectively obtaining study data from many researchers may be cumbersome.

95. Assessment of consistency of the results is needed (analysis of heterogeneity). If the consistency of results is adequate, the studies can be taken to estimate a single entity i.e. their estimates are compatible and can be interpreted in a similar fashion. Alternatively, significant differences between study results indicate that their study setting, participants, measurements or other methodological issues differ to the extent that they may affect the findings. The factors underlying the differences should be explored to assess what causes the heterogeneity. Two types of statistical methods can be applied in the analysis. In the absence of major heterogeneity, a fixed effect model can be used, while heterogeneous study results require application of a random effect model. Fixed effect models are appropriate when a common effect estimate is assumed across the different studies. A random effect model is applicable when the effect estimate is considered to vary across studies, i.e. there is statistical heterogeneity of the effect estimate [B3], which is usually assessed by the Der Simonian & Laird Q statistic and the  $I^2$  – statistic quantifying the percentage of variation across the included studies that is due to heterogeneity

rather than chance. Both statistics have limitations and alternatives have been proposed [C4, C6]. Reports on meta-analyses of several outcomes may include both models, depending on the heterogeneity between studies on the respective outcomes. For example, Little et al. in their meta-analysis of circulatory disease and exposure to low-level ionizing radiation applied both fixed and random-effect models for the computation of common effect estimates [L5].

96. The advantage of the joint estimate is an increased precision of the central estimate, i.e. improved stability and reduced random error by virtue of combining data from several studies. So far, meta-analyses have rarely been conducted specifically for the Committee's evaluations. This approach requires specific statistical and methodological expertise, and is not feasible or recommended in cases of substantial heterogeneity between studies in terms of scope (exposure or outcome) or procedures, or for studies of low quality.

Table 4. Example of narrative approach to describe strengths and limitations of studies dealing with diagnostic exposure (based on table 17 of annex A [U3])

<i>Study</i>	<i>Strengths</i>	<i>Limitations</i>
EXTERNAL HIGH-DOSE-RATE EXPOSURE		
Diagnostic examinations		
TB fluoroscopy: Massachusetts [B2, D4, S8]	Incidence study with long-term follow-up (50 years) Individual dosimetry based on patient records and measurements Unexposed TB patients comparison group Fractionated exposure occurred over many years Dose–response analyses	Uncertainty in dose estimates related to fluoroscopic exposure time and patient orientation Questionnaire response probably under ascertained cancers Debilitating effect of TB may have modified radiation effect for some sites, e.g. lung
Diagnostic X-rays (U.S. health plans) [B1]	Information on diagnostic X-rays abstracted from medical records Surveillance bias unlikely, since cases and controls were at equal risk for having X-ray procedures recorded and malignancy diagnosed	Potential for ascertainment bias, e.g. through early diagnosis of a malignancy Analyses based on number of X-ray procedures rather than actual doses
TB fluoroscopy: Canada [H6, H7]	Large number of patients Unexposed TB patients comparison group Individual dosimetry for lung and female breast Fractionated exposure occurred over many years Dose–response analyses	Mortality limits comparisons with breast cancer incidence series, e.g. time response Uncertainties in dosimetry limit precise quantification of risk Different dose responses for female breast cancer between one sanatorium and the rest of Canada may indicate errors in dosimetry, differential ascertainment or differences in biological response
Diagnostic medical and dental X-rays: Los Angeles [P3, P4]	Dosimetry attempted on the basis of number and type of examinations	No available records of X-rays Potential for recall bias in dose assessment Doses likely to have been underestimated
Diagnostic X-rays: Sweden [I2]	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 (U.S. Scoliosis Cohort Study) [D7]	Adolescence possibly a vulnerable age for exposure Dosimetry undertaken on the basis of number of films and breast exposure Dose–response analysis	Comparison with general population potentially misleading, since scoliosis associated with several breast cancer risk factors (e.g. nulliparity) Dose estimates may be subject to bias and to random error

## E. Reaching an overall conclusion from the evidence synthesis

97. The final part of the evaluation of epidemiological studies should provide insight into the confidence of the overall conclusions and risk estimates obtained. Previously, a hierarchy of evidence (or evidence pyramid) was used by scientists working in EBM to provide a simplified approach to classify evidence quality according to study type. Meta-analyses of several well-conducted randomized controlled trials were considered by the scientific EBM community to provide the best empirical evidence. At the bottom of the hierarchy, expert opinions and case series were located. This pyramid was primarily geared towards evidence from therapies and other interventions.

98. Nowadays, a more articulated approach with wider assessment of various aspects of evidence has been developed within the Grading of Recommendations Assessment, Development and Evaluation (GRADE) collaboration for the Cochrane Library and has also been adopted by some international institutions involved in guideline development, including the World Health Organization [W2]. The GRADE categorization [G4] is usually specific to an outcome, for example cancer site-specific incidence. GRADE methodology provides a formalized way to categorize the quality of evidence for this outcome, leading to a four-level quality grading as high, moderate, low or very low.

99. For GRADE, the initial categorization of the evidence considers randomized (start with: high quality) or non-randomized designs (start with: low quality). Following this, several additional issues are assessed, which can lead to either a down- or an upgrading of the overall quality. Risk of bias, inconsistency across studies (heterogeneity), imprecision (small outcome numbers, wide confidence intervals) and indirectness (i.e. the available evidence covers issues that are distant from the actual topic of interest for the review) and also suspicion of publication bias all lead to a downgrading, whereas a large effect size, a dose-response relationship and indications of a likely underestimation of the effect (plausible direction of bias) support an evidence quality upgrading. For example, this allows for the rating of evidence from well-conducted observational cohort studies on radiation-associated leukaemia risk as high quality if several strengths of the studies on this outcome are demonstrated and lead to upgrading. Details of the GRADE methodology are provided by the GRADE working group [G4] and numerous articles [G7, S5].

100. Development of GRADE, particularly its application to and development for non-clinical areas, including environmental or other exposure, is ongoing. However, GRADE can be used with some adaptations for many different study designs, notably observational evidence as typical in radiation epidemiology. For the Committee, the GRADE framework can provide orientation and guidance. However, as randomized controlled trials are generally absent from the evidence body in radiation epidemiology, the focus in the scientific field of relevance for the Committee's evaluations is in detailed and specific documentation on critical assessment of the specific aspects of studies of radiation effects, as described in section IV.C.

101. A GRADE-informed UNSCEAR evidence synthesis approach should include the following:

(a) The evidence on radiation effects is assessed per health outcome. For cancer, if the case numbers for specific cancer types are sufficiently large, it is preferable to focus on these types and less on large groupings, for example all cancers, all solid cancers; however, smaller groups of cancer based on pathophysiological similarities may be useful. For other health outcomes, reasonably non-heterogeneous outcome groups should be specified. This is consistent with the Committee's approach to provide outcome-specific assessments of radiation effects [U1, U3].

- (b) The following core criteria for the synthesis are used (with associated GRADE terms in brackets):
- Strengths and limitations (risk of bias) across studies, using the quality rating for included studies as described in section IV.C;
  - Heterogeneity (inconsistency) between the various studies with regard to the radiation effect assessed;
  - Precision of effects and uncertainty (imprecision);
  - Applicability to specific topic of interest for the Committee (indirectness);
  - Publication bias.
- (c) The overall evidence (e.g. concerning the presence of a radiation effect) is rated as either high, moderate or low. For cohort and case-control studies, an initial rating as moderate is used, and for geographical/temporal correlation studies, time-series and cross-sectional studies a ranking as low is the starting point.
- (d) If the individual studies forming the evidence base have been found to have particular strengths and no or few limitations, the joint evidence from these studies is upgraded to moderate (for geographical/temporal correlation and cross-sectional studies) or high quality (cohort, case-control studies). Upgrading can also be considered if a large effect size is found by the available studies (or the majority of them) and if a dose response from studies with sound dosimetry can be demonstrated.
- (e) Conversely, if few strengths and several, clearly serious, limitations are noted for the included studies, the joint evidence is downgraded to low quality (for those with initially moderate quality). Suspicion of publication bias, preferably supported by formal analysis of this bias type, always leads to downgrading.

102. The Committee requires a clear justification of evidence synthesis judgements for upgrading or downgrading the overall quality of evidence from the body of studies included in the assessment. It is worth noting that a joint framework—such as the one presented here, and also the GRADE approach—does not ensure consistency of conclusions on evidence, but provides for transparent and explicit judgements on the research results assessed and summarized. An explicit and transparent approach helps to reduce errors, facilitates critical review of the evidence, and improves communication of information. However, this transparency relies on careful documentation [G8].

103. Transparent organization and reporting of evidence is also an important step towards reducing differences of understanding and subsequent interpretation between expert evidence synthesis, the way the Committee uses this synthesis, and public understanding of the topic. To support transparency and clarity, standardized vocabulary and terminology with clear definitions are required. This would also help to ensure that reports can be translated accurately into other languages.

104. The Committee's draft evaluations, including syntheses of epidemiological evidence, have always been subject to close scrutiny and discussion at its annual sessions. This is an important step in continuous quality control and encompasses all steps of scientific report development, with critical revisions from experts with different scientific backgrounds. The Committee also assesses the consistency and plausibility of epidemiological evidence synthesis with results from biology and toxicology, and indicates research needs arising from the overall assessment. The identification of uncertainties regarding the respective topic and possible approaches to their reduction will usually be part of the Committee's research recommendations.

## V. CONCLUSIONS

105. Individual epidemiological studies provide the basic evidence on radiation effects, and this annex provides guidance on assessing the quality of individual studies and of the synthesis of evidence from several studies. Methods of evidence synthesis have evolved considerably during recent decades. The current methodological standards define procedures for literature search, evaluation of quality, combining research results and grading the overall strength of evidence. The current methods of evidence synthesis are systematic reviews, which are regarded as the state-of-the-art scientific standards for pooling research evidence and superior to traditional narrative reviews. These developments have been applied in EBM, risk assessment and other fields.

106. The Committee will benefit from adopting a framework that is informed by these scientific developments. However, the specific nature and scientific contents of radiation epidemiological studies speak against a mechanistic application of generic quality criteria. Therefore, this annex provides an UNSCEAR approach to radiation epidemiological study quality assessment and to synthesis of findings across studies. The approach provides for increased methodological rigour, which could enhance the degree of coherence, transparency and objectivity in assessments. Although the methodological guidelines generally developed for systematic reviews are not always applicable for reasons including lack of study on specific exposure, overall paucity of evidence, and lack of comparability between available studies, the Committee seeks, nevertheless, to ensure that quality considerations guide their scientific assessment of the information provided by the respective evaluation.

107. The evidence synthesis approach outlined in this annex is focused on evidence from epidemiology. For a full assessment of scientific areas of interest to the Committee, more evidence—from, for example, radiobiology, radiation dosimetry and physics—is required. In principle, similar criteria apply to the selection and inclusion of literature from other sciences into the respective UNSCEAR evaluations. However, different scientific approaches, study designs, publication traditions and many other variations characterize these sciences, calling for a measured approach in transferring insights from this annex to other fields.

108. Overall, the Committee aims to work with a quality-oriented systematic review approach for its evaluation wherever applicable, based on the concepts described in this annex. While the focus on study quality and the explicit review of strengths and limitations of radiation epidemiology studies is a long-standing feature of the Committee's work, using quality criteria in a systematic way as outlined here has not been always applied to UNSCEAR reports that rely on epidemiological data. In summary, a high degree of transparency and a systematic approach to collecting, analysing and interpreting information for the Committee's evaluations and assessments will help to maintain the high scientific standard necessary for its widely appraised reports.

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## ANNEX B

# EPIDEMIOLOGICAL STUDIES OF CANCER RISK DUE TO LOW-DOSE-RATE RADIATION FROM ENVIRONMENTAL SOURCES

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## I. INTRODUCTION

### A. Background and aims

1. The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) defined low dose rates of low-linear-energy-transfer (LET) radiation as those below 0.1 mGy per min averaged over an hour [U4, U12]. The effect of different low dose rates on the magnitude of cancer risk after exposure to ionizing radiation is, as yet, unclear. In the particular case of exposure to high-LET ionizing radiation, such as radon and its progeny inhaled into the lung, an inverse exposure-rate effect (also called a protraction enhancement effect) was detected from high cumulative exposure but was not seen for low cumulative exposure [G8, L9, W3]. In an inverse exposure-rate effect, for equal total dose, a greater risk is incurred by those whose total dose is accumulated at a lower rate over a longer duration than at a higher rate over a shorter duration. Regarding low-LET radiation, as pointed out by the UNSCEAR 1972 Report [U3], animal studies suggested that risks per radiation dose at lower dose rates could be lower than those at higher dose rates. The report also suggested that the risk estimates based on epidemiological studies of groups exposed at high dose rates would be overestimated for doses and dose rates received from environmental sources.

2. The Committee in its UNSCEAR 2000 Report suggested that the cancer risk coefficients per unit dose obtained from human populations exposed to low-LET radiation at low dose rates were not different from those obtained for the Japanese survivors of the atomic bombing, although the estimates have wide confidence intervals\*<sup>1</sup> [U6]. However, the Committee also pointed out that much still remained to be learned despite extensive knowledge of radiation risk gained through epidemiological investigations [U6]. Since then, new results obtained from various epidemiological studies have been published on low-dose-rate exposure to low-LET radiation from environmental sources, including studies on high natural background radiation (HNBR) areas and other settings.

3. Some populations are exposed to natural background radiation at levels that are several fold higher than the average worldwide [H4, N4, T3]. In addition, some populations have been exposed to low-dose-rate radiation from environmental releases of radioactivity due to human activities [H11, K8, P11, T18]. Epidemiological studies of these populations exposed to radiation delivered at low dose rates over long periods leading to cumulative doses up to several hundred milligrays (mGy) offer an opportunity to investigate the health effects associated with low-dose-rate radiation exposure. The Committee is well aware of the importance of such studies, but past UNSCEAR reports have not fully discussed the direct evidence of health effects due to low-dose-rate exposure [U5, U6, U8].

4. The epidemiological studies of populations exposed to environmental sources of radiation offer an opportunity to obtain risk estimates for the induction of cancer from low-dose-rate radiation exposure up to a cumulative dose of 500 mGy or more [B15]. The interest in the risk of cancer and other health effects in the general population due to radiation exposure at low doses (<100 mGy [U13]) and low dose rates has increased as a consequence of the Fukushima Daiichi nuclear accident on 11 March 2011 [W2]. A systematic examination of the risks associated with radiation exposure at low doses and low dose rates is, therefore, particularly timely.

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<sup>1</sup> Technical terms are explained in a detailed glossary, and are marked with an asterisk (\*) the first time that they appear.

5. The Committee discussed the relevance of the dose and dose-rate effectiveness factor in the context of scientific evaluations of epidemiological studies of cancer risk from low-dose-rate exposure, which is defined as the reduction in effect per unit dose observed at low doses and low dose rates, compared with the effect per unit dose at high doses and high dose rates and first introduced by the International Commission on Radiological Protection (ICRP) [I3] for radiation protection purposes and then used by the Committee in its UNSCEAR 1993 Report [U4] to estimate cancer risk at low-dose and low-dose-rate radiation exposure on the basis of data obtained from high-doses and high-dose-rates.

6. At the time of applying the concept, the Committee defined low doses as those of 200 mGy or less and low dose rates as 0.1 mGy/min (averaged over one hour) or less for low-LET radiations such as X-rays and gamma rays [U4]. Meanwhile, the Committee has defined low dose by doses of less than 100 mGy [U13]. The Committee concluded generally that response functions would depend on a large number of factors that the scientific evidence for a reduction in the radiation-induced effects at low doses and low dose rates relative to acute exposures with moderate or high doses could not be expressed by a single value. Instead, the Committee is evaluating the effect of dose and dose rate by cancer type separately, and continues to review the developments in epidemiological, biological and statistical analyses that contribute to improved inference and estimation of low-dose and low-dose-rate health effects. Further, because radiation protection is not within the remit of the Committee, the use of such a reduction factor concept will not be discussed in this annex.

## B. Scope and study selection

7. The present annex reviews epidemiological studies of cancer risk from exposure to low-dose-rate radiation from environmental sources, concentrating on studies with quantitative risk estimates derived from individual dose assessment. All major cohort and case-control studies on environmental exposure to natural and human-made sources of radiation that fulfil this requirement and were published by 2016 are included. The literature search was based on the PubMed database, and also on reference lists of identified reports and studies reported by experts to ensure the inclusion of studies published outside peer-reviewed journals. The review is based on studies that provide quantitative risk estimates per unit dose based on individual exposure estimates. The strengths and weaknesses of these studies, including their design and methods of dose estimation, are considered. Biodosimetric information is also included in order to explain the dosimetric quantities and to clarify any limitations and uncertainties associated with the current estimates of the health risk from low-dose and low-dose-rate environmental radiation exposure.

8. Some ecological (geographical correlation) studies and studies using standardized mortality ratio and/or standardized incidence ratio (SIR) (with the general population as a reference) are also described, but they are not evaluated in detail because of the inherent limitations. They can assess correlations between various population characteristics, and relate average levels of exposure to overall disease occurrence patterns, but cannot assess whether exposure and disease occur in the same individuals (see annex A). Some studies of environmental radiation exposure are not covered here because of their low statistical power (small study size), lack of dose–response analyses, or major methodological limitations. Studies evaluating cancer risk among residents in the vicinities of nuclear power plants, nuclear fuel processing plants and uranium mines or mills, or populations exposed to atmospheric bomb testing fallout were not included, except where substantial environmental exposure resulting in doses well above the normal background level has been documented and quantitative risk estimates reported.

9. The Hanford Thyroid Disease Study [D6] could not evaluate the risk of thyroid cancer due to the small number of malignant cases. Likewise, the studies on cancer risk among residents of Marshall Islands due to fallout from atomic weapons testing did not provide meaningful risk estimates for cancer related to radiation exposure due to the small number of cases [S18]. Studies of residents in Utah and Nevada, United States did not have individual dose estimates or failed to provide quantitative risk estimates per unit dose [G3, S27]. Studies on cancer risk due to fallout from the Semipalatinsk test site in Kazakhstan had methodological shortcomings [A1, B9]. Some case-control studies of leukaemia did not evaluate dose response in a quantitative fashion and therefore failed to provide quantitative risk estimates comparable with other studies [A20].

10. This annex does not cover thyroid cancer risk after the Chernobyl accident because this was thoroughly reviewed by the Committee in its UNSCEAR 2008 Report [U11]. Studies on cancer other than childhood leukaemia in the Russian Federation and Europe after the Chernobyl accident are also excluded. These studies might be considered ecological (geographical correlation) analyses, because the dose estimation relies solely on area-based assignments and not on strictly individual characteristics. Such area-based exposure estimates are regarded as inferior to individual dose estimates, as they have greater uncertainty.\* Further, dose levels among residents of areas contaminated by the fallout are very low so that the power to discern an effect is low. However, several important studies on childhood leukaemia in relation to background radiation published in the 2010s are included. These include major studies on natural background radiation, and also a large study in areas with a considerable fallout level from the Chernobyl accident.

11. Further, this annex excludes epidemiological studies of radon exposure because they have already been well documented by the Committee in its UNSCEAR 2006 Report (annex E) [U9] and others (e.g. [T9, W8]). Worker studies, while relevant to effects of low-dose-rate exposure, differ from environmental radiation exposure in the sense that they have a narrower range of exposed populations with limited generalizability, and were also covered in the UNSCEAR 2006 Report [U9]. Hence, they are mentioned only briefly.

12. Epidemiological studies of cancer risk associated with both external and internal exposure to ionizing radiation were the subject of extensive reviews by the Committee in its UNSCEAR 1994, 2000 and 2006 Reports [U5, U6, U8]. The UNSCEAR 2000 Report [U6], described the limitations of statistical power and the possibility of bias\* or confounding\* frequently constraining the ability to detect small increases in cancer risk. The report also emphasized that not all epidemiological studies were equally informative or of similar quality, and illustrated this point using some examples of dose-response relationships obtained from epidemiological studies and assessed their ability to detect cancer risk at low dose.

13. As noted by the Committee in its UNSCEAR 2006 Report [U8], epidemiological studies always have the possibility of bias or confounding, which may give rise to spurious results. Bias in a study may be defined as any process at any stage in the design or conduct of a study that tends to produce results or conclusions that differ systematically from the truth [S6]. Critical bias can arise in case ascertainment, subject selection and exposure assessment. Confounding is another major cause of erroneous results, and is caused by correlations between radiation exposure and other risk factors of the health outcomes studied [U8]. Thus, it should be noted that, particularly in low-dose studies, even a small degree of bias or confounding can distort study results substantially due to the small true excess risk. Therefore, consideration of methodological issues is especially important in such studies.

14. A detailed outline of procedures and quality criteria for the assessment of epidemiological studies is given in annex A, along the lines of guidance used in past UNSCEAR reports [U6, U8]. Annex A emphasizes a comprehensive selection of studies, with a consistent approach in evaluating the potential

for bias and the contribution to the question being evaluated. These include (a) selection bias\* in the study population; (b) information bias\* with regard to exposure and outcome; (c) confounding by other risk factors for the health outcome of interest; (d) statistical power (study size relative to dose level, background risk and length of follow-up); (e) availability of dose estimates for the relevant organ at individual level; (f) information on other sources of radiation exposure than that being evaluated, which is needed to avoid exposure misclassification\*; and (g) comprehensive assessment of the outcome based on consistent diagnostic criteria. The procedures, as described in annex A, were applied here when reviewing epidemiological studies of cancer risk from exposure to low-dose and low-dose-rate radiation from environmental sources.

15. In accordance with annex A and the Governing Principles<sup>2</sup> of the Committee, potential conflict of interest of investigators was evaluated for all studies included in this annex. No conflict of interest jeopardizing impartiality was reported in the studies discussed here, though several lacked explicit statements. Funding sources were reported by most studies and some had received support from sources that may have financial interests.

## II. STUDIES ON ENVIRONMENTAL EXPOSURE RESULTING FROM HUMAN ACTIVITIES

### A. The Techa River Cohort studies in the Russian Federation

#### 1. Setting and sources of exposure

16. The Techa River is a medium-sized river that flows from a small lake located near the Mayak Production Association, a plutonium production complex, about 100 km northwest of Chelyabinsk City in the Southern Ural Mountains in the Russian Federation. The Techa River flows for about 240 km through rural areas in Chelyabinsk and Kurgan Oblasts in the Ural regions (an oblast corresponds to a province, a large geographical region) before merging with the Iset River. In the early 1950s, there were 41 villages on the river banks (26 in Chelyabinsk Oblast and 15 in Kurgan Oblast) with populations ranging in size from fewer than 100 to slightly more than 3,000 inhabitants. There were only 10 communities with populations of over 1,000 [K11].

17. Doses from background sources of natural radiation for the Techa River communities were the same as for other communities in the region. The average annual external background dose for the rural residents of Chelyabinsk Oblast is about 0.83 mSv a<sup>-1</sup> [S20]. The average annual effective dose from <sup>40</sup>K is equal to 0.2 mSv a<sup>-1</sup>. Doses from radon and its daughters in the Techa River region were 1.7–6.2 mSv a<sup>-1</sup> [Z8].

18. There were three potential sources of exposure related to the Mayak Production Association in the Ural region: (a) dumping of radioactive waste into the Techa River in the early 1950s; (b) the explosion (non-nuclear) of a storage tank in 1957 (the Kyshtym accident) that created the Eastern Ural

<sup>2</sup> [http://www.unscear.org/unscear/en/about\\_us/governingprinciples.html](http://www.unscear.org/unscear/en/about_us/governingprinciples.html)

Radioactive Trace (EURT); and (c) the dispersion of radioactive dust in 1967. The radioactive contamination resulted from the huge accumulation of radioactive waste from atomic weapon production at the Mayak Production Association, which began operating its first atomic reactor and radiochemical plant for plutonium separation in 1948. The process of plutonium separation at this plant resulted in the accumulation of a large amount of liquid waste consisting of mixtures of radionuclides. Beginning in March 1949, when the specially designed tanks that were initially used for storing liquid radioactive waste proved to be of limited capacity, another approach was used which involved releases of liquid waste into the Techa River, and into the Karachay Lake [D9]. Dumping radioactive waste into the river and Kyshtym accident caused contamination by long-lived radionuclides, mainly  $^{90}\text{Sr}$  (a half-life of 28.8 years), in a large area in the Ural region.

19. As the nature and extent of the releases became apparent, a number of countermeasures were undertaken. These included application of engineering, administrative and agricultural radiation protection activities and, most importantly, resettlement. Although the efficacy of these measures proved to be low because of the delays in implementation, between 1954 and 1960 up to 8,000 people residing in 19 villages on the upper and middle reaches of the river were resettled. For those who continued living in the Techa riverside villages, restrictions were imposed on use of the river and the floodplain for any purposes. It should be noted that a portion of the Techa riverside residents were once more exposed to radiation due to the waste storage tank explosion in 1957 [A6].

## 2. Study population and follow-up

### (a) Study population

20. The first specialized medical examinations for residents of the Techa riverside villages took place in 1951, two years after the initial releases. The examinations were performed by visiting teams of specialists from the Biophysics Institute, USSR Ministry of Health, and the Mayak Production Association Clinic. Since 1955, the residents of the Techa riverside villages have been followed up by physicians of the clinic of the Urals Research Centre for Radiation Medicine (URCRM) under the Federal Medical-Biological Agency of the Russian Federation [A7, A10, K11]. The URCRM is working closely with local hospitals, specialized oblast health centres and organizations (e.g. Office of Health Statistics, oncology dispensaries), and its clinic is the only health centre specializing in radiation medicine with the goal of rendering medical services to the exposed population of the Ural region. Thus, the exposed people have received specialized medical examinations and treatment at the same health centre for a long period (over six decades).

21. In 1967, the URCRM research staff initiated the process of identifying all people who lived in Techa riverside villages between 1950 and 1960, using five major sources of data: (a) local tax books; (b) medical examination records; (c) population surveys; (d) lists of evacuees resettled in uncontaminated villages; and (e) death certificates (for residents who died in the 1950s). Primarily, the Techa River Cohort (TRC) included residents who were born before 1 January 1950, and lived in a Techa riverside village in the period from 1 January 1950 through 31 December 1952, at the time the highest amounts of radioactive waste were released. The development of the Techa River Dosimetry System (TRDS), which exists in two versions (TRDS-2000 and TRDS-2009) provided a means for the enhancement of the TRC by including residents who had come to live in the Techa riverside area in the period from 1953 through 1960 (late entrants). Thus, the TRC now includes those born before 1 January 1950 who lived in riverside villages at any time during the period from 1 January 1950 through 31 December 1960. As of 2011, the TRC included 29,730 persons. Table 1 shows the

distribution of TRC members by sex, ethnicity and age as of 1 January 1950. The preponderance of women over men in the TRC (58% vs 42%), especially in the age group  $\geq 15$ , is connected with the consequences of World War II.

Table 1. Distribution of TRC members by age, sex and ethnicity

Age group (year) <sup>a</sup>	Men			Women			Total TRC
	Total	Slavs	Tartars/ Bashkirs	Total	Slavs	Tartars/ Bashkirs	
<1	556	78.6%	21.4%	476	77.5%	22.5%	1 032 (3.5%)
1–14	3 971	77.0%	23.0%	4 168	75.5%	24.5%	8 139 (27.4%)
15–49	6 517	81.0%	19.0%	9 168	80.6%	19.4%	15 685 (52.7%)
$\geq 50$	1 514	81.2%	18.8%	3 360	85.4%	14.6%	4 874 (16.4%)
All ages	12 558	79.7%	20.3%	17 172	80.2%	19.8%	29 730 (100%)

<sup>a</sup> As of 1 January 1950.

### (b) Follow-up

22. The follow-up of the exposed population has been conducted by the URCRM research staff with due observance of privacy codes, and under the control of the URCRM Internal Review Board. The URCRM database is constantly updated through input of new information on health status, findings of medical examinations, cancer cases, birth of children, changes of family names due to marriage, and changes of addresses.

23. Health status information was verified via regular interviews of exposed residents at the URCRM clinic, which they visit regularly to have medical examinations, and via interviews at their places of residence. Information obtained from Chelyabinsk and Kurgan Oblast address bureaus was also used for this purpose. The main sources of information on cause of death were death certificates obtained from regional health statistics offices (ZAGS) and medical death certificates (completed at the time of death). All underlying causes of death determined by local physicians were reviewed by oblast ZAGS officers, and also by the URCRM trained coders. All death certificates for residents of the study catchment area for the period 1950 through 1996 were copied from archives of the Chelyabinsk and Kurgan Oblasts ZAGS; and original medical death certificates from 1997 through 2007 were received from the Chelyabinsk and Kurgan Oblast ZAGS. According to the data of the Chelyabinsk Oblast Statistics in 2013–2014, 25% of deaths occurred in hospitals. It is believed that such a proportion was lower in the past. During the Soviet period, more than 90% of hospital deaths underwent autopsy, and autopsy was obligatory for all deaths at home among men younger than 60 years old and women younger than 55. Generally, autopsy rates were 20–30% [Z3], with similar rates in TRC members.

24. Since there are some limitations in the ascertainment of incident cancer cases for Kurgan residents, the cancer incidence analyses are currently limited to the subcohort of TRC members who were exposed originally in Chelyabinsk Oblast. This group has been called the Chelyabinsk Oblast subcohort, which accounts for 60% of the total TRC. Since the mid-1950s in the former USSR, and currently in the Russian Federation, all diagnosed cancer cases are required to be registered at the oblast oncology dispensaries [K11]. A certificate called the cancer notification form is filled out for every cancer case diagnosed for the first time, and is registered in the raions (districts) through which the Techa River flows (five raions of Chelyabinsk Oblast and two raions of Kurgan Oblast). Copies of cancer notification forms have been regularly collected by URCRM staff since 1956. Additional

information sources include case histories and outpatient charts retained at the URCRM and other health centres in Chelyabinsk City, interviews with the next of kin, cytology and histology logs kept by the Chelyabinsk Oblast Oncology Dispensary, records of the Oblast Oncology Bureau of the medical-social commission of experts, and the unified computer registry for the exposed South-Ural population. The updated URCRM database contains virtually complete information on cancer diagnoses among the exposed population registered in five regions of Chelyabinsk Oblast and Chelyabinsk City during 1956–2016.

25. Follow-up for leukaemia incidence in Chelyabinsk and Kurgan Oblasts started in 1953. In 1953–1954, the sources of information for leukaemia patients exposed in the Southern Urals were clinical records of the Ozyorsk town hospital and the Clinical Department of the Moscow Biophysics Institute, copies of which are stored in the URCRM archives. Since 1955, the URCRM clinical department has been functioning as a major haematology centre providing treatment and medical assistance to people exposed in all the Techa riverside raions [K15].

26. In the TRC study, a substantial proportion (14%) of cohort members are known to have moved to nearby cities and towns in Chelyabinsk, Sverdlovsk and Kurgan Oblasts, and a small proportion (3–4%) moved to distant areas [K10]. The dates and places of migration have been obtained from address bureaus in the relevant oblast and were included in the MAN-database, which was created in the URCRM to support the follow-up of exposed people [A8]. The loss to follow-up\* status was unrelated to dose levels (non-selective). For cohort members living outside the Chelyabinsk or Kurgan Oblasts, the chance of determining current vital status or date and cause of death is small because it is not feasible to send queries to address bureaus throughout the country. Also, URCRM staff do not have access to ZAGS records in other areas [K11]. The catchment area for non-leukaemia malignancies is limited to the five Chelyabinsk raions in the original catchment area and Chelyabinsk City.

27. Descriptive characteristics of the cohort, namely, catchment area, follow-up period, cases included in the mortality and incidence studies in different periods, are presented in table 2. The “lost to follow-up” group includes persons who were excluded from analysis after migration from the catchment area (the exact date of migration is known) or after the latest ascertainment of their vital status in the catchment area (i.e. migrants and persons with unknown status taken together). Migration rates for incidence analysis, especially for solid cancers, were higher than for mortality analysis because the catchment area for solid cancer incidence analysis was limited to five Chelyabinsk Oblast raions and Chelyabinsk City whereas for the mortality analysis, the catchment area included the whole Chelyabinsk and Kurgan Oblasts.

Table 2. Summarized characteristics for TRC studies performed in different periods

Study	Cohort size <sup>a</sup>	Period of follow-up	Person-years	Catchment area <sup>b,c</sup>	Lost to follow-up <sup>d</sup> (%)	Unknown cause of death (%)	Number of cases
Leukaemia mortality, TRDS-2000 [K16]	29 873	1950–1999	865 811	MCA	23.5 (14.0+9.5)	11	61 (including 12 CLL)
Leukaemia incidence, TRDS-2009 [K18]	28 223 <sup>e</sup>	1953–2007	847 877	MCA	21.5 (14.8+6.7)	9.8	99 (including 27 CLL)
Solid cancer mortality, TRDS-2009 [S3]	29 730	1950–2007	927 743	MCA	22.7 (15.8+6.9)	9.0	2 303 (22 bone cancers excluded)
Solid cancer incidence, TRDS-2009 [D5]	17 435 <sup>f</sup>	1956–2007	472 788	ICA	26.8 (21.1+5.7)	9.2	1 933 (excluding non-melanoma skin cancers)

<sup>a</sup> Numbers of cohort members differ in different years because periodically duplicates were identified (most of them were women who changed their family names at marriage).

<sup>b</sup> MCA (mortality catchment area) includes two oblasts: Chelyabinsk Oblast+Kurgan Oblast.

<sup>c</sup> ICA (incidence catchment area) includes five raions in Chelyabinsk Oblast+Chelyabinsk City.

<sup>d</sup> % of migrants+% of persons with unknown status at the end of follow-up are indicated in parenthesis.

<sup>e</sup> Number of cohort members excluding those who had died or migrated from MCA before 1 January 1953.

<sup>f</sup> Number of cohort members excluding those who had died or migrated from ICA before 1 January 1956.

### 3. Dosimetry

#### (a) Radiation source terms

28. The main source of environmental contamination was the release of liquid radioactive waste into the Techa River in 1949–1956. Massive releases started in September 1950 and reached a maximum in October 1951. The TRDS-2000 and TRDS-2009 estimates of the releases are shown in figure I. The total release for 1949–1951 was estimated as  $1.14 \times 10^{17}$  Bq [D16, S12]. The releases represented a mixture of the radionuclides <sup>89</sup>Sr, <sup>90</sup>Sr, <sup>137</sup>Cs, <sup>95</sup>Zr, <sup>95</sup>Nb, <sup>103</sup>Ru, <sup>106</sup>Ru and rare-earth isotopes. About half of the waste was released late in 1951 [D16]. Parameters of the Techa River source term used in TRDS-2000 were taken from the Mayak Production Association reports based on expert estimates [I6, J8]. More reliable estimates were used in TRDS-2009 [D16, G4, G5].

29. There were routine releases from the radiochemical plant and accidental releases due to leaks of high-level waste from the special tank-storage facility [D16]. A major accidental release took place during 8–12 October in 1951. On 28 October 1951, major releases were switched to Karachay Lake, and this resulted in a significant decrease in discharges into the Techa River in the subsequent five years. The releases into the river totalled  $3.5 \times 10^{14}$  Bq in 1952 and  $(2-7) \times 10^{13}$  Bq a<sup>-1</sup> in 1953–1956 (figure I). In 1956, the river bed of the upper Techa was dammed, and the penetration of radioactivity to the lower parts of the river decreased to about  $7 \times 10^{12}$  Bq a<sup>-1</sup>. The construction of another dam and bypass canals in 1963 effectively isolated the contaminated upper Techa region.

30. The routine and accidental releases differed in characteristics such as radionuclide composition and distribution of activity released in solution and adsorbed on solid particles. The characteristics of typical routine releases and the major accidental release are shown in table 3.

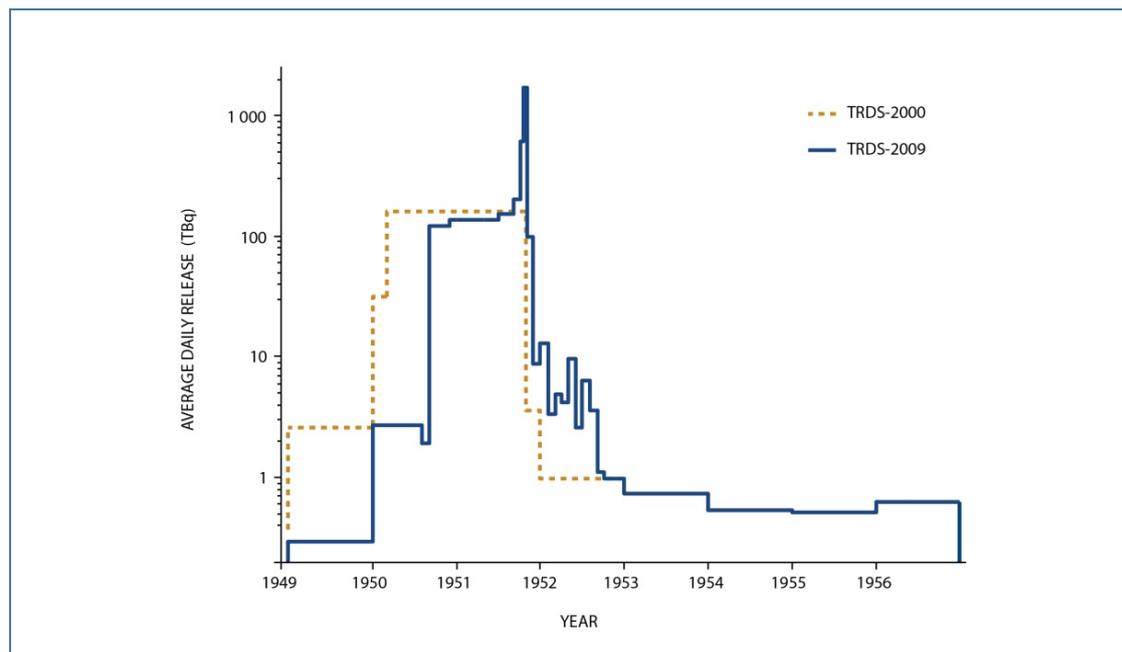
31. In September 1957, a tank with high-level waste exploded and discharged  $7.4 \times 10^{16}$  Bq into the atmosphere. The fallout from the radioactive plume formed the EURT. About 66% of the activity was  $^{144}\text{Ce}+^{144}\text{Pr}$ ; 25% was  $^{95}\text{Zr}+^{95}\text{Nb}$ ; 5.5% was  $^{90}\text{Sr}+^{90}\text{Y}$  and 0.04% was  $^{137}\text{Cs}$  [A19, B2, J8].

Table 3. Amounts of radionuclides that entered Techa River with routine and accidental releases (in soluble form and adsorbed on solid particles) for particular calendar periods, as reconstructed [S12]

Nuclide	Routine release in $\text{TBq d}^{-1}$ (September 1950–April 1951)			Accidental release in $\text{TBq d}^{-1}$ (8–12 October 1951)		
	In solution	On solid particles	Total	In solution	On solid particles	Total
$^{90}\text{Sr}$	2	0.7	2.7	50	200	250
$^{89}\text{Sr}$	18	6	24	30	120	150
$^{137}\text{Cs}$	16	0	16	50	200	250
$^{106}\text{Ru}$	6	11	17	60	240	300
$^{144}\text{Ce}$	0.2	5	5.2	550	2 200	2 750
$^{85}\text{Zr}$	2.5	4	6.5	100	400	500
$^{85}\text{Nb}$	3.7	6	9.7	150	600	750

Figure I. Previous (TRDS-2000) and new (TRDS-2009) estimates of dynamics of total activity of radioactive releases from Mayak Production Association into the Techa River in 1949–1956 (according to [D16])

Averages for one-month periods are given for October 1951–September 1952



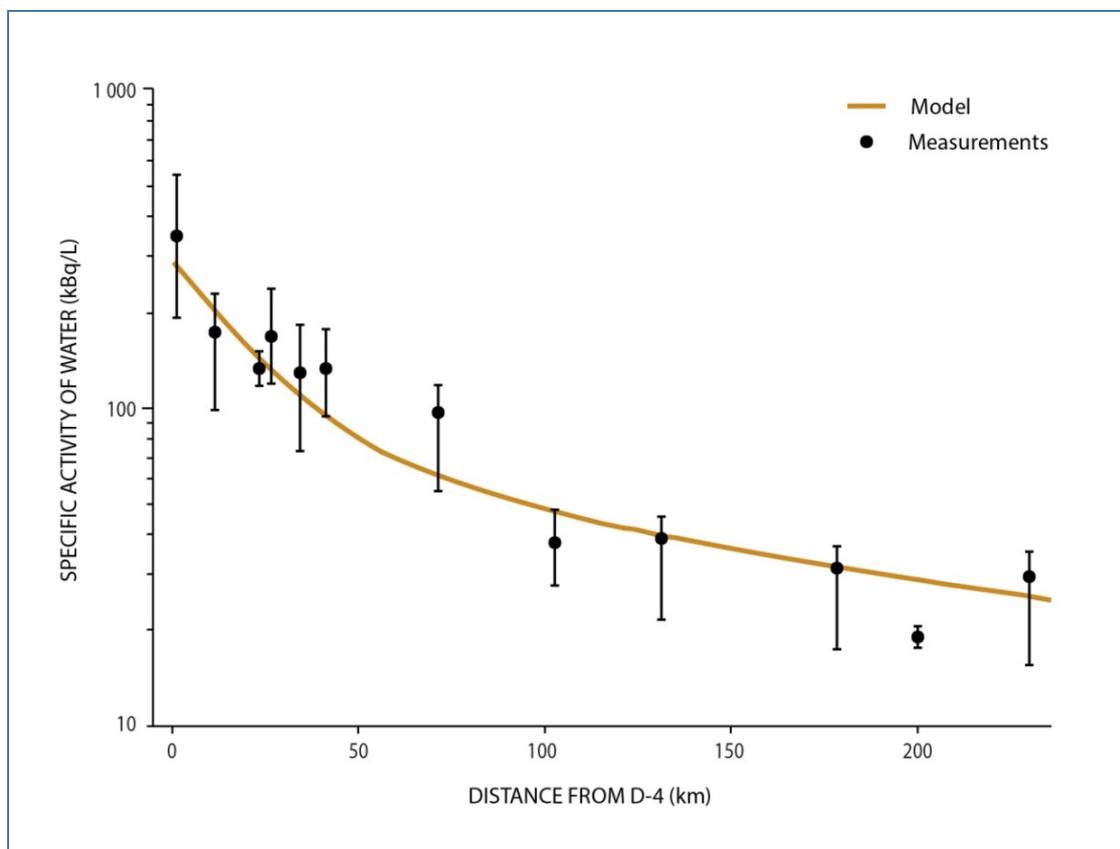
### (b) Environmental radionuclide levels

32. The first data on environmental contamination in the area adjacent to the Mayak Production Association in the early 1950s had been presented in archived documents, which were later published in peer-reviewed journals [A11, A12, I6]. The level of river water contamination decreased with distance from the point of release due to dilution with non-contaminated water, sedimentation of suspended particles in up-river ponds and sorption of radionuclides by bottom sediments and floodplain soils along the river.

33. Models describing radionuclide transport in the Techa River were developed to evaluate the concentration of particular radionuclides in the water, bottom sediments and flooded soils, for the initial period of contamination (1949–1951) when environmental monitoring data were scarce [M5, S10, S12, V6]. A simple model described in a study by Vorobiova and Degteva [V6] was used in the TRDS-2000 for dose reconstruction purposes. An improved model, developed after the TRDS-2009, correlates the revised parameters of the source term and available historical data on environmental contamination [S12]. The model output provides concentrations of all source-term radionuclides, including short-lived radionuclides in the river water, bottom sediments and floodplain soils at different distances from the site of radioactive releases. The outputs of the model show good agreement with historical measurements (figure II).

Figure II. Specific (total beta) activity of water in relation to distance along free-flowing Techa River in 1951 (according to [S12])

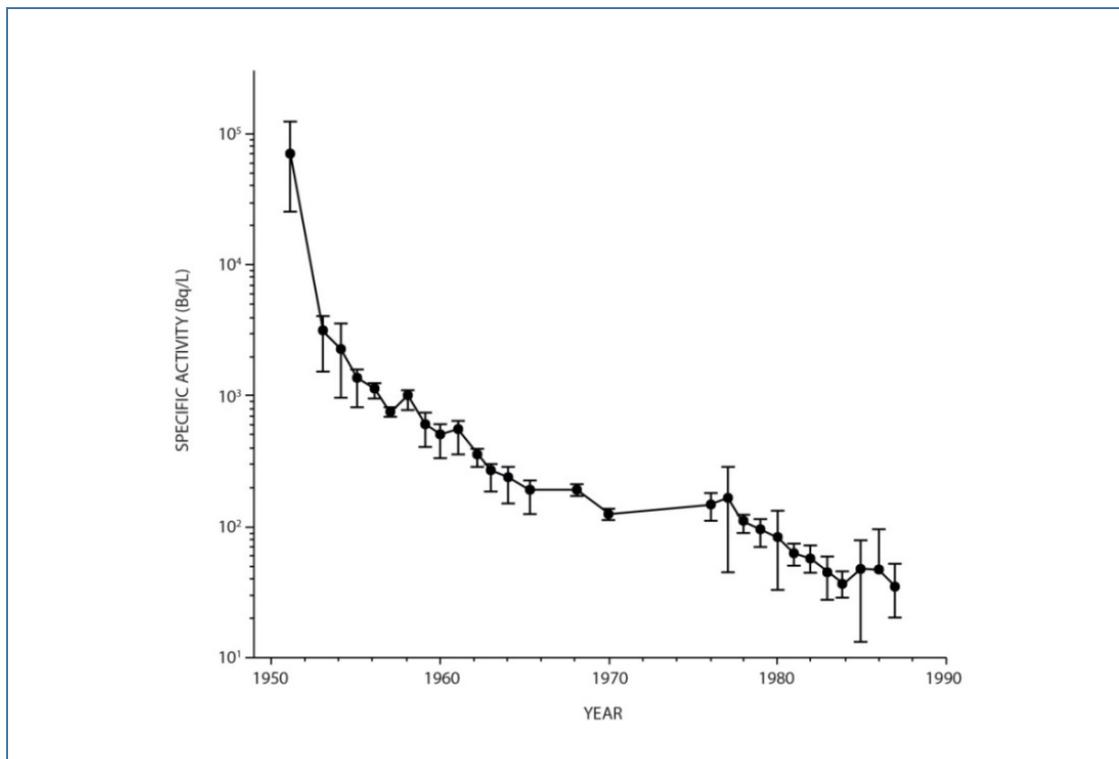
D-4 is the designation of dam number 4 located at 7 km from the release site and separated the free-flowing Techa River from up-river ponds. Vertical bars indicate standard deviations of measurements



34. Temporal changes that occurred in contaminated areas is described in the scientific literature [B4, M4, V6, V7]. Figure III shows that the specific activity of water decreased with time as a result of reduction and subsequent cessation of discharges and of radioactive decay of radionuclides [T14]. Since the 1970s, river water contamination was predominantly due to  $^{90}\text{Sr}$ , and the concentration of  $^{137}\text{Cs}$  in water was an order of magnitude less [M4].

35. A fairly rapid decrease in the levels of radioactive contamination was observed in the EURT after 1957 due to decay of  $^{95}\text{Zr}$ ,  $^{95}\text{Nb}$ ,  $^{106}\text{Ru}$  and  $^{144}\text{Ce}$  [A19, B2, J8]. Since the fifth year after the accident, soil contamination was almost completely due to  $^{90}\text{Sr}$ .

Figure III. Specific (total beta) activity of water in Techa River measured in different calendar years near the reference settlement Muslyumovo located at 78 km from release site [T14]



### (c) The Techa River Dosimetry System (TRDS)

36. The TRDS version created in 2000 (TRDS-2000) was used initially to derive risk coefficients for TRC members [K15, K16, K17]. An improved version, TRDS-2009, introduced in 2009, calculates deterministic values of dose estimates and is currently used to derive risk estimates [D5, K18, P12, S3]. TRDS-2017, under preparation, will incorporate improvements made since 2009, including the use of a two-dimensional Monte-Carlo procedure that will result in the calculation of stochastic dose estimates.

37. Dose reconstruction in the TRDS was based on the use of a large number of measurements of long-lived radionuclides in the human body [K12, K14] and in the environment, and also on the measurements of exposure rates performed directly in places where people lived. The traditional approach of analysing all steps of the pathway of exposure was used as a backup only when other approaches were exhausted, in particular for reconstruction of doses from short- and intermediate-lived radionuclides released into the Techa River in 1949–1951 [D9, D10, D12, D13].

38. The TRDS calculates doses from the major routes of environmental exposure: external exposure from staying (mainly living and working) in the areas along the banks of the Techa River and in the region of the EURT; and internal exposure from intakes acquired along the banks of the Techa River and in EURT villages. Individual residence history data are used for dose calculations. The time of the end of dose accumulation is also determined individually (e.g. date of death or date of emigration).

#### (d) External exposure

39. The absorbed doses due to external exposure were estimated on the basis of dose measurements of gamma rays (a) along the banks of the river; (b) on the shore within a few hundred metres from the water in specified areas of villages; and (c) inside some of the houses [D8]. Outdoor measurements were conducted periodically at 25 monitoring posts along the shoreline of the river. Dose rates along the river decreased significantly with distance from the discharge point. Measurements were also performed at different distances from the shoreline in a residential area located on the upper part of the Techa River [D12, D13] because substantial external exposure occurred when people were in the contaminated floodplain [D12, D13].

40. The ratios between outdoor and indoor air kerma rates were obtained from a 1954 survey of 10 houses, and were used to estimate the indoor absorbed dose in air. The length of time spent on the river bank and the indoor occupancy factors were derived from observational data obtained in the 1950s. For hours spent at each of those three locations, age-specific values were used [D10]. The occupancy factors are based on limited historical data, and the uncertainty in external dose estimation due to these factors is unlikely to be improved after more than 50 years.

41. The TRDS provides average external dose estimates for groups of subjects of the same age who lived at the same time in the same location on the Techa River. External doses significantly decreased with distance from the site of release (figures IV and V). The external dose rate was highest in 1951, and then it decreased with time.

42. The cumulative absorbed dose to an organ  $o$  of a resident who lived at location  $L$  on the Techa River in the period from  $t_{begin}$  to  $t_{end}$  was calculated according to the following equation:

$$D_{o,L}^{ext} = \int_{t_{begin}}^{t_{end}} P_{riv}^L(t) [T_1^{age} + R_{out/riv}^L (T_2^{age} + R_{in/out} T_3^{age})] A_o^{age} dt$$

where:

$D_{o,L}^{ext}$  = absorbed dose of external exposure in organ  $o$  accumulated to individual who lived at location  $L$  in the period from  $t_{begin}$  to  $t_{end}$ ;

$P_{riv}^L(t)$  = absorbed dose rate in air near the river shoreline at location  $L$  in year  $t$ ;

$R_{out/riv}^L$  = ratio of dose rate in air outdoors at homes to the dose rate by the river at location  $L$ ;

$R_{in/out}$  = 0.45 - ratio of dose rate indoors to that outdoors (derived from historical exposure-rate measurements);

$A_o^{age}$  = conversion factor from absorbed dose in air to organ  $o$  (function of age);

$T_1^{age}$ ,  $T_2^{age}$ ,  $T_3^{age}$  = periods of time spent by residents on river bank, outdoors and indoors, respectively (functions of age); TRDS-2009 includes the dose-conversion factors for 23 organs/tissues [E1, P4, S5, S15].

43. Dose rates in air above the river shoreline  $P_{riv}^L(t)$  are shown in figures IV and V [S10]. The dose rate in air at the river bank was evaluated with the use of data on radionuclide concentrations in the floodplain soil for all villages located at different distances from the release site [S10, S12] and coefficients obtained by Monte-Carlo simulations of air kerma [E1]. The modelled dose rates along the river (figures IV and V) depend on site-specific contamination of the river shore determined by topography, and soil and hydrological properties. A notable peak in the dose rate at a distance of 50 km (figure IV) is determined by a presence of a blind fork, which resulted in increased sorption of radionuclides in this stagnant reservoir. The dip in the dose rate at 202 km (figures IV and V) is determined by the fact that the floodplain in this location was washed with clean water from a non-contaminated tributary of the Techa River. Modelled values within the uncertainty range are in reasonable agreement with the data of the systematic monitoring of exposure rate, which was carried out on the Techa River banks from the summer of 1952 (figure V).

Figure IV. Dose rate in air at Techa River shoreline at different distances downstream from the site of radioactive releases derived from the Techa River transport model and source terms for different months of 1951 [S10]

Modelled dose rates depend on site-specific contamination of the river shore determined by local topography and hydrological properties

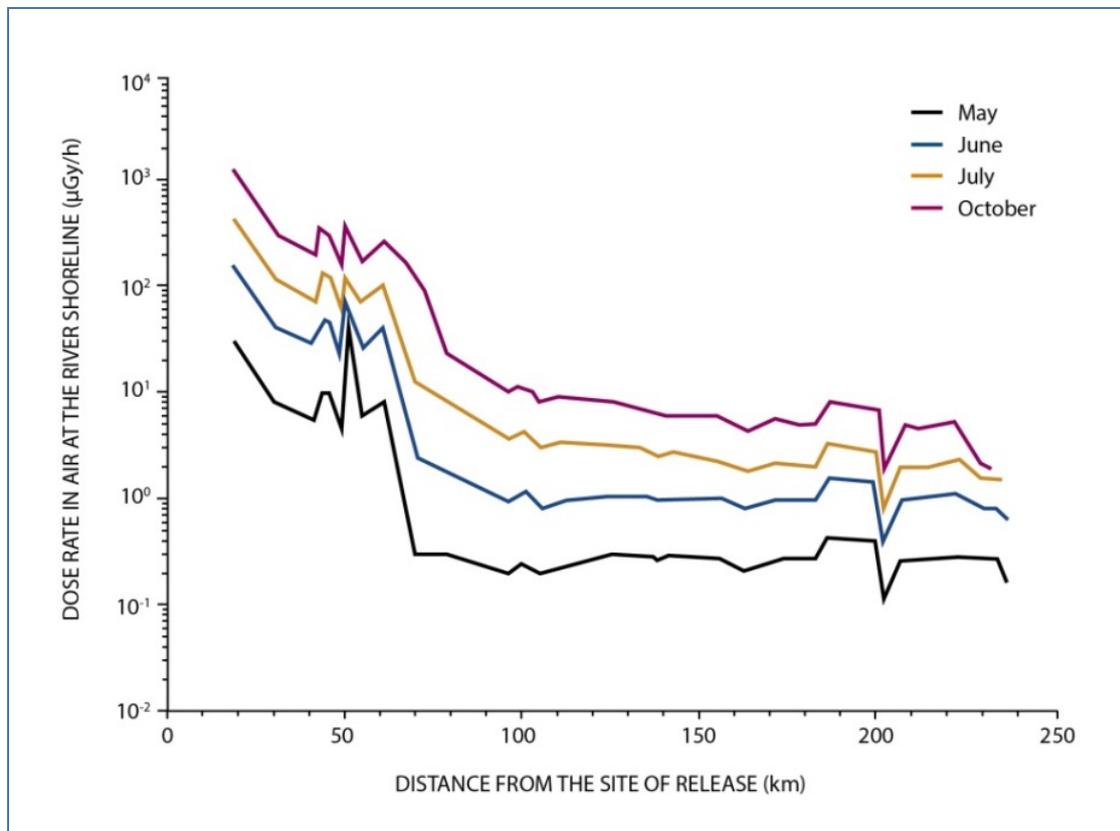
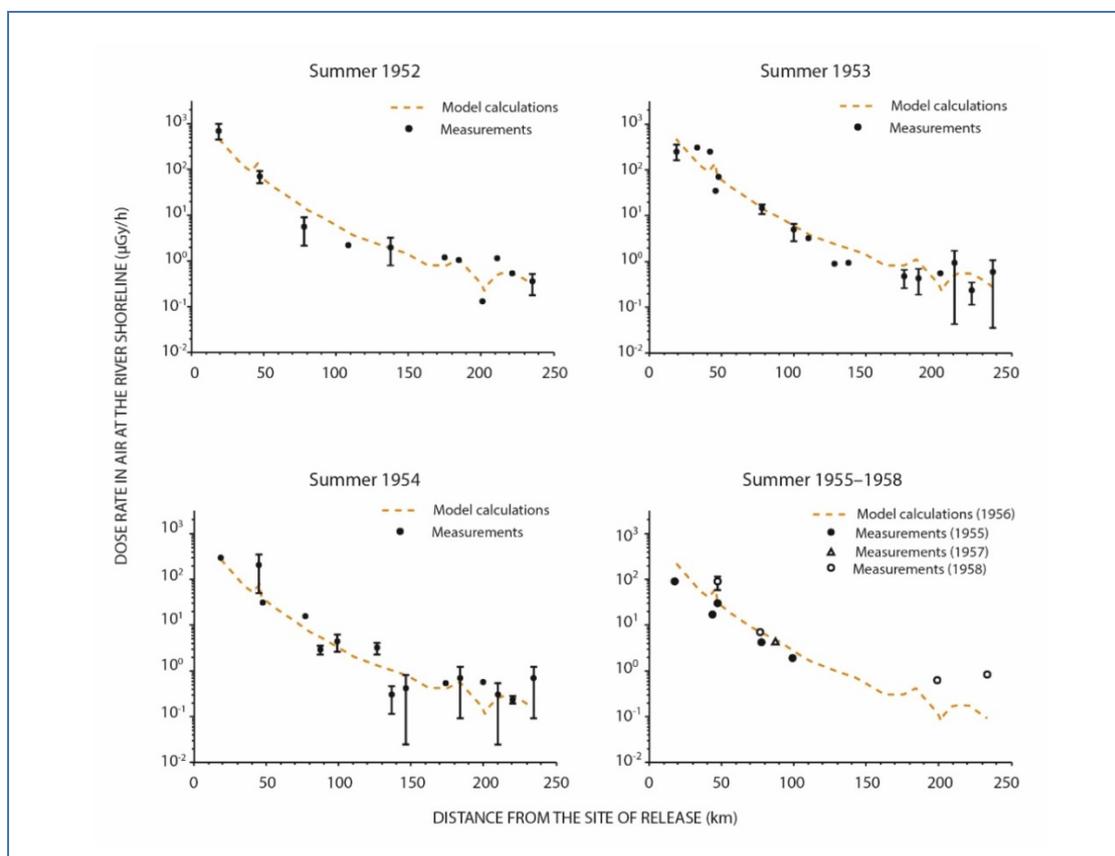


Figure V. Modelled and measured dose rate in air at Techa River shoreline at different distances downstream from site of radioactive releases in 1952–1958 [S10]

Vertical bars indicate standard deviations for repeated measurements, single measurement results are shown without uncertainties



44. Outdoor-to-river bank ratios ( $R_{out/riv}^L$ ) were derived from exposure-rate measurements performed at different distances from the shoreline in different locations [V7]. The village-average values of  $R_{out/riv}^L$  were used in the TRDS.

45. Parameters  $T_1^{age}$ ,  $T_2^{age}$ ,  $T_3^{age}$  were derived from data from the 1950s of typical lifestyle patterns for different age groups of the Techa riverside residents [D13]. Age-dependent conversion factors from absorbed dose in air to absorbed dose in organs ( $A_0^{age}$ ) were taken from the literature [E1, P4].

46. Three methods were used for validation of external doses on the Techa River: the luminescence method with bricks [B17, J1, T5, W9]; the electron paramagnetic resonance (EPR) method with human teeth [D11, S14]; and the fluorescence in situ hybridization (FISH) method with human lymphocytes [B8, D11, V9]. Luminescence measurements of anthropogenic dose in bricks from old buildings located on the Techa River banks were converted to cumulated dose in air and the results were found to be consistent with calculations performed using the TRDS parameters [T5, T6, U2]. EPR- and FISH-based estimates of external dose for residents of settlements located in the upper reaches of the Techa River were consistent with the TRDS-based absorbed doses in tooth enamel and muscle [D17].

47. For reconstruction of external dose on the EURT, dose rates in air per unit-deposition density of  $^{90}\text{Sr}$  were used. These values and data on original soil contamination by  $^{90}\text{Sr}$  for different settlements were published by Bakurov et al. [B2].

### (e) Internal dose reconstruction

48. Internal exposure was due to ingestion of radionuclides through drinking river water and consuming local foodstuffs. An extraordinarily powerful flood in April to May 1951 led to the radioactive contamination of the land adjacent to the river. The flood-lands were used by some of the inhabitants for cattle breeding and for making hay. Up to this point radionuclides had been ingested mainly with water; now, contaminated food began to play a role, especially milk and vegetables from flooded kitchen gardens.

49. The reconstruction of internal dose relies strongly on the results of measurements of  $^{90}\text{Sr}$  in residents of the Urals, which includes the results of nearly 10,000 post-mortem measurements of radionuclide concentration in bone samples obtained in 1951–1993, the results of in vivo measurements of surface-beta activity of anterior teeth for 17,500 persons (1959–1997), and measurements of  $^{90}\text{Sr}$ -body burden by means of a unique whole-body counter for 20,500 persons (1974–1997) [D13, K12, K14, T15].

50. According to a basic approach to internal dose estimation, the absorbed dose in organ  $o$  accumulated through calendar year  $Y$  for a resident who lived at location  $L$  on the Techa River in the period from  $t_{begin}$  to  $t_{end}$  is calculated as:

$$D_{o,L}^Y = \sum_{y=t_{begin}}^{t_{end}} \sum_r I_{y,r,L}^*(\tau_i) DF_{r,o,Y-y}(\tau_i)$$

where

$D_{o,L}^Y$	=	absorbed dose of internal exposure in organ $o$ accumulated through calendar year $Y$ by individual $i$ who lived at location $L$ in the period from $t_{begin}$ to $t_{end}$ ;
$y$	=	year of intake of radionuclides;
$r$	=	identifier of ingested radionuclide ( $^{89}\text{Sr}$ , $^{90}\text{Sr}$ , $^{95}\text{Zr}$ , $^{95}\text{Nb}$ , $^{103}\text{Ru}$ , $^{106}\text{Ru}$ , $^{137}\text{Cs}$ , $^{141}\text{Ce}$ , $^{144}\text{Ce}$ );
$\tau_i$	=	the age of individual $i$ in year $y$ ;
$I_{y,r,L}^*$	=	intake function (Bq) for year $y$ , radionuclide $r$ , and location $L$ (function of age $\tau$ , related to $y$ );
$I^*$	=	$I \times \zeta_i$ , where $\zeta_i$ is a modifier predetermined for individual $i$ equal to $1$ or $IMR_i$ or $HSR_i$ ;
$DF_{r,o,Y-y}$	=	conversion factor ( $\text{Gy Bq}^{-1}$ ) for dose accumulated in organ $o$ in year $Y-y$ from intake of radionuclide $r$ in year $y$ (function of age, related to $y$ ); TRDS-2009 includes the dose-conversion factors for 23 organs/tissues [E1, P4, S5, S15].

51. The intake function  $I_{y,r,L}$  is a complex, time-dependent function derived from a combination of data from tooth beta counting and the whole-body counter. The village-average intake function  $I_{y,r,L}$  for each year  $y$  is calculated as:

$$I_{y,r,L}(\tau) = I_{y,R}^{Sr90} \times \alpha_{\tau,R}^{Sr90} \times f_L^{Sr90} \times R_{y,r/Sr}^L,$$

where

$$I_{y,R}^{Sr90} = \text{}^{90}\text{Sr intake for adult residents of the reference settlement in year } y \text{ (Bq);}$$

$$\alpha_{\tau,R}^{Sr90} = \text{}^{90}\text{Sr intake for the other age group } \tau \text{ relative to that for adults living in the reference settlement } R;$$

$$f_L^{Sr90} = \text{ratio of } ^{90}\text{Sr intake for location } L \text{ to } ^{90}\text{Sr intake for residents of the reference settlement;}$$

$$R_{y,r/Sr}^L = \text{ratio of radionuclide } (r)\text{-to-}^{90}\text{Sr intake for location } L \text{ in year } y.$$

52. The  $^{90}\text{Sr}$  intake in the reference settlement  $R$  ( $I_{y,R}^{Sr90}$ ) during the first years ( $y$ ) after the beginning of the discharges was reconstructed using the data on  $^{90}\text{Sr}$  measurements in teeth, and supplementary data on water consumption and diet composition for adults and children, and measurements of  $^{90}\text{Sr}$ -body burden in adults [T15]. A new method of solving an inverse problem was developed by using an integral equation associating  $^{90}\text{Sr}$ -intake dynamics with the age-dependency of  $^{90}\text{Sr}$  content in teeth. This allowed the assessment of the relative intake function for adult residents of the reference settlements during the period of maximum intake [Z2]. Parameters of the integral equation, describing ratios of semi-annual  $^{90}\text{Sr}$  intake for different age groups to that for adults living in the reference settlement, were evaluated on the basis of data on the daily composition of diet [T15].

53. The  $^{90}\text{Sr}$  intake depends on the village of residence, which is actually a surrogate for the source of drinking water (contaminated river/wells). The assessment of the village-average  $^{90}\text{Sr}$  intake is based on the assumption that the ratio between  $^{90}\text{Sr}$  intake in a particular settlement and  $^{90}\text{Sr}$  intake in Muslyumovo is equal to the ratio between the average value of  $^{90}\text{Sr}$ -body burden for the particular settlement and the corresponding value for Muslyumovo, obtained on the basis of internal radiation dose assessment with whole-body counter.

54. Radionuclides other than  $^{90}\text{Sr}$  were also released into the Techa River, including  $^{137}\text{Cs}$  and shorter-lived uranium-fission products ( $^{89}\text{Sr}$ ,  $^{95}\text{Zr}$ ,  $^{95}\text{Nb}$ ,  $^{103,106}\text{Ru}$ ,  $^{141,144}\text{Ce}$ ). Because river water was the main source of internal exposure, ratios of radionuclide concentrations to that of  $^{90}\text{Sr}$ , calculated using the Techa River model were used for assessment of their intakes with river water [D9, D10]. In addition, the intake of  $^{137}\text{Cs}$  with cows' milk was considered in TRDS-2009 because it became a major pathway after the flood in April 1951 [T14].

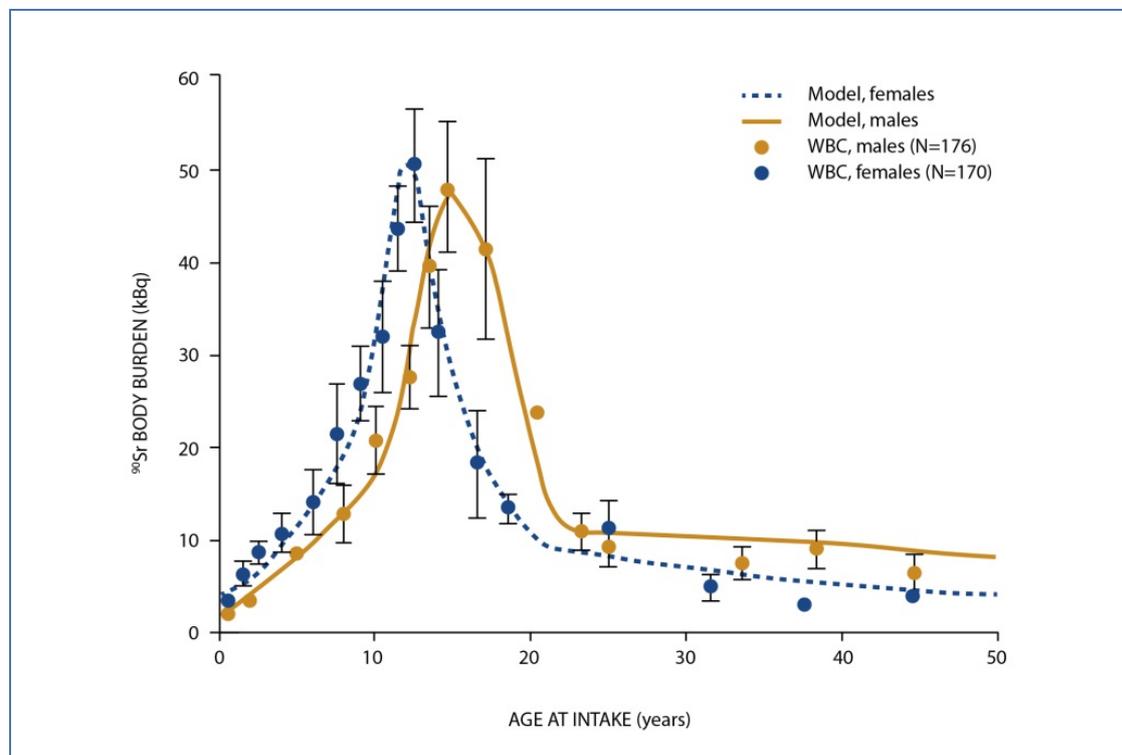
55. Radionuclide intakes normalized per  $1 \text{ Ci/km}^2$  of  $^{90}\text{Sr}$  deposition in the EURT area were derived from measurements of radionuclides in local foodstuffs in reference settlements [T13]. Data on  $^{90}\text{Sr}$  deposition for other EURT settlements were used to reconstruct the intake for the residents [B2].

56. Dose-conversion factors representing absorbed dose in organ per unit intake ( $DF_{r,o,y-y}$ ) were calculated using biokinetic models (describing time-dependent retention of radionuclide in source-tissues) and dosimetric models (describing energy deposition in target-tissue from radiation emitted by source-tissues). The dosimetric model of bone tissue was used for calculation of dose absorbed in red bone marrow (RBM) from  $^{89,90}\text{Sr}$  incorporated in the skeleton [S24]. Dose conversion factors for other radionuclides were based on the models from the ICRP Publication 67 [I4].

57. A special age- and sex-dependent biokinetic model was used for  $^{89,90}\text{Sr}$  dose calculation [S8, S13]. This model has a similar structure to the ICRP-67 model (described by Leggett [L3]) and is based on the same approach. The difference is that the model parameters were evaluated separately for men and women in a wider age range (0–80 years). The Techa River data on  $^{90}\text{Sr}$  in humans, recent data on age- and sex-dependencies of calcium content in the skeleton, and data on bone remodelling were used for parameter evaluation. Figure VI shows that model calculations, corresponding to intake levels in Muslyumovo, satisfactorily describe  $^{90}\text{Sr}$ -body burdens obtained from whole-body counter radiation monitoring. The age peaks in  $^{90}\text{Sr}$ -body burden correspond to the maximum in skeletal calcium accretion rate associated with the growth spurt at puberty (13 years for females and 15–17 years for males).

Figure VI. Age-dependencies in  $^{90}\text{Sr}$ -body burdens for residents of Muslyumovo 30 years after beginning of intake (according to [S13])

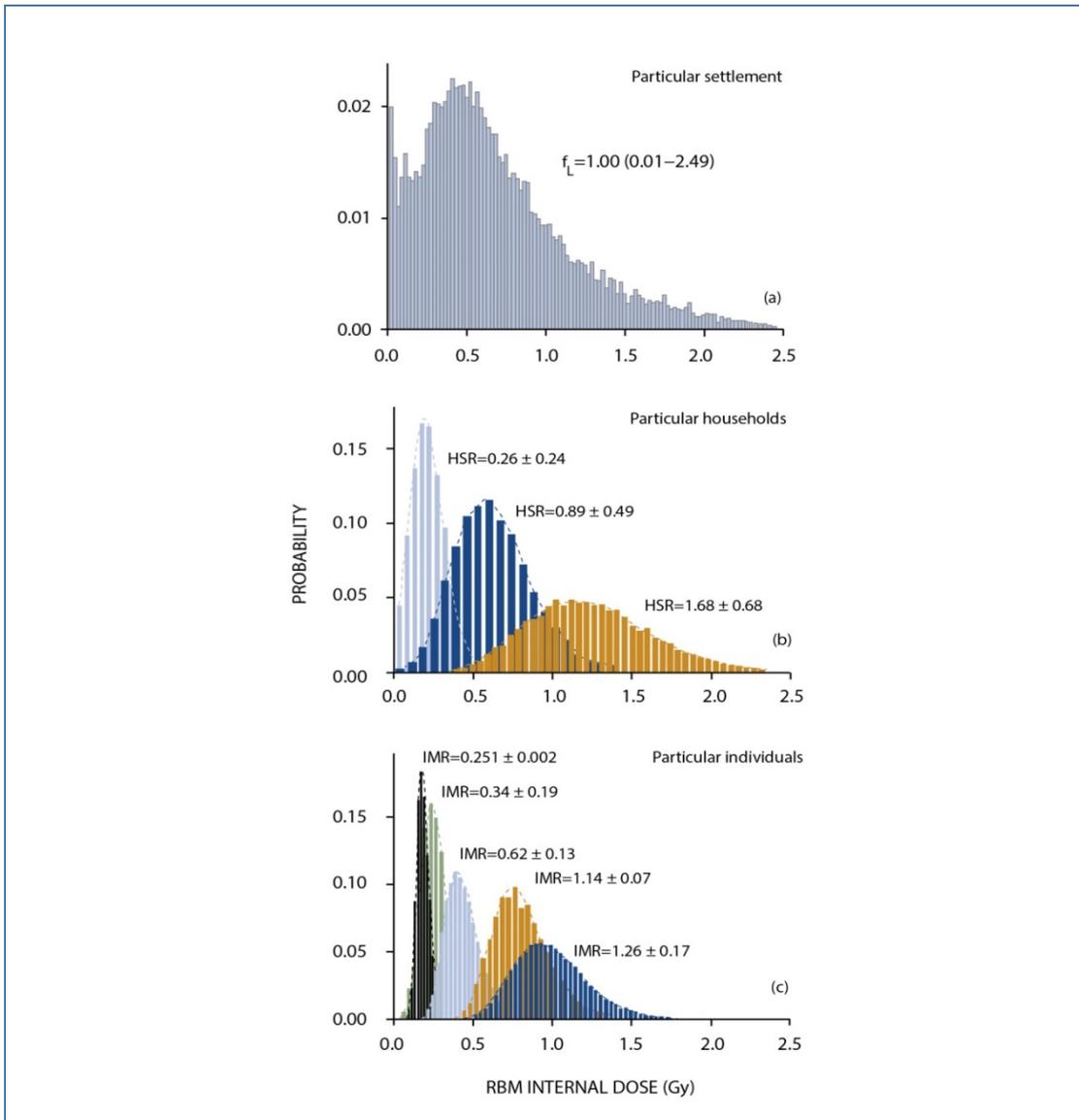
Calculations obtained with the age- and sex-dependent model are compared with whole-body counter data averaged for males and females; the peak ages correspond to the age at growth spurt at puberty (13 years for females and 15–17 years for males)



58. TRDS-2009 includes different protocols for the calculation of internal dose depending on the quality of individual input data (figure VII). For persons with whole-body counter dosimetry, the value of individual-to-model ratio (IMR) is determined as the average of the ratios of an individual's whole-body counter radiation measurements to the respective reference-model values. IMRs serve as age- and time-normalized values, which permit reduction in uncertainty in internal dose estimates. The uncertainty in the IMR value depends on the number of measurements with whole-body counter and their dispersion for a particular person. For those who do not have individual measurements, the value of household-specific relationship (HSR) can be determined as the average of IMRs for measured members of a household. The refinement of individual internal dose is based upon IMR and HSR for 27% of the entire TRC [D14, S9].

Figure VII. Probability distributions of estimates indicating uncertainties in RBM internal doses for residents of Muslyumovo: (a) village-average dose estimate used in TRDS-2000; (b) household-specific dose estimates; and (c) individual dose estimates (according to [D14])

HSR: household-specific relationship, IMR: Individual-to-model ratio



### (f) Medical exposure

59. TRC members were subjected to routine medical exposure in regional hospitals of rural areas of Chelyabinsk and Kurgan Oblasts similarly to other residents. Routine medical diagnostic X-ray examinations were conducted with a frequency of 570–620 procedures per year per 1,000 persons, and resulted in annual effective doses of 0.6–0.8 mSv per person [P8]. The doses from routine X-ray procedures for TRC members were, on average, the same as for other people in the region.

60. At the same time, TRC members were invited to the URCRM clinic for special surveys, which included X-ray examinations. About 22% of TRC members (6,411 persons) received diagnostic X-ray examinations over the period 1956–2000. Those who were invited to the clinic were more likely to have health problems related to chronic radiation exposure. Therefore, there is a possibility that their cumulative doses of medical exposure dose are related to individual radiation dose from environmental exposure.

61. Reconstruction of individual medical radiation doses at the URCRM clinic is based on data on X-ray diagnostic procedures, including fluoroscopy, available for each person examined. Approximately 1,000 TRC members underwent fluoroscopy of the stomach. Organ dose per typical X-ray procedure was calculated with the use of a phantom. The calculation took into account the X-ray examination parameters characteristic for the X-ray machines used at the URCRM clinic [D15, S11]. Individual doses from medical exposure varied substantially from person to person, and were different for different organs (table 4). Due to the skewed distribution, the mean was higher than the 75th percentile for some organs. However, those doses are not large enough to distort the excess relative risk\* (ERR) estimate per unit dose substantially among residents with relatively high cumulative doses. In particular, only 1.5% of TRC members received a stomach dose exceeding 100 mGy, and medical exposure to the RBM contributed only 5% to the overall dose [D15, S11].

Table 4. Distribution of absorbed dose due to medical exposure of TRC members at the URCRM clinic [D14, D15]

Organ	Absorbed dose (mGy)			
	Mean	Median	25th percentile	75th percentile
Bone marrow	27	16	1.3	34
Bone surface	37	17	2.4	42
Breast	11	6.1	1.1	12
Small intestine	24	4.6	0.03	19
Upper large intestine	21	4.4	0.03	21
Lower large intestine	12	1.6	0.002	7.4
Lungs	33	20	3.2	40
Stomach	33	23	0.3	38

### (g) Results of dose reconstruction

62. The mean annual stomach dose estimates for the Techa River incidence cohort [D5] based on TRDS-2009 are shown in table 5. The annual stomach dose peaked in 1951 and reached 28 mGy a<sup>-1</sup>. From 1951 to 1960, the dose rate decreased by two orders of magnitude and the decline continued also after that, at a slower rate. Annual average doses in 1951 decreased with distance from the release site, from approximately 200 mGy a<sup>-1</sup> in the upper reaches to about 20 mGy a<sup>-1</sup> in the middle course and roughly 4 mGy for the lower parts of the river [P12]. The mean cumulative stomach dose for TRC members was 43 mGy and the median was 12 mGy, with a maximum of approximately 1 Gy [D7].

63. The mean annual RBM doses for the Techa River leukaemia incidence study based on TRDS-2009 are also shown in table 5. The RBM dose rate showed a similar time trend to that of the stomach dose, but the levels were substantially higher, and decreased more slowly with time. In 1951, the annual doses were close to 400 mGy a<sup>-1</sup> in the upper reaches, approximately 200 mGy a<sup>-1</sup> in the middle course and roughly 50 mGy a<sup>-1</sup> for the lower parts of the river [P12]. Although the cumulative doses to some individuals in the TRC are substantial, they were accumulated over many years of exposure. The external and internal dose rates for even the most-exposed individuals were more than two orders of magnitude lower than the current definition of low dose rate of 0.1 mGy/min. The mean cumulative RBM dose for TRC members was 0.43 Gy and the median was 0.27 Gy. The maximum RBM dose in the TRC exceeded 5 Gy [D7].

Table 5. Mean dose rates for the period (1950–1980) of the Techa River incidence studies [D5, K18]

Calendar year	Mean absorbed dose rate (mGy a <sup>-1</sup> )	
	Stomach	RBM
1950	5.9	68
1951	28	135
1952	14	60
1953	9.7	50
1954	5.9	38
1955	1.7	27
1956	1.0	21
1957	0.59	17
1958	0.37	14
1959	0.36	11
1960	0.31	9.4
1970	0.06	2.3
1980	0.02	0.8

64. In RBM dose, the relative contribution of external exposure to the internal exposure was dependent on the distance from the releasing point since <sup>90</sup>Sr, the major internal-exposure contributor to RBM dose, reached areas far down the river. In settlements located in the upper Techa region (within about 75 km from the release site), external exposure was the main source of RBM dose. In the lower Techa region, more than 50% of RBM dose was from internal exposure [D12, D13].

65. TRDS-2009 included the calculation of doses from confounding exposure due to residence on the EURT area for 16% of the TRC (other cohort members did not reside in the EURT area). For the average cohort member, most of the dose came from residence in villages along the Techa River, and the contribution from EURT was less than 1% [D7].

#### (h) *Uncertainties of dose estimations*

66. Preliminary analysis based on a Monte-Carlo simulation, assuming different distributions for each parameter, gave an estimated ratio of the 95% range of values of individual doses. The magnitude of uncertainties varied depending on location and duration of individual exposure, but the results from reference individual calculations indicated that the range of uncertainty was about a factor of four to five for the external doses [N6, N8].

67. Regarding external exposure, a sensitivity analysis indicated that key parameters contributing to the uncertainty were outdoor/river bank dose rate ratio (45%) and dose rate at the river bank in 1951 (20%). Major efforts were recently undertaken to decrease the uncertainty in these parameters [S10].

68. Internal dose calculations have uncertainties associated with the biokinetic and dosimetric models used. Study-specific conversion factors were used instead of standard factors and the quantities reported here are from original publications and not always consistent across studies. The main source of uncertainty is the inter-individual biological and behavioural differences between the study subjects [S13]. For internal doses estimated using the TRDS-2000, the range of uncertainty (ratio of the 95% range of values of the dose distribution) depended on sources of drinking water, which were specific for different riverside settlements [N6]. For villages with the Techa River as the sole source of drinking water, the range of uncertainty was a factor of 20 to 30. For villages with mixed sources (contaminated river and non-contaminated wells), the ratio of the range could be over two orders of magnitude. This indicated that the uncertainty in internal dose could be greatly reduced by using the individual whole-body counter results. This was later realized in TRDS-2009 [D14, S9]. In other words, the reconstruction of internal dose relies strongly on the results of  $^{90}\text{Sr}$  measurements taken from about one third of TRC members.

69. An approach has been developed which identifies the nature of the various input parameters and calculation methods incorporated in the TRDS-2009, and a stochastic calculation model has been prepared to estimate the uncertainties in the dose estimates [N7]. This approach is based on a two-dimensional Monte-Carlo analysis [N8, N9]. A two-stage Monte-Carlo computer code is used; its output agrees with the deterministic version of TRDS-2009 and it can separate the influence of shared/unshared parameters and uncertainties due to grouping/measurement (Berkson/Classical error\*), for various exposure pathways. The first results for RBM internal dose by Napier et al. [N7] showed that the individual dose estimates from the Techa River appeared to be log-normally distributed with a geometric standard deviation of about 2 to 2.5; uncertainties in individual dose estimates from EURT have a geometric standard deviation of about 3 (but the doses are much smaller). Generally, the uncertainties in cumulative stomach dose are less than those for RBM. While both organs are exposed to similar external doses, the individual variability in stomach dose from an intake is small but the individual variability in deposition and retention in bone tissues over long time periods increases the uncertainties in bone marrow dose, although dose to both organs remains strongly correlated.

### (i) *Biological dosimetry*

70. The first cytogenetic studies of the Techa riverside residents were performed 20 years, and then 40–50 years, after the onset of exposure. The findings showed an increased frequency of unstable chromosome aberrations (dicentrics and rings) in peripheral blood lymphocytes of exposed persons compared to unexposed persons of the same sex and age. However, no dependence on the RBM dose was found [A9, P6, V4, V8].

71. The frequency of stable aberrations (translocations) was first estimated in 1993 for residents of the middle and lower Techa regions [A5]. No demonstrable difference was found between 34 exposed and 10 unexposed (control) subjects [A5]. The next study was based on a more representative sample of persons who lived in the upper and middle Techa regions (73 exposed and 39 unexposed participants) and showed a significantly increased mean frequency of translocations among exposed persons compared to the controls ( $12.8 \pm 1.5$  and  $5.7 \pm 1.0$ , respectively, per 1,000 cells) [B8]. The highest translocation frequency was observed in persons who had lived permanently in the Techa riverside villages during the maximum radioactive release (1950–1951) [B8].

72. In 2009–2012, an international study using the FISH method examined two exposed groups: 18 residents of the middle Techa region, who were exposed predominantly due to ingestion of  $^{89,90}\text{Sr}$ ; and 20 residents of the upper Techa, who were exposed to both external and internal radiation [V9]. In the first group, a significant linear relationship between translocation frequency and individual RBM dose from incorporated  $^{89,90}\text{Sr}$  was found [V9]. The slope of  $0.006 \pm 0.002$  translocations/GE cell/Gy found in this group allowed quantification of the translocations caused by exposure to  $^{89,90}\text{Sr}$ . Individual doses from external exposure estimated from the FISH results for the second group ranged up to 2.1 Gy. The average FISH-based dose of external radiation for the second group was estimated as  $0.48 \pm 0.16$  Gy [V9].

73. The main objective of the recent biodosimetry studies was validation and verification of external dose estimates by comparing the TRDS-based doses for TRC members with the results of two independent methods: EPR measurements of tooth enamel (I) and FISH analysis of chromosome translocations in circulating lymphocytes (II). The main issue in the application of the EPR and FISH methods for external dose reconstruction for the Techa riverside residents was the contribution of strontium radioisotopes incorporated in teeth and bones [D11, D17]. A methodology for adjustment for the effects of  $^{89,90}\text{Sr}$  on the FISH results was developed [V9]. In order to estimate and subtract doses from incorporated  $^{89,90}\text{Sr}$ , the EPR and FISH assay measurements of  $^{90}\text{Sr}$ -body burdens were used and  $^{90}\text{Sr}$  concentrations in dental tissue estimated by the luminescence method [D17, S14].

74. Comparative analysis of EPR and FISH results in residents of the upper reaches of the Techa River during the period of radioactive discharges (133 persons) was performed in 2015 [D17]. The dose estimates derived from EPR and FISH measurements and adjusted for the confounding strontium were consistent: the mean values tended to decrease with distance along the river from 0.51–0.55 Gy for the villages located close to the site of radioactive release to 0.13–0.16 Gy for the more distant villages. The upper bound of individual estimates for both methods was estimated as 2.2–2.3 Gy [D17].

75. The findings from recent biodosimetry studies were used for validation of the TRDS-2009 [D17]. Individual doses were calculated using a TRDS code for each subject in the EPR and FISH studies on the basis of their age at exposure and residence histories. For correct comparison with the EPR- and FISH-based estimates, two sources of exposure accounted for external exposure and internal exposure from  $^{137}\text{Cs}$  incorporated in the subjects' soft tissue. The EPR- and FISH-based estimates were in agreement within the uncertainty bounds the TRDS-based absorbed doses in tooth enamel and muscles. The agreement supported the validity of external doses calculated with the TRDS-2009 [D17].

## 4. Cancer incidence and mortality

76. Analyses of cancer and leukaemia risk for TRC members were performed repeatedly over a long period of follow-up of the cohort [D5, E2, E3, K15, K16, K17, K18, P12, S3]. The first studies [K8, K9] covered 32- and 39-year follow-up periods (1950–1982, 1950–1989) and were limited in terms of quality and completeness of information and of dose estimates [D8, K13]. Despite their limitations, the results of these studies suggested that the mortality from leukaemia and solid cancers increased with increasing radiation dose. Also, they implied that the TRC had future potential to provide quantitative estimates of the risk of chronic low-dose-rate radiation exposure for an unselected general population. Over the subsequent period, the TRC was expanded to include the residents in the riverside villages from 1953 through 1960; and the total number of cohort members has reached about 30,000. The information accumulated in the URCRM as of 2013 included data on cancer cases for TRC members in the catchment area for 1956–2012, and deaths in the two-oblast catchment area for 1950–2007 [S3]. A dosimetry system (TRDS-2000) for the TRC with individual dose estimates was developed. The dosimetry system was improved and updated in 2009 (TRDS-2009) owing to availability of new information on exposure sources and radioactive mixture hold-up time, and also to improvements in the model itself (as described before in the dosimetry section). The internal exposure dose estimation in the TRC study has considerable uncertainties. It should be pointed out that those uncertainties are not fully taken into account in cancer risk estimation. Therefore, caution should be exercised when the magnitude of risk estimate per dose unit is discussed.

### (a) *Solid cancer incidence and mortality*

77. The main methodological features of the TRC study are summarized in tables 6 and 7. Detailed analysis of solid cancer mortality risk for 29,730 subjects over the period 1950–2007 based on the TRDS-2009 was reported in 2013 [S3]. This updated analysis obtained risk estimates of a linear dose response between radiation exposure from the Techa River contamination and cancer mortality consistent with the previous findings [K16]. During the follow-up period, 2,303 solid cancer deaths were registered in the mortality catchment area with 927,743 person-years. For men, lung, stomach and oesophagus cancers were the most frequent causes of cancer death. For women, uterine (corpus and cervix), stomach and breast cancers accounted for the largest numbers of cancer deaths. The ERR for mortality from all solid cancers was 0.061 per 100 mGy (95% CI: 0.004, 0.127).

78. The ERR estimates in the linear dose–response models did not change greatly when the analyses excluded the 22 bone and 73 colon cancers (ERR=0.054 per 100 mGy; P=0.07). These analyses have been performed because the doses to the bone and colon were markedly higher than the stomach doses, which were relevant for most other solid cancers. Doses to the bone surface were markedly higher due to exposure to <sup>90</sup>Sr and other radionuclides, and doses to the colon were higher due to the contribution from short-lived radionuclides, which had low levels of absorption in the gastrointestinal tract and, therefore, mostly influenced the colon dose [S3].

79. It is estimated that approximately 2% (49.7) of solid cancer deaths were associated with radiation exposure (table 8). While allowing for a linear-quadratic dose response provided no evidence against linearity (P>0.5), a pure-quadratic dose response described the data as well as a simple linear model. There was no evidence of a threshold. The potential influence of various factors on the estimated risk coefficient but no statistically significant differences were found due to the uncertainties remaining unchanged [S3]. Overall, the findings of the TRC study demonstrate that major uncertainties in the quantitative risk estimate in the low-dose range remain, despite the confirmed dose response.

Table 6. Techa River cancer mortality study (1950–2007) [S3]

<i>Characteristic</i>	<i>Description</i>
Study design	Cohort study
Study population	Eligible subjects were those born before 1950 and living in 41 villages of Chelyabinsk and Kurgan Oblasts along the Techa River during the period 1950–1960 (N=29 730). Those subjects were identified by extensive review of official documents, including taxation books, vital statistics and medical records during the period between the late 1960s and the 1980s
Outcome	Cancer mortality
Identification of cancer deaths	Chelyabinsk Oblast (region) and Kurgan Oblast were the catchment areas of mortality follow-up. The primary sources of vital status information are the regional address bureaus and the office of the civil registrar (ZAGS). The sources of cause of death information were death certificates from ZAGS or Regional Statistical Bureau Office
Follow-up/migration	The follow-up period was 1950 onwards. At the end of follow-up, approximately 23% of the cohort had migrated out of the catchment area (i.e. distal migrants)
Exposure	The TRDS-2009 was used and the mean cumulative stomach dose was 0.035 Gy. Radiation exposure resulted from a combination of external radiation exposure from contaminated river sediments and flood plain soil, and internal exposure from the consumption of contaminated water, milk and food products. Internal exposure was primarily from <sup>90</sup> Sr and <sup>137</sup> Cs but also <sup>89</sup> Sr and, to a lesser extent, from other uranium fission products. Parameters for external dose reconstruction were derived from exposure-rate measurements performed in the 1950s in different locations near the river bank and also from modelling radionuclide deposition in river sediment and soil. The external dose rate peaked in 1951 and has declined over time  Extensive efforts have been made to reconstruct exposure for cohort members and to reduce the uncertainties, which were found to be relatively large in TRDS-2000. A thorough uncertainty analysis is in progress
Confounding	Only demographic information (sex, age at entry, attained age, ethnicity, oblast of exposure) is available (the cohort is 80% Slav and 20% Tartar and Bashkir)
Medical exposure	Medical exposure was not substantial and was not taken into account in the risk analysis
Statistical power	No formal power calculations were reported but, in retrospect, result precision appears sufficient to detect overall cancer risks. However, statistical power is not sufficient to detect risks for individual cancer sites
Analysis	The main analysis was to estimate an ERR per unit dose, which was estimated using Poisson regression methods
Main results	ERR for mortality from all solid cancers was 0.061 per 100 mGy (95% CI: 0.004, 0.127)

Table 7. Techa River cancer incidence study (1956–2007) [D5]

<i>Characteristic</i>	<i>Description</i>
Study design	Cohort study
Study population	A subset of the TRC. This subcohort (N=17 435) includes cohort members born before 1950, initially exposed in riverside villages of Chelyabinsk Oblast, alive and not known to have had cancer prior to 1 January 1956, who lived near the river in five Chelyabinsk Oblast raions and Chelyabinsk City at some time between 1 January 1956 and 31 December 2007
Outcome	Cancer incidence
Case ascertainment	Since the mid-1950s, all diagnosed cancer cases have been required to be registered at the oblast oncology dispensaries [K11]. URCRM staff have collected copies of cancer notification forms registered in the catchment areas since 1956. Additional sources of information include case histories and outpatient charts kept at URCRM and other health centres in Chelyabinsk City, interviews with next of kin, cytology and histology logs kept at the Chelyabinsk Oblast Oncology Dispensary, records of the Oblast Oncology Bureau of the medical-social commission of experts, and the unified computer registry for the exposed South-Ural population. Health status information was verified via regular interviews of exposed residents at the URCRM clinic, which they visited regularly to undergo medical examinations. Regarding leukaemia cases, the URCRM database is considered to contain complete information on patients registered in the catchment areas since 1953 because its clinical department has been functioning as the main haematology centre providing treatment and medical assistance to the residents in the catchment areas
Confounding	Data on smoking were recorded during the interviews of cohort members who visited the URCRM clinic. When smoking history information only prior to age 20 was available, cohort members were treated as having unknown smoking status. Smoking history was summarized using a simple time-dependent variable with three categories: ever-smoker, never-smoker and unknown smoking status. Smoking status was considered to be unknown prior to the date at which they first provided information on their smoking history. Individual information on smoking intensity and duration were not available for these analyses
Medical exposure	Medical exposure was not taken into account in risk analysis
Statistical power	No formal power calculations were reported, but in retrospect, precision of results appears sufficient to detect overall cancer risks similar to LSS based on confidence interval width. Statistical power was not sufficient to detect risks similar to those in LSS for individual cancer sites, assessing departure from linearity or differences in risks between subgroups
Analysis	The main analysis was to estimate an ERR per unit dose, which was done using Poisson regression methods. The median dose to the stomach was 15 mGy (mean 52 mGy) based on TRDS-2009. Results provide ERR values taking into account a smoking status
Main results	For solid cancer incidence ERR per 100 mGy 0.077 (95% CI: 0.013, 0.15), for leukaemia incidence ERR of 0.12 per 100 mGy (95% CI: 0.04, 0.25)

Table 8. Excess solid cancer mortality cases by dose category using TRDS-2009 in TRC [S3]

<i>Dose category (Gy) with 5-year lag period</i>	<i>TRDS-2009</i>		
	<i>Person-years</i>	<i>Background cases</i>	<i>Excess cases</i>
0	132 593	149.7	0
<0.01	386 880	951.9	2.9
0.01–<0.05	273 436	777.9	10.2
0.05–<0.1	63 297	174.4	6.8
0.1–<0.15	27 651	80.3	5.8
0.15–<0.3	21 707	51.5	6.5
0.3–<0.5	21 074	63.7	16.1
≥0.5	1 105	4.0	1.4
Total	927 743	2 253.4	49.7

80. The results regarding solid cancer incidence risk analysis for the Chelyabinsk Oblast subcohort of the TRC, based on doses estimated using the TRDS-2009, were published by Davis et al. [D5]. Of the cases, 19% overall were based on death certificate alone (lower proportion after 1990). The values of the ERR for radiogenic solid cancer development estimated for the Techa River subcohort supplement those from the mortality analysis for the total Techa cohort, and present clear evidence of an increased rate of solid cancer with radiation exposure. While incidence and mortality analyses gave comparable ERR estimates, there are several major differences in the analyses. As was indicated above, since comprehensive data on cancer incidence are available only for cohort members initially exposed in Chelyabinsk Oblast, the incidence cohort contains only about 60% of the full TRC and loss to follow-up due to migration was more common than in the mortality analysis.

81. Despite the reduced cohort size and follow-up time (1956–2007) for solid cancer incidence data, the analyses were based on approximately the same number of cases (1,933 cases, excluding non-melanoma skin cancers) as the previous mortality analyses (2,303 deaths). Fifty per cent of the 1,933 solid cancers were diagnosed in men. The most common sites for men were the lung (30%) and the stomach (22%), while the most common sites for women were the uterus (including cervix uteri) (21%), the stomach (16%) and the breasts (12%) [D5].

82. The dose response with adjustment\* for ever vs never smoking, was significant ( $P=0.02$ ) in a linear ERR model. The estimated ERR per 100 mGy was 0.077 (95% CI: 0.013, 0.15). The risk estimate without smoking adjustment was 0.087 per 100 mGy (95% CI: 0.02, 0.16). Table 9 summarizes the distribution of solid cancer incidences, person-years and fitted values in five-year lagged cumulative dose categories. Using a linear dose–response model, it was estimated that 61 of the 1,933 cases (3%) were associated with radiation exposure. There is no indication that a linear-quadratic model fitted better than a simple linear model ( $P=0.2$ ). A pure-quadratic dose-response model gave an ERR of 0.022 per 100 mGy (95% CI: 0.005, 0.04), which is less than half of that predicted by the linear ERR model. When non-parametric smoothing was used, the results suggested that the response over the low-dose region (<0.1 Gy) falls between the linear- and pure-quadratic models [D5].

Table 9. Observed and fitted solid cancer incidence from linear-ERR smoking-adjusted models using TRDS-2009 (1956–2007) [D5]

Dose category (Gy) with 5-year lag period	Person-years	Observed cases <sup>a</sup>	Fitted cases	
			Background <sup>b</sup>	Excess <sup>b</sup>
0	11 870	17	16.2	0.0
>0–0.01	154 221	630	600.1	2.5
>0.01–0.05	196 764	799	871.5	16.6
>0.05–0.1	58 522	246	179.9	9.1
>0.1–0.15	23 616	105	96.1	8.6
>0.15–0.3	16 731	71	59.9	9.2
>0.3	11 065	65	47.9	15.3
Total	472 788	1 933	1 871.7	61.3

<sup>a</sup> Solid cancers among cohort members resident in the catchment area at the time of diagnosis (including alive and death-certificate-only cases) excluding non-melanoma skin cancers.

<sup>b</sup> The number of background and excess incidences are based on a linear ERR model without effect modification.

83. Site-specific analyses based on the linear model showed statistically significant radiation dose effects only for cancers of the oesophagus (ERR=0.46 per 100 mGy; 95% CI: 0.04, 1.2) and uterus (ERR=0.21 per 100 mGy; 95% CI: 0.01, 0.51). Oesophageal cancer risk estimates were modified by ethnicity and sex, but not by smoking. While the solid cancer rates are attenuated when oesophageal cancer estimates are removed (ERR=0.063 per 100 mGy; 95% CI: 0.00, 0.14), a dose–response relationship is present and it remains likely that radiation exposure has increased the risk for most solid cancers, despite the lack of power to detect statistically significant risks for specific sites [D5].

84. As these results indicate, while these data provide the evidence of dose response, there is considerable uncertainty about the magnitude of the risk at very low doses. Adjustment for smoking reduced the overall ERR from 0.087 per 100 mGy to 0.077 per 100 mGy (95% CI: 0.013, 0.15). ERR per unit dose tended to increase with attained age and age at entry, though there was little indication of effect modification\* (P>0.5 for the interaction\* terms). The ERR was comparable for men and women.

### (b) Leukaemia incidence

85. The TRC offers an opportunity to assess leukaemia risk after long-term exposure not only to external gamma radiation, but also to internal exposure of RBM due to <sup>90</sup>Sr. Internal exposure of the population due to ingestion of river water and local food products resulted in significant intakes of bone-seeking <sup>90</sup>Sr which, unlike the uniformly distributed <sup>137</sup>Cs, is accumulated mostly in the bone tissue and bone marrow. RBM contains the precursors of haematopoietic tissue, and a disturbance of haematopoietic processes may lead to the development of leukaemia. It may be assumed, therefore, that leukaemia represents one of the main reactions of the body to radiation exposure manifest in some members of the TRC. In the process of long-term follow-up of the cohort, leukaemia risk was assessed repeatedly [K8, K9, K15, K16, K18, O4]. In spite of their many limitations, the studies were able to provide a reasonably precise estimate of dose response for leukaemia incidence.

86. The results reported by Krestinina et al. in 2013 (in the framework of the Russian-American project) extended the period of follow-up by two years from the previous report [K15]. The mean cumulative RBM dose was 0.42 Gy. The newer dosimetry included a larger contribution of <sup>89</sup>Sr in the

period of maximum releases (1950–1951), and it increased the RBM dose due to internal exposure to  $^{137}\text{Cs}$  [D7]. The wider dose range reflected a better individualization of the TRDS-2009 dose estimates.

87. About 848,000 person-years have accumulated for cohort members residing in Chelyabinsk and Kurgan Oblasts over the 55-year follow-up period, and 170 haematopoietic malignancies (including 99 first primary leukaemia cases, 18 Hodgkin's diseases, 36 non-Hodgkin's lymphomas and 17 multiple myelomas) were identified. No leukaemia cases were identified in cohort members who had not yet reached 10 years of age, and only three cases in those aged 10–20 years. The number of leukaemia cases was 45 in males and 54 in females; 68 cases in Slavs and 31 in Tartars/Bashkirs; and 83 out of 99 leukaemia cases in those aged 40 or older. Leukaemia types and confirmation rates are shown in table 10. More than half of the leukaemia cases (58 out of 99) were classified as chronic, and 41 as acute or subacute. The diagnosis was microscopically confirmed for 82% of the cases. The proportion of cases identified solely from death certificates—often referred to as death certificate only (DCO)—has declined over time, ranging from about 25% for the years prior to 1990 to less than 10% over the last 17 years of follow-up.

Table 10. Microscopic confirmation rates of leukaemia types for TRC members [K18]

Type of leukaemia	Cases	Microscopic confirmation (%)	Mean age (year)
Acute myeloid	8	100	48
Acute lymphoid	1	100	76
Other acute/subacute <sup>a</sup>	32	72	51
Chronic myeloid	25	88	57
Chronic lymphoid	27	89	64
Other or unspecified <sup>b</sup>	6	50	62
Total	99	82	57

<sup>a</sup> Includes one acute monocytic leukaemia case, two acute erythraemia cases, two subacute leukaemia cases, and 27 cases classified as acute leukaemia of unspecified type.

<sup>b</sup> Includes three cases classified as myeloid leukaemia of unspecified type and three classified as leukaemia of unspecified type.

88. It was estimated, on the basis of a linear dose–response model, that 32% of the 99 leukaemia cases were associated with radiation exposure, with an estimated linear ERR of 0.12 per 100 mGy (95% CI: 0.04, 0.25). There was no evidence of a dose response for CLL (ERR=0.01 per 100 mGy; 95% CI: <0, 0.12). The analysis, focusing on leukaemia other than CLL, showed that about 47% of the non-CLL leukaemia cases were associated with radiation exposure. Table 11 presents the observed numbers of non-CLL leukaemia cases by dose category, along with estimates of the number of expected cases obtained from the baseline rates\* and radiation-associated excess cases based on a simple linear dose–response model with no effect modification. For non-CLL leukaemia, the ERR per 100 mGy in a linear dose–response model was 0.22 (95% CI: 0.08, 0.54).

89. The model fit did not improve by adding a quadratic term ( $P>0.5$ ). In contrast to the previous studies, the analysis conducted in 2013 showed that a pure-quadratic dose-response model was also positive (ERR=0.009 per 100 mGy; 95% CI: 0.003, 0.019), but it did not fit the data quite as well as did the linear model. There was no evidence of statistically significant modification of the radiation-associated risk of non-CLL leukaemia by sex (for females, RR=1.0; 95% CI: 0.14, 6.7), or ethnicity (for Tartars/Bashkirs relative to Slavs, RR=1.4; 95% CI: 0.58, 4.4). It was also found that ERR tended to increase with attained age, but this effect was not statistically significant ( $P>0.5$ ).

Table 11. Observed and fitted cases of leukaemia other than CLL in TRC using TRDS-2009 cumulative dose categories [K18]

Marrow dose (Gy) with a two-year lag	Person-years	Observed cases	Calculation based on fitted model		
			Background cases	Excess cases	Attributable fraction (%)
<0.01	100 034	6	4.4	0	0
0.01–0.05	102 300	2	4.7	0.3	6
0.05–0.1	55 077	4	2.5	0.4	13.8
0.1–0.2	109 182	10	5.1	1.5	22.7
0.2–0.5	222 137	13	10.1	6.8	40.2
0.5–1.0	152 752	20	6.9	10.1	59.4
>1.0	106 395	17	4.6	14.7	76
Total	847 877	72	38.3	33.8	46.9

90. Overall, the TRC study has been one of the most important new studies in the past decades and it has contributed to evidence about cancer risk from radiation. While challenges remain to quantify the dose–response relationship at low doses, risk estimates from this study provide important information about cancer risks from long-term whole-body radiation exposure, which can be applicable in other settings with an accident resulting in wide-scale environmental contamination. Results for leukaemia are based on relatively small numbers of cases, but they are unlikely to be affected by confounding or selection bias. The risk estimates from analyses of mortality reported in 2005 [K16] and incidence reported in 2013 [K18] differ more widely than those for solid cancers. Incomplete case ascertainment and diagnostic verification may add misclassification and could bias the risk estimates downward. For solid cancer results, the pattern of site-specific findings, with significant excess risks found only for oesophageal and uterine cancers, is not consistent with other major studies. The patterns of effect modification by age and sex are not similar to the Life Span Study (LSS), but the differences in risk by subgroup are small and should not be overemphasized. Adjustment for incomplete smoking information reduced the risk estimates for solid cancer, which suggests that there may be residual negative confounding. The different exposure modes, including long period of exposure and a marked internal radiation component may also contribute to the differences between the two studies.

91. The strengths of the TRC include a wide range of doses, long follow-up time, and availability of data on both cancer incidence and mortality. Exposure in the TRC population is complex, as it involves both external and internal exposure, and has varied over time, which adds to the uncertainties in estimated doses. However, extensive work on characterization of exposure, including uncertainties, is an advantage. Nevertheless, the uncertainties in dose estimates remain large. Incidence data are not, however, available for the entire cohort, and their quality is suboptimal, particularly for the early period. Furthermore, information on confounding factors is scarce. The proportion of subjects lost to follow-up (>20%) and deceased with unknown cause (roughly 10%) was relatively high.

## B. Studies of residents in $^{60}\text{Co}$ -contaminated buildings in Taiwan, China

92. A building constructed with radioactive building material was found in Taipei City in 1992. The source of the radiation was steel contaminated with  $^{60}\text{Co}$ , which was suspected to have been obtained illegally with scrap metal [A17]. One of the major steel reprocessing factories in Taiwan, China, mishandled a  $^{60}\text{Co}$ -orphan source and melted it during a steel-rod (rebar) manufacturing process during 1982–1983, producing radioactive steel, which was used throughout northern Taiwan, China. By the end of 2000, 1,607 housing units in 181 buildings were found to have radioactive rebar [C4]. All the buildings with radiation contamination were built between 1982 and 1984. Many families had resided in these buildings for various periods, mostly around 10 years. Regarding the method to estimate annual dose received by residents, Chen stated [C4]: “The highest specific point or space dose equivalent rate was taken as the dose equivalent rate for that room or compartment for further calculation”.

93. Chromosome aberrations of peripheral lymphocytes were examined in 30 residents (17 males and 13 females) in radiation-contaminated buildings. The estimated cumulative radiation doses for those residents ranged from 20 to 280 mSv. As a control group, 15 individuals (eight males and seven females) from laboratory personnel were recruited. G-banding was carried out for at least 500 metaphase spreads for each individual with the exception of one sample. All the recognizable structural aberrations of chromosomes or chromatids were recorded. The frequency of cells with aberrant chromosomes in residents of buildings with radiation contamination was non-significantly larger (4.5% vs 3.6%) than that in the control group [C3]. However, Liu et al. [L7] showed dicentric frequencies of 0.69 vs 0.33 in 136 residents compared with 15 non-exposed controls. A study of 90 exposed and 45 non-exposed subjects showed a higher frequency of any structural chromosomal aberration in exposed women (3.9 vs 3.0 per 100 cells), but no significant difference by exposure status in men (3.8 vs 3.5 per 100 cells) [W4]. The time since last exposure was not clearly reported.

94. Another study examined 1,913 exposed residents (average age: 18 years) of the contaminated buildings. Blood samples were taken five–eight years after relocation. The control group of this study consisted of 176 residents in a local community (average age: 30 years). Lymphocytes were cultured for 48 hours and a total of 208,900 metaphases were prepared. Increased frequencies of translocations (2.1 vs 0.2 per 1,000), and also rings and dicentrics (0.6 vs 0 per 1,000 for both) were reported in the exposed group relative to the control group [H7]. The elapsed time since end of exposure may be too long to observe an effect on unstable aberrations (dicentrics and rings). The frequency of stable aberrations (translocations) appears very high, given the dose level. In the interpretation of these results, it should be borne in mind that unstable chromosomal aberrations such as dicentrics are eliminated over time and are not expected to occur any longer when several years have elapsed since the end of radiation exposure.

95. Hwang et al. examined cancer risk in a cohort of 7,271 residents in cobalt-contaminated buildings with a dose assessment system known as the Taiwan cumulative dose (TCD), using questionnaires of house occupancy and building structure [H10]. The average excess cumulative dose was approximately 47.8 mSv (range: <1–2,363 mSv), with incremental annual dose on average 10 mSv  $\text{a}^{-1}$  (ranging up to >1,400 mSv  $\text{a}^{-1}$ ), though the distribution was highly skewed with 79% receiving <5 mSv  $\text{a}^{-1}$ . The subjects were identified from the national household registry and linked to other registries using national identification numbers. A questionnaire survey was conducted, but the data were not used in the analysis. A total of 1,025 persons were excluded due to lack of individual occupancy factors. A follow-up of the cohort for 1983–2002 (on average 16.1 years) accumulated 101,560 person-years at risk. The start of the follow-up was the date of moving into a contaminated building. Deaths in the cohort were ascertained by record linkage with the National Mortality Registry of Taiwan Province of

China, which had been maintained by the Bureau of Health Statistics since the early 1950s. Person-years of follow-up are reported, but not numbers of deaths or people emigrating. Cancer cases were identified through the National Cancer Registry, which was established in 1979 by the Department of Health, and which collects information on all newly diagnosed cancer patients from all health-care sectors in Taiwan, China. The proportion of cases based on death certificate alone was 10% in 1990–1994 and 3% in 1995–1999. Standardized incidence ratios (SIRs), adjusted for age and sex, were calculated with regional reference rates. The latent periods of leukaemia and solid cancers were assumed to be two and ten years, respectively. After the latent period, the follow-up of the cohort ascertained seven leukaemia cases and 88 cases of all cancers excluding leukaemia. The SIR for leukaemia, except for chronic lymphocytic leukaemia (N=7), was 2.2 (95% CI: 0.9, 4.6). The SIRs for all cancers excluding leukaemia were 0.7 (95% CI: 0.5, 0.9) for men and 0.9 (95% CI: 0.7, 1.2) for women. For dose-gradient analyses, only three dose categories were compared (<1, 1–50 and >50 mGy). A non-significant trend was observed for leukaemia and a significant trend reported for breast cancer. The decreased risk for all cancers excluding leukaemia suggests methodological problems with possible explanations including confounding, selection bias and incomplete follow-up or case ascertainment.

96. Extended follow-up of the same cohort reported 117 cancer cases diagnosed during the period between 1983 and 2005, with average follow-up of 19 years. No expected numbers were given to assess the overall cancer risk. In this study, quantitative risk estimates were obtained unlike in the earlier paper. A trend with radiation dose was observed for leukaemia, excluding chronic lymphocytic leukaemia, with an ERR of approximately 1.9 per Gy (90% CI: 0.1, 3.1) on the basis of six cases (one fewer than in the previous report). Breast cancer (N=17) also exhibited a suggestive increase in risk with dose (ERR=0.012 per 100 mGy; 90% CI: -0.01, 0.21). All solid cancers (N=106) showed an ERR of 0.03 per 100 mGy (90% CI: -0.04, 0.09) [H11]. Only linear risk estimates were reported, and no data shown by dose category to allow more detailed assessment of the findings. The authors chose to show 90% confidence interval instead of 95%, presumably based on a one-sided hypothesis test of radiation exposure increasing the cancer risk (see also annex A).

97. The limitations of the study of <sup>60</sup>Co-contaminated buildings include uncertainties in exposure assessment, low statistical power and lack of confounder control. Exposure assessment is not described in depth and the dosimetric quantities are not defined in detail. Interviews and questionnaires were used to reconstruct doses retrospectively on the basis of recalled occupancy and time spent in each room of the residence. Such estimates could be obtained for 86% of the cohort members. Dose-rate measurements were not conducted extensively, but rather concentrated on performing large numbers of measurements in a small number of residences and people to provide models for characterizing typical dose rates [H11, L2, T18]. Extensive dose reconstruction efforts were also hampered by subsequently installed shielding and replacement of contaminated rebars. No indicators of data quality for case ascertainment (such as proportion of microscopically verified cases, death certificate only cases, or cases with unknown primary site) were reported. A questionnaire survey was conducted, but no data were reported on any of the major confounders. The confidence intervals seem very narrow, given the sample size, which raises some concerns about the statistical analyses. However, the study was included in this annex, despite the clear methodological limitations and small study size, because it uses individual dose estimates and is able to provide a quantitative risk estimate so that it fulfils the key inclusion criteria. Table 12 summarizes the study of <sup>60</sup>Co-contaminated buildings in Taiwan, China. Recently, an update of the study has been published with extended follow-up, larger numbers of cancer cases and some site-specific analyses [H8].

Table 12. Summarized characteristics of the cohort study of residents in <sup>60</sup>Co-contaminated buildings in Taiwan, China

<i>Characteristic</i>	<i>Description</i>
Study design	Partly retrospective and partly prospective cohort study
Study population	A cohort of 6 242 residents of approximately 100 buildings constructed using <sup>60</sup> Co-contaminated steel (rebars) since 1982
Outcome	Cancer incidence
Mortality follow-up	Mortality registry by Bureau of Vital Statistics
Cancer case ascertainment	Cancer cases ascertained from the population-based cancer registry
Follow-up/migration	From the computerized household registration system
Exposure	Exposures reconstructed retrospectively from self-reported occupancy by building area. Cumulative doses calculated from time-weighted mean dose rates
Confounding	No data on confounding factors reported; questionnaire data on occupation and education mentioned in reports
Medical exposure	Information on medical radiation exposure was not collected
Statistical power	No formal power calculations reported
Analysis	Hazard ratios per 100 mGy reported leukaemia and all solid cancer combined, and also some individual cancer types. Adjustment for gender and year of birth was used. A minimum latency of two years for leukaemia and 10 years for solid cancers was used
Main results	For solid cancer incidence ERR of 0.03 per 100 mGy (90% CI: -0.04, 0.09)

### III. STUDIES OF ENVIRONMENTAL EXPOSURE TO NATURAL RADIATION

98. Natural background radiation, which originates from the terrestrial environment, varies tremendously worldwide and within countries as well. The average annual dose from external terrestrial radiation is 0.48 mSv, with typical values ranging 0.3–1 mSv a<sup>-1</sup> [U10]. The primary radioactive elements in the earth's crust that lead to human exposure are potassium, uranium, thorium, and their radioactive decay products (e.g. radium, radon). A high natural background radiation (HNBR) area is defined as an area where the total cosmic radiation and natural radioactivity in soil, indoor and outdoor air, water and food lead to chronic external and internal exposure to the public [H4]. The annual effective dose in HNBR areas has been classified into four levels: low (approximately 5 mSv a<sup>-1</sup>) or about twice the global average of 2.4 mSv a<sup>-1</sup> reported by UNSCEAR [U10]; intermediate (5–20 mSv a<sup>-1</sup>); high (20–50 mSv a<sup>-1</sup>); and very high (>50 mSv a<sup>-1</sup>) [S22, S23]. In this chapter, major cancer epidemiological studies in HNBR will be described. They focus on areas where typical annual doses from external terrestrial gamma radiation alone is of the order of magnitude of 2 mSv a<sup>-1</sup>, and cumulative lifetime doses are in range of 20–50 mSv and higher.

## A. Studies in Karunagappally, Kerala, India

### 1. Radiation sources

99. The mineral monazite, an anhydrous phosphate of the cerium group of the rare earths, was named by Breithaupt [B18]. Monazite sand is an orthophosphate of thorium and rare earths and typically contains thorium oxide (8% on average) and uranium oxide (0.3% on average) along with phosphorous pentoxide, rare earths, titanium oxide, cerium oxide, iron oxide and silicon dioxide [B11, O5, S29]. Most monazite is various shades of yellow. Shades of yellowish brown, brown, reddish brown, red, yellowish green, green, and greenish brown are locally common in detrital monazite from streams and lakes and in accessory monazite in schist, gneiss, granite and, particularly, pegmatite [O5].

100. The large monazite deposits in the coastal belt of Kerala, India, were discovered already in 1909 [K19]. The coastal zone from Chavara-Neendakara in the south to Purakkad in the north, which is flanked by the Arabian Sea in the west and Western Ghats in the east, is known to have thorium-containing monazite sand and a large quantity of other minerals. The radiation dose in terms of air kerma ranges from  $<1$  to  $45 \text{ mGy a}^{-1}$ . The HNBR area extends from the outlet of the Ashtamudi Lake in the south up to the Kayankulam Lake in the north. There is a canalized lagoon on the eastern side and the Arabian Sea on the west. So this area constitutes an island, which is 55 km long, and 0.5 km wide in the south and 1.5 km wide in the north. It has alternating bands of light and heavy minerals up to a depth of about 15 m [W7].

101. The beach boulders, include khondalites, chamockites, gneiss and granites, are lying in the hinterland granulitic terrain in parts of Tamil Nadu and Kerala. They were brought to the sea by fluvial transportation [P2, S30]. The largest of these streams, the Kallada River, empties into the Ashtamudi Lake, which is separated from the Arabian Sea by the Neendakara bar. The Warkilli series of sedimentary rocks in the lake are further transported to the coast by rivers that drain into the sea. The rocks of the Warkilli series are intermediate host rocks for monazite between the original source rocks and the beach boulders. Three rivers in the south of Kerala, i.e. Neyyar, Karamana and Vamanapuram, are also suspected of transporting more radioactive elements than the larger Kallada River due to higher levels of radioactive minerals in the hinterland rocks [P10].

102. Monazites and other heavy minerals in the beach are considered to be reconcentrated by wind, waves and currents. Ordinarily, monazite makes up less than 10% of the beach sand, possibly about 2–3% of the raw sand [B20, K1, W1]. However, at favourable localities, such as the coastal region of Chavara-Neendakara, tidal currents and waves selectively remove minerals of low specific gravity and leave behind minerals of high specific gravity [O5]. The raw black sand, however, contains 50–90% of ilmenite and 3–30% of monazite, containing 8% of  $^{232}\text{Th}$  on average [I7, O5]. Coastal configurations and sea currents in the south of Kerala are also suspected to be factors contributing to the deposition of these elements in the Chavara-Neendakara area [P10].

103. The first report of the WHO's Expert Committee on Radiation (Effects of Radiation on Human Heredity) was published in 1959 [W7]. It mentioned that "one untapped source of information suggested was the study of populations exposed to relatively large amounts of background radiation, that is, radiation of the order of one 'rem' per year", and that "the Kerala area of India would appear to be the only area now known, which might profitably be investigated". According to the report, approximately 60,000 people living in the radioactive milieu of the Chavara-Neendakara area were subjected to low-level chronic radiation exposure and presumably have been exposed for generations.

104. The WHO report summarized the population characteristics in the 1950s. The main features were: (a) approximately half the population were Christian and the rest Hindu; (b) the great majority lived from fishing; and (c) the percentage of literacy was high. Consanguineous marriages were fairly common among the Hindus. It was preferred that a man married his full cousin who was his paternal aunt's daughter (and therefore, would probably be brought up in another village). Among Hindus, full cousin marriage rate was considered to be about 10–20%.

105. The infant mortality rate in this area was higher than 100 per 1,000 live births, indicating that public health conditions in this area were poor, though the situation has improved in Kerala since the 1960s. Twelve deaths per 1,000 births were reported in 2011, while it was as high as 44 deaths in the entire country [O1].

## 2. Study population

### (a) Cohort characterization

106. *Baseline survey.* The Chavara-Neendakara area is in the coastal belt of the Karunagappally taluk (administrative district). A cohort of all residents in the Karunagappally taluk (population size: 385,103 according to the population census in 1990) was established in the 1990s to evaluate the health effects of HNBR [N4]. From 1990 to 1997, house-to-house visits were conducted to measure indoor and outdoor air kerma rates and to collect personal information using a standardized questionnaire. This included questions on sociodemographic factors, lifestyle, including dietary habits, and tobacco and alcohol use. In total, this household survey collected personal information on 359,619 subjects in 71,674 households, which corresponds to 93% of the population and 94% of households in Karunagappally by the 1990 census. No attempt was made to re-interview the cohort members.

107. Among male adults (aged 30–84 years), 73% were Hindu and 18% Moslem. Only 6% were illiterate. More than 60% of the study subjects said they had smoked bidis in the past or did so currently. Bidi is made of 0.15–0.25 g of sun dried flaked tobacco rolled into a conical shape in a dried rectangular piece of Temburni leaf (*Diospyros melanoxylon*) and a thread securing the roll [S26]. Among the subjects aged 70 or older at the time of interview, bidi smokers accounted for more than 70%. Tobacco chewing was reported by 24% of the cohort members and, among those aged less than 70 at the time of interview, more than 50% were past or current tobacco chewers. Approximately 50% were past/current alcohol drinkers [J4]. The most popular alcohol beverages in this population are locally produced, including toddy (palm wine) and arrack (a strong liquor made from coconut flowers, sugarcane or other locally grown plants) [J5]. Fishing is the main source of livelihood for the coastal residents. Among men aged 30 years or older, fishermen and farmers accounted for nearly 20% of residents. However, since this group was reported to have 20–30% higher lung cancer incidence than the other occupational groups [J6], it is strongly suspected that smoking is a more common habit than in other occupations.

108. Among adult women (aged 30–84 years), 72% were Hindu and 20% Moslem. Among the female cohort members, fewer than 5% were fisherwomen and farmers, and 17% were illiterate. Tobacco smoking and alcohol drinking are rare among women [J4].

109. In summary, the population in Karunagappally and other areas in Kerala evidently has better public health and education levels than found in other areas in India. The main industry in Karunagappally was agriculture until the late 19th century. Since then, it has been rapidly urbanized.

Fishing is the main source of livelihood for the coastal residents. Further, a regional cancer registry has been in existence since 1990, interviews have been conducted with most of the population, and efforts have been made to obtain dose estimates based on measurements for individuals. However, there is evidence of under-ascertainment of cancer cases. The International Agency for Research on Cancer (IARC) stated in 2002 “However, the percentage of cases with primary site unspecified or ill-defined is very high, as is the proportion of cases registered on the basis of a death certificate alone, suggesting a degree of under-ascertainment” [N2].

110. For radiation risk analysis, six panchayats, including four panchayats with relatively high environmental doses (Alappad, Chavara, Neendakara and Panmana) and two panchayats with relatively low environmental doses (Oachira and Thevalakkara), were chosen in coastal areas. The Kollam area was not included since this area is much more urbanized than the Karunagappally taluk, as pointed out by WHO’s Expert Committee on Radiation [W7]. The control areas in this cohort are Oachira and Thevalakkara panchayats, located in the northern and eastern areas of this taluk. This decision is compatible with the WHO committee’s notion, which is that: “a defined strip of north of Kayamkulam bar would probably be most suitable as a control area”. The population of those six panchayats selected for radiation-related risk analysis consisted of 173,067 individuals. This subcohort will hereinafter be called “the radiation subcohort”.

111. There were 71,399 men and women aged 30–84 in this subcohort. Those younger than 30 were excluded because (a) cancer risk was low in that age group and (b) the cumulative radiation dose was expected to be relatively low. Rare-earth technology workers, who might have been exposed to various types of occupational exposure (N=1,196), and those who had died or had been diagnosed with cancer before the baseline survey were excluded. Thus, there were 69,958 individuals for statistical analysis.

### (b) Follow-up

112. Cancer cases in the cohort were ascertained by the cancer registry in Karunagappally, established in 1990. One of the main activities to identify cancer cases was monthly routine visits to the Regional Cancer Centre in Trivandrum, which is situated 70 km south, and is the comprehensive cancer centre in the state of Kerala. More than half of the cancer cases registered in the Karunagappally cancer registry were those who sought medical treatment in the Regional Cancer Centre [J6]. Further, annual visits to the following medical facilities were conducted: (a) Trivandrum Medical College Hospital in Trivandrum; (b) major pathological laboratories in the Karunagappally taluk and its neighbouring areas and in Trivandrum; and (c) all the hospitals and medical practitioners in the Karunagappally taluk. In addition, three to four times a year, the registry workers visited three primary health centres in the taluk, which have cancer screening facilities. Cancer cases were also ascertained by (a) monthly clinics to provide follow-up care for local cancer patients, and (b) the cancer screening camps conducted twice a year on average in all panchayats in the taluk. The registry data have been included in the recent editions of “Cancer Incidence in Five Continents”, which indicates that it fulfils the quality requirements for inclusion in IARC monographs [I2].

113. Death reports were obtained from the death registers kept in the health statistics divisions of the panchayats. Visits to homes of the deceased were made to supplement information on the cause of death. The extent of migration of radiation subcohort members (N=173,067), including control-area residents, was assessed by conducting a door-to-door survey of all the households in 2001. Movement within the panchayat was 9.5% while migration to outside the taluk was 6% in the 13-year study period. Most migration took place for job opportunities in the Gulf countries. Only 0.7% was lost to follow-up.

114. The entry into the cohort was the date of interview, which ranged from 1 January 1990 to 31 December 1997. The follow-up ended on the date of (a) cancer diagnosis; (b) death; (c) migration out of the study area; (d) attainment of 85 years; or (e) the 31 December 2005 (follow-up termination), whichever occurred first. In person-year calculations, the migration that had taken place until the migration survey in 2001 was taken into account.

### 3. Dosimetry

115. The HNBR in Karunagappally is mainly from thoron progenies and relatively high air kerma rates are found mainly in the coastal zone of Karunagappally taluk. In the Karunagappally study, exposure was mainly from external gamma [N4] and indoor air kerma rate measurements were made at every house in the 1990s. Outdoor dose rates were measured only at the front gate. Air kerma rates at school or at work locations (including sea for fishermen and farmland for farmers) were not measured. Information that would enable an evaluation of the correlation between ambient dose rates at school (or at work) and in the home was not available. Because women tended to stay at home longer than men, the cumulative dose estimates for women seemed more reliable than those for men. Sex- and age-specific house occupancy was determined on the basis of information collected from the survey of randomly selected residents in the study area (N=7,711). No information was available on occupancy at home and other locations for each resident. The indoor and outdoor air kerma rates of those panchayats are shown in table 13.

Table 13. Annual air kerma in six panchayats in Karunagappally, Kerala, India

Annual air kerma (mGy a <sup>-1</sup> )	Panchayats					
	Oachira	Thevalakkara	Panmana	Neendakara	Alappad	Chavara
INDOOR MEASUREMENTS						
Median	1.07	1.22	2.29	2.52	3.14	3.90
Maximum	9.18	9.56	21.4	53.6	25.3	42.9
OUTDOOR MEASUREMENTS						
Median	0.92	1.07	3.21	4.21	4.51	5.28
Maximum	12.1	29.8	30.6	76.5	43.1	63.0

116. Individual radiation dose (excluding cosmic rays) was estimated from the HNBR area on the basis of outdoor and indoor air kerma rates, taking into account sex- and age-specific occupancy factors. One indoor and one outdoor measurement of air kerma rates from gamma rays were conducted in 71,674 houses, using seven sodium iodide (NaI) detector-based scintillometers and six plastic scintillometers, which were designed and supplied by the Bhabha Atomic Research Centre, Mumbai, India. All these were cross-calibrated every day using a standard <sup>137</sup>Cs source in the laboratory before field measurements were made. The mean of three readings was taken for every measurement. For indoor measurement, the room with maximum occupancy was selected and the readings were taken in the centre of the room at a height of 1 m above the ground for five minutes. For outdoor measurement, five-minute readings at a height of 1 m above the ground were taken at a point 3 m away from the main entrance of the house.

117. Information on house occupancy was not collected through the baseline survey. As the population in the radiation cohort was very large, only a sample population was interviewed to obtain information on the fraction of time spent indoors and outdoors [N3]. In 2002, 2% of all houses were randomly

selected and information on occupancy was obtained for 7,711 residents (3,783 males and 3,928 females) in all age groups living in the selected houses. The house occupancy factor varied from 0.5 to 0.89 depending on sex and age, which are comparable with the value of 0.8 cited by UNSCEAR [U7].

118. Assuming the air kerma values for the cosmic ray component of the measured radiation level to be 0.227 mGy a<sup>-1</sup> for indoors and 0.252 mGy a<sup>-1</sup> for outdoors [A4, B13, U4, U7], the annual absorbed dose for each individual was calculated using the formula:

$$\text{Annual colon/RBM dose (mGy)} = [(K_{\text{indoor}} \text{ y}^{-1} - 0.227) \times \text{OF}_{\text{indoor}} + (K_{\text{outdoor}} \text{ y}^{-1} - 0.252) \times \text{OF}_{\text{outdoor}}] \times \text{CF}$$

where  $K_{\text{indoor}} \text{ y}^{-1}$ , and  $K_{\text{outdoor}} \text{ y}^{-1}$  are annual mean indoor and outdoor air kerma rates for the ward or panchayat. OF is the occupancy factor and CF is the conversion factor for air kerma to organ-specific absorbed dose presented in the ICRP Publication 74 [I5]. The CF for <sup>232</sup>Th used in the present study was 0.782 for the colon and 0.791 for RBM. The CFs for children aged 1–14 years and infants aged less than one year were increased by 10% and 30%, respectively. Colon dose was used for risk analysis since the LSS reports of cancer risk analysis of atomic bombing survivors also used it [P14]. Assuming that the external radiation from HNBR was whole-body exposure, total body exposure was represented by absorbed dose of the colon. The cosmic ray component (0.252 and 0.227 mGy a<sup>-1</sup> outdoors and indoors, respectively) was subtracted from the measured dose in order to estimate the radiation dose from terrestrial radiation exposure. The individual cumulative dose was calculated by adding up the annual dose over time and the average was reported as 161 mGy in the exposed cohort [N4].

119. Information on migration was taken into account when estimating the cumulative dose of the cohort subjects in the following manner. When migration occurred into the Karunagappally taluk, the mean outside and inside radiation doses of the Oachira panchayat (a control area) were assigned to the ages of the immigrants before migration. When a subject moved within the Karunagappally taluk, the average outdoor air kerma rate of the ward in which the house was located and the average indoor air kerma rate of all the houses in the same ward were assigned. If the ward was not known, the mean outdoor air kerma rate of the panchayat was taken.

120. The measurements of scintillometers was compared with thermoluminescent dosimeters (TLD), which showed a good correlation (regression coefficient 0.97) [N4]. It would have been ideal to use TLD for dose measurements but using it for measuring the outdoor and indoor dose of 75,000 houses would have been extremely difficult. In order to calculate the annual dose based on scintillometer spot readings, it was necessary to confirm the correlation between the spot reading and long-term exposure levels. For this purpose, TLD measurements and scintillometer spot readings were conducted for one year in 800 houses, randomly selected from 12 panchayats. Natural calcium fluoride powder was placed inside a brass capsule with a diameter of 3 mm, a length of 8 mm and a wall thickness of 1.5 mm. About 50 mg of the powder was dispensed inside the capsule using a vibrator volume dispenser. Two such capsules were placed inside a plastic locket with a wall thickness of 2 mm. The locket was placed inside the house taped below a cot or table at a height of 50–100 cm above the ground in a room with maximum occupancy. The TLD was read under a constant nitrogen flow of 5 L min<sup>-1</sup>, using a Harshaw 3,000 reader calibrated with a <sup>137</sup>Cs source. The dose was measured in quarterly integrating cycles for the whole year at the same place. A scintillometer reading was taken at the same height in the same house every quarter. The mean of the four spot readings (μR h<sup>-1</sup>) was converted to the annual dose (mGy a<sup>-1</sup>), using a conversion factor of 0.0765 (= 8.73 × 24 × 365.25/10<sup>6</sup>) [N3].

121. The study examined the correlation between scintillometer readings converted to annual dose and the annual dose evaluated using TLD. The correlation coefficient was 0.93 and the TLD dose was 0.97 times the scintillometer-based annual dose. The scintillometer measured an outdoor dose at the door and indoor doses at each house, and individual doses had a wide distribution. However, the high

correlation coefficient indicates that the major radiation source of studied subjects are from the residence and areas near the residences. The annual radiation doses ( $\text{mGy a}^{-1}$ ) used in the cancer risk analysis were obtained by converting the scintillometer-based annual dose to TLD equivalent annual dose, multiplying by 0.97.

### (a) *Internal exposure*

122. Indoor radon and thoron concentrations, and also thoron progeny, were measured in 259 dwellings of the Karunagappally taluk: 183 in HNBR areas and 76 in low-background-radiation areas [O3]. Internal doses due to ingested and inhaled radionuclides were not considered in the cumulative dose estimation, but measurements were made to evaluate them. This survey used the passive monitoring device named raduets, which has a twin-cup monitor with two CR-39 solid-state nuclear track detectors to measure indoor thoron and radon gas concentrations separately. Indoor thoron progeny concentrations (equilibrium equivalent thoron concentrations) were also determined, using a passive device with CR-39 solid-state nuclear track detectors to count alpha particles emitted only from deposited thoron progenies. The monitors were deployed for about six months. Indoor radon gas concentrations in the study area were low (table 14), below  $10 \text{ Bq m}^{-3}$  in most houses [O3]. Indoor radon gas and thoron gas concentrations had no correlation. Similar results were obtained in the second series of the survey (table 14).

123. The median effective annual dose from indoor radon and its progeny was estimated as 0.1 and that from thoron decay products as  $0.4 \text{ mSv a}^{-1}$  (table 15). It is also noted that radon and thoron gas concentrations and thoron progeny concentration were not correlated with the indoor air kerma rate obtained from instantaneous measurements by a semiconductor detector with electrostatic collection, grab sampling of thoron progenies and a CsI (TI) scintillation survey meter. The absence of significant correlation could be explained with the fact that building material contained uranium decay series nuclides, thorium decay series nuclides and  $^{40}\text{K}$ , which are major contributors to air kerma rate in the study area. However, the magnitude of their contributions can vary from house to house. Another explanation may be that the rate of entry of thoron in a dwelling is highly variable according to the building material and to the flooring. Mean indoor concentrations of radon and thoron progeny are also slightly lower in HNBR areas than in other areas.

124. The meals of residents did not contain a large proportion of food grown in their neighbourhood. Therefore, it is unlikely that lifetime radiation doses from internal exposure differed substantially between areas within Karunagappally. The thorium burden of 87 residents in Karunagappally was determined by a thoron-in-breath analysis [N3, N5]. The mean  $^{232}\text{Th}$  body burden for 16 subjects from normal background level areas (mean  $0.72 \text{ mGy a}^{-1}$ ) was 6.3 Bq. For 33 subjects from medium background radiation level areas (mean  $2.04 \text{ mGy a}^{-1}$ ), the mean  $^{232}\text{Th}$  body burden of 8.9 Bq was estimated and 38 subjects from high-background radiation areas (mean  $15.64 \text{ mGy a}^{-1}$ ) had a mean of 10.91 Bq. These results show that the subjects from high and medium indoor radiation level areas show a significant increase in the thorium body burden ( $P=0.0094$ ) compared to those from low indoor radiation level areas.

Table 14. Indoor radon and thoron gases and thoron progeny concentrations in Kerala, India [O3]

Survey <sup>a</sup>	Source	Houses (NA <sup>b</sup> )	Concentration (Bq m <sup>-3</sup> )		
			Mean	Median	Range
1st survey	HNBR <sup>c</sup> areas				
	Radon	53 (22)	5±3	4	1–13
	Thoron	68 (7)	53±28	46	15–128
	Thoron progeny	66 (9)	2.15±1.57	1.48	0.59–6.72
	Other <sup>d</sup> areas				
	Radon	37 (13)	8±5	9	1–21
2nd survey	Radon	48 (2)	47±44	31	11–212
	Thoron progeny	44 (6)	2.32±1.51	1.91	0.36–8.00
	HNBR <sup>c</sup> areas				
	Radon	80 (28)	5±4	4	1–30
	Thoron	104 (4)	26±20	20	3–151
	Thoron progeny	63 (45)	1.56±1.01	1.21	0.52–5.72
Other <sup>d</sup> areas	Radon	14 (13)	7±11	4	1–43
	Thoron	26 (1)	30±35	16	7–133
	Thoron progeny	18 (9)	1.69±1.74	1.22	0.45–7.53

<sup>a</sup> The first survey was conducted during June 2010–February 2011. The second survey was conducted during December 2010–June 2011. In both studies, raduets were in place for about six months.

<sup>b</sup> NA: data are not available (“below the detectable level” is included). The lower limit of detection for radon and thoron measurements are around 1.0 Bq m<sup>-3</sup> and 2–43 Bq m<sup>-3</sup>, respectively. The lower limit of detection for thoron progeny measurement is 0.003 Bq m<sup>-3</sup>.

<sup>c</sup> The HNBR areas are Panmana, Neendakara, Alappad and Chavara panchayats in Karunagappally taluk.

<sup>d</sup> Other areas are Oachira and Thevalakkara panchayats in the taluk.

Table 15. Effective doses from internal exposure due to inhalation of indoor radon and thoron progeny in Kerala, India [O3]

The conversion of indoor radon and thoron concentrations to effective doses was based on [U7]

Area	Source	Houses <sup>a</sup> (NA <sup>b</sup> )	Effective dose (mSv)		
			Mean	Median	Range <sup>c</sup>
All areas	Radon	184 (76)	0.14±0.12	0.10	0.02–1.07
	Thoron	191 (69)	0.55±0.40	0.40	0.10–2.24
	Total	191 (69)	0.65±0.44	0.50	0.13–2.60
HNBR areas	Radon	133 (50)	0.12±0.09	0.09	0.02–0.75
	Thoron	129 (54)	0.52±0.38	0.39	0.15–1.88
	Total	129 (54)	0.61±0.39	0.49	0.18–1.98
Other areas	Radon	51 (26)	0.19±0.18	0.16	0.02–1.07
	Thoron	62 (15)	0.60±0.44	0.44	0.10–2.24
	Total	62 (15)	0.74±0.52	0.64	0.13–2.60

<sup>a</sup> Two series of the survey in 260 houses: 183 in Panmana, Neendakara, Alappad and Chavara panchayats (HNBR areas) and 77 in Oachira and Thevalakkara panchayats (other areas) in Karunagappally taluk.

<sup>b</sup> NA: data are not available (“below the detectable level” is included).

<sup>c</sup> Range: effective doses from the concentrations “below the detectable level” or being not evaluated are excluded [O3].

## (b) Biological dosimetry

125. Researchers from the Bhabha Atomic Research Centre, Mumbai, India carried out cytogenetic investigations on newborns (from 1986 to 2007) in conjunction with a study of congenital anomalies to estimate and compare the incidence of karyotype anomalies (both structural and numerical) and the frequency of chromosomal aberrations (both stable and unstable aberrations) following in utero radiation exposure [R1]. A total of 1,267,788 metaphases from 27,295 newborns (14,062 males and 13,233 females) were analysed for chromosomal aberrations and karyotype anomalies, of which 17,298 newborns (964,390 cells) were from HNBR areas ( $>1.5 \text{ mSv a}^{-1}$ ), and 9,997 newborns (303,398 cells) were from relatively low-level background radiation areas ( $<1.5 \text{ mSv a}^{-1}$ ). There were 162 (5.94%) karyotype anomalies (90 numerical and 72 structural) observed in these newborns, of which 95 were from HNBR areas (55 numerical and 40 structural) and 67 (35 numerical and 32 structural) from the relatively low-background radiation areas (the control area). Newborns in the two areas had no statistically significant difference in the frequency of overall karyotype anomalies (5.49% vs 6.7%). Its relative frequency (RF) was 0.82 (95% CI: 0.60, 1.12). No statistically significant area difference was observed for numerical anomalies (3.18% vs 3.5%; RF: 0.91; 95% CI: 0.59, 1.39) or structural anomalies (2.31% vs 3.2%; RF: 0.72; 95% CI: 0.45, 1.15). The data did not suggest any dose-related trend in numerical, structural or overall karyotype abnormalities.

126. The spontaneous frequency of different types of chromosomal aberrations in those newborns was analysed and reported per 10,000 cells. The two groups showed no significant difference in the baseline frequency of dicentrics ( $1.90 \pm 0.14$  in HNBR-area group and  $2.01 \pm 0.26$  per 1,000 in the control-area group; RF: 0.94; 95% CI: 0.71, 1.26). Similarly, baseline frequency of stable aberrations (translocations, inversions) in the two groups did not show any statistically significant differences ( $4.42 \pm 0.19$  in HNBR areas as compared to  $4.17 \pm 0.21$  in the control area; RF: 0.80; 95% CI: 0.67, 0.96).

No area difference was found in the frequency of all chromosomal aberrations, which included dicentrics, translocations, inversions, rings, fragments and minutes ( $8.32 \pm 0.29$  in HNBR areas and  $9.29 \pm 0.55$  in the control area; RF: 0.89; 95% CI: 0.78, 1.02) [C5, R1].

127. The spontaneous frequency of micronuclei was determined in 271 newborns (61 from the control area and 210 from HNBR area) born to mothers between 17 and 37 years of age (mean maternal age:  $24.1 \pm 4.2$  years). The frequency of micronuclei in newborns was  $1.40 \pm 0.12$  per 1,000 binucleated cells in the control and  $1.33 \pm 0.04$  in HNBR areas. When the samples were categorized into six different groups on the basis of the level of background radiation, no dose response was observed. The spontaneous frequency of micronuclei in newborns in HNBR and control areas showed no statistically significant difference, suggesting that slightly elevated levels of background radiation during the foetal period had no significant effect on induction of micronuclei in the newborns [D2].

128. To assess the effect of HNBR on the adult population, chromosomal aberrations in lymphocytes of adult individuals living in HNBR areas were investigated at the Regional Cancer Centre, Kerala [H2]. Blood samples from the female inhabitants, aged 30–58 years, in the HNBR and control areas were collected and examined for the frequency of dicentric and ring chromosomes in peripheral lymphocytes. The selected subjects had been born and brought up in the HNBR area or in the control area, and had been living there for a minimum of 30 years. A total of 23,673 cells from eight subjects in HNBR areas and 23,718 cells from eight subjects in control areas were examined. The estimated individual cumulative doses in the control area were 12–18.5 mSv (average = 15.6 mSv, SD = 2.4 mSv) and those in the HNBR area were 16.8–402.6 mSv (average:  $187.5 \pm 157.7$  mSv). The cytogenetic analysis revealed that the average numbers of chromosomal aberrations per 1,000 cells were  $0.76 \pm 0.77$  in control areas and  $13.8 \pm 6.8$  in HNBR areas.

129. No increase in DNA double-strand breaks in terms of gamma-H2AX was found in 61 adult residents of the HNBR areas compared with 30 from the control area in mononuclear cells from peripheral blood ( $0.095 \pm 0.009$  and  $0.084 \pm 0.004$  per cell;  $P = 0.22$ ) [J2].

130. In another cytogenetic study, the frequencies of micronuclei were analysed in 94 adult men from the HNBR areas and 47 from control areas [J2, K2]. An average of 1,835 binucleated cells per individual were scored. The mean frequencies of micronuclei in the HNBR ( $11.7 \pm \text{SD } 6.6$ ) and control areas ( $11.6 \pm 6.7$ ) were not statistically significantly different ( $P = 0.59$ ).

131. No differences in telomere length were found in two studies examining adults or newborns in the HNBR area compared with the control area. In the adult study with 233 exposed subjects the mean telomere length was  $1.22 \pm 0.15$  for the lowest and  $1.12 \pm 0.11$  for the highest group [D3]. In the newborn study, the average was  $1.03 \pm 0.01$  in the 128 exposed and  $1.10 \pm 0.03$  in the 43 control infants [D4], however, it is not indicated whether adjustment for age was used in the adult analysis.

#### 4. Cancer incidence

132. In the Karunagappally cohort study of 69,958 subjects [N4], a total of 1,349 cancer cases were reported. The three most common cancers were oropharyngeal, lung and breast cancer (220, 189 and 125 cases, respectively). Of the cancer cases, 13% had an unknown primary site. In addition, there were 30 leukaemia cases (including 10 CLL).

133. Statistical analysis was based on the data in cross-tabulations by sex, attained age (five-year category) and other covariates. The entry into the cohort was the date of the baseline survey (date of interview). Poisson regression analysis of grouped survival data [B19] was conducted. To allow for a

possible latent period between radiation exposure and its consequences, cumulative doses were lagged by 10 years for all cancers except leukaemia where a lag of two years was used. Statistical power was not calculated prior to the establishment of this cohort.

134. Assuming a linear dose response, the ERR of all cancers except leukaemia in relation to cumulative dose was estimated using the following Poisson regression model:

$$H_0(\text{sex, attained age, follow-up interval, bidi smoking, education, occupation}) [1 + \beta D]$$

where D is cumulative radiation dose calculated over time, and  $\beta$ , the coefficient of D, describes the relative change in rates associated with dose.  $H_0$  is the baseline cancer rate, depending on sex, attained age, follow-up intervals and other covariates (sociodemographic factors and bidi smoking). Analysis of cohort data, stratified\* by sex, attained age, and follow-up interval, showed no excess cancer risk from exposure to terrestrial gamma radiation.

135. The excess relative risk of all cancers, excluding leukaemia, was estimated to be  $-0.013$  per 100 mGy (95% CI:  $-0.058, 0.046$ ). In site-specific analysis, no cancer site was significantly related to cumulative radiation dose (ERR=0.03 per 100 mGy for oropharyngeal and 0.01 for digestive tract cancer, lower confidence bounds not defined, upper bounds approximately 0.25). Leukaemia was not significantly related to background radiation (ERR=0.6 per 100 mGy, lower confidence limit not defined, upper limit 34). The follow-up period of the Karunagappally cohort study was recently extended by four years. The major methodological features of the Karunagappally study are summarized in table 16.

136. The Kerala programme of studies has several strengths: (a) the cumulative dose to date, 161 mGy average, is relatively large; (b) potential confounding factors such as tobacco use and socioeconomic status (SES) have been obtained by interview and can be adjusted for in the analysis; and (c) a cancer registry, described in Cancer in Five Continents (IARC), has existed since 1990 and thus data on cancer incidence (but not mortality) are available. Details of smoking adjustment were not, however, reported. The baseline interview covered the amount of both cigarette and bidi smoking, and also smoking status at interview (never, past, current), but the study report mentioned only adjustment for "bidi smoking". However, there are uncertainties in dose estimates mainly due to exposure outside the residence, lack of exposure data for full residential history, and use of aggregate estimates rather than individual data for occupancy. The numbers of cases for several cancer sites are still relatively small. A quarter of the cases lacked pathological verification of the diagnosis. Furthermore, case ascertainment may be incomplete, given the low health-care level in the area. The primary occupation is fishing and, currently, there are few major environmental pollutants in these coastal regions, but potential differences in lifestyle between the populations of the high exposure area on the coast and the lower exposure area further inland need to be considered. Migration was also taken into account when calculating individual cumulative dose [J3, N1, N2]. In summary, while the findings in this study are reasonably robust, the confidence intervals obtained from the study are still wide and cannot convincingly discount risks similar to those reported from the LSS.

Table 16. Summarized characteristics of the Karunagappally cancer incidence study [N4]

<i>Characteristic</i>	<i>Description</i>
Study design	A prospective cohort study
Study population	A cohort of 69 958 residents whose information was collected at the time of baseline survey (1990–1997). Those who were diagnosed with cancer before the time of baseline survey were excluded from the cohort
Outcome	Cancer incidence
Mortality follow-up	Official vital statistics supplemented by the field surveys conducted by investigators
Cancer case ascertainment	Cancer cases in the cohort were ascertained by the cancer registry in Karunagappally, established in 1990
Follow-up/migration	Surveys to identify out-migrants were conducted in 2000 and 2001
Exposure	Individual cumulative colon doses from external irradiation were estimated on the basis of measured indoor and outdoor air kerma dose rates and sex- and age-specific occupancy factors. Indoor and outdoor air kerma dose rates were measured at each house. Information on house occupancy factors was obtained from a survey of 7 711 residents in 2002. The uncertainties in the estimates of individual cumulative colon doses have not been evaluated
Confounding	Data on socioeconomic status (SES) and lifestyle factors were collected in the baseline survey conducted during 1990–1997
Medical exposure	Information on medical radiation exposure was not collected
Statistical power	No formal power calculations are available, confidence interval width does not distinguish between effect size similar to LSS and no risk
Analysis	The main analysis was to estimate an ERR per unit dose, which was estimated using Poisson regression methods. Cumulative dose was lagged by 10 years for solid cancer risk analysis. Subjects used for analysis were those aged 30 years or older at the time of baseline survey and attained ages of 30–84 during the follow-up period, which starts at the time of baseline survey and ends at the time of migration, death, cancer development or the end of follow-up (the end of year 2005)
Main results	For incidence of cancer other than leukaemia ERR –0.01 per 100 mGy (95% CI: –0.06, 0.05)

## B. Studies in Yangjiang, Guandong Province, China

### 1. Radiation sources

137. The Yangjiang area in Guandong Province, China, is known for its natural HNBR. In this region, fine particles of monazite are washed down the mountains by rain to the surrounding basin regions, giving rise to soil with high levels of radioactive nuclides such as  $^{232}\text{Th}$  and  $^{238}\text{U}$  [Y2]. Morishima et al. suspected that the main source of HNBR was the natural radioactive nuclide concentrations in building material using such soil [M6]. The average annual doses of external radiation from natural sources, including thorium, in the HNBR and control areas were estimated to be 2.10 and 0.77 mSv a<sup>-1</sup>, respectively [M6, Y2].

## 2. Population characterization and follow-up

138. The HNBR area of Yangjiang covering a total area of about 540 km<sup>2</sup> [H5], consists of the Dong-anling and Tongyou regions, which had 21,838 and 44,786 residents, respectively, at the time of the national census conducted on 1 January 1979. The residents are of the Han nationality, and 90% of the population had been living in those areas for six or more generations. The control area of the study is the Wudianmeihua region in Enping, located 50 km west of Dong-anling, which is 60 km east of Tongyou. Wudianmeihua had 25,924 residents at the time of the census. The primary occupation is farming, which might involve some exposure to insecticides.

139. The cohort consists of approximately 90,000 residents of the study area, including control areas, who were alive as of 1 January 1979. The most recent study analysed the mortality data of 31,604 men and women who attained the age of 30–74 during the follow-up period of 1979–1998 [T3]. It was decided to exclude those younger than 30 years because: (a) cancer risk was low in that age group; (b) the cumulative radiation dose was expected to be relatively low; and (c) childhood cancer is considered to have aetiological backgrounds different from adult cancer. In addition, cumulative doses remain relatively low for those young age groups. Those aged 75 years or older were also excluded from the analysis, because the elderly were less likely to seek medical care for cancer and chronic non-cancer diseases and, thus, the inclusion of this age group might result in a lower accuracy of diagnosis.

140. In order to compare lifestyles, socioeconomic conditions and other factors in the study areas, Chinese investigators conducted studies on confounding factors including diet and nutrition, drinking water, pesticide residue and aflatoxin B1 in food, medical radiation exposure, tobacco smoking and alcohol consumption. The studies showed that the distribution of those potential confounding factors did not substantially differ in the two areas [T4, Z4]. However, no individual-level data were collected on major cancer risk factors for the cohort members.

141. In order to ascertain deaths in cohort members, trained local census takers surveyed the hamlets of the study areas to collect information on deaths and migration of inhabitants in each hamlet. The collected information was recorded on a demographic survey sheet prepared for each household in the hamlet. The task group on the mortality follow-up survey then visited the study areas and reviewed the survey sheets. In order to ascertain the cause of death, they visited the relevant hospitals in the study areas, reviewed medical records of deceased subjects and extracted relevant information. If necessary, the task group revisited the local village doctors and the family members or next of kin to collect further information on the cause of death. The underlying causes of death were determined on the basis of pathological information for 240 (26%) deaths.

## 3. Dosimetry

142. The doses from external radiation from HNBR in Yangjiang are due mainly to gamma rays from radionuclides of the <sup>232</sup>Th decay series. Indoor air kerma rates were measured at approximately one third of houses at a village selected for indoor dosimetry (measurements available for the analysis covered 8,028 households in total). Therefore, the individual cumulative dose for a resident is based on the average dose in the village of residence. However, inter-house differences were not large [M6]. Indoor and outdoor ambient gamma dose rates were 110–370 and 100–220 nGy h<sup>-1</sup>, respectively. Doses received from indoor terrestrial radiation were estimated to be 0.6–1.8 mSv a<sup>-1</sup> [O2]. Outdoor air kerma rates were measured in most of the locations where a villager spent some time, and were found to be more heterogeneous than indoor absorbed dose rates in air [M6, Y1, Y2]. Although the hours spent in each location in a village differ by sex, age and occupation, whether those points were taken

into account or not is unclear. It should be noted, however, that indoor exposure contributes more to the total dose than outdoor exposure in this study area. House occupancy factors were collected by a survey of approximately 5,291 subjects during 1991–1993 [T3, Y1]. Air kerma rates in schools or workplaces were measured. More detailed descriptions on dosimetry are given below.

143. Individual radiation dose from the HNBR was estimated on the basis of outdoor and indoor air kerma rates and sex- and age-specific occupancy factors. Environmental dose rates were measured with Chinese NaI (TI) scintillation survey-meters, FD71 or FD3013 [Y2]. In every hamlet, indoor measurements were conducted in about one third of all households, and measurements for 8,028 households in total were available for the analysis. Indoor gamma radiation doses were measured in the main bedroom, the sitting room and the kitchen in each of those households. Outdoor doses were measured on main roads, alleys, open recreational areas, rice paddies, areas adjacent to wells, dry land and the banks of ponds for each hamlet.

144. House occupancy factors specific for sex and age were obtained from a questionnaire survey of 5,291 subjects (0–92 years old, mean age=54, SD=22) in over 88 hamlets conducted from 1991 to 1993 [Y1]. Age categories were listed in five-year periods between 30–34 and 70–74. The sex- and age-specific occupancy factors represented the time spent in bed, and at the other indoor places [Y1, Y2].

145. The annual absorbed dose for each individual  $D_{\text{individual}} \text{ y}^{-1}$  (mGy) was calculated using:

$$D_{\text{individual}} \text{ y}^{-1} = [(K_{\text{main bedroom}} \text{ y}^{-1} - CR_{\text{indoor}} \text{ y}^{-1}) \times OF_{\text{main bedroom}} + (K_{\text{other rooms}} \text{ y}^{-1} - CR_{\text{indoor}} \text{ y}^{-1}) \times OF_{\text{other rooms}} + (K_{\text{outdoor}} \text{ y}^{-1} - CR_{\text{outdoor}} \text{ y}^{-1}) \times OF_{\text{outdoor}}] \times CF$$

where  $K_{\text{main bedroom}} \text{ y}^{-1}$ ,  $K_{\text{other rooms}} \text{ y}^{-1}$  and  $K_{\text{outdoor}} \text{ y}^{-1}$  are annual doses for the main bedroom, for the rooms other than the main bedroom, and for outdoors, respectively;  $CR_{\text{indoor}} \text{ y}^{-1}$  and  $CR_{\text{outdoor}} \text{ y}^{-1}$  are indoor and outdoor annual cosmic ray doses, respectively;  $OF_{\text{main bedroom}}$ ,  $OF_{\text{other rooms}}$  and  $OF_{\text{outdoor}}$  are the occupancy factors for the main bedroom, for the rooms other than the main bedroom, and for outdoors, respectively; and CF is the conversion factor for air kerma to organ-specific absorbed dose given in ICRP Publication 74 [15].

146. The  $D_{\text{main bedroom}}$  is an average gamma radiation dose measured 1 m above the floor in the main bedrooms of ten houses in the hamlet where the study subjects were living at the time of the dosimetry survey. The  $D_{\text{other rooms}}$ , the indoor dose for the rooms other than the main bedroom, was also the average dose that was calculated using the same approach as the  $D_{\text{main bedroom}}$ .  $D_{\text{outdoor}}$  is the average of gamma radiation dose measured at 1 m above the ground in public places and farmland in the corresponding hamlet. The individual cumulative dose was calculated by integrating the annual dose over time [S28, Y2].

147. Using this formula, colon dose was calculated and was used for risk analysis. Assuming that the external radiation from HNBR was whole-body exposure, this was represented by the absorbed dose of the colon (as in the Indian cohort study). This is the same approach as that used by the LSS of solid cancer risk analysis of the Japanese atomic bombing survivors, which also used colon dose to analyse solid cancer risk [P14]. For leukaemia risk analysis, RBM dose was calculated using this formula. The CF of  $^{232}\text{Th}$  used in the present study was 0.627 for the colon and 0.791 for RBM. The CFs of children aged 1–14 years and infants aged less than one year were increased by 10% and 30%, respectively. The cosmic ray component was subtracted from the measured dose in order to estimate the radiation dose from terrestrial radiation exposure by using an air kerma value for the cosmic ray component of the measured dose of  $0.259 \text{ mGy a}^{-1}$  for indoors and  $0.288 \text{ mGy a}^{-1}$  for outdoors [A4, B13, U4, U7].

148. Morishima et al. measured indoor and outdoor air kerma rates, using a NaI(Tl) scintillation survey meter (Aloka TCS-166) in 200 houses in the Madi hamlet in the HNBR area, and in 22 houses in the control area (Hampizai hamlet) with a dose rate less than  $0.1 \mu\text{Gy h}^{-1}$  [M6]. They also conducted

individual dosimetry, using electronic pocket dosimeters (Aloka PDM-101) and TLDs (National Co. UD-200S), which were set for 24 hours and two months, respectively. The scintillation survey meters could not measure cosmic rays which were outside the scope of detectable energy of the device, so the measured data were corrected accordingly. There was wider variation in dose rates in HNBR areas than in control areas. In the HNBR region, dose rates tended to be higher indoors than outdoor rates due to radiation from building material. Also, the relationship between environmental and individual dose rates was less straightforward.

#### (a) *Internal exposure*

149. A small survey (N=215) using radopots was conducted in 2003 to measure indoor radon concentrations [O3]. The average indoor radon concentration was  $37 \text{ Bq m}^{-3}$  (SD=44; range=3, 284). In a recent radon and thoron survey, using raduets, of 59 houses in four hamlets in Yangxi and Yangdong counties (HNBR areas) during about six months, indoor radon and thoron concentrations showed wide variations from house to house. The mean indoor radon concentration was  $124 \text{ Bq m}^{-3}$  (median 115) and the average indoor thoron concentration was  $1,247 \text{ Bq m}^{-3}$  (median 859) [K20]. The radopot and the raduet used in those surveys were passive monitoring devices with CR-39 solid-state nuclear track detectors. The internal dose due to ingested and inhaled radionuclides was not considered in the cumulative dose estimation.

150. Air kerma rate was also measured using a CsI (TI) scintillation pocket survey meter in the bedrooms of eight houses in the same hamlets. It is noted that the air kerma rate was not correlated with radon and thoron gas concentrations or thoron progeny concentration obtained from instantaneous measurements by a semiconductor detector with electrostatic collection and grab sampling of thoron progenies. The estimated effective doses from internal exposure to radon/thoron and from external exposure are summarized in table 17. Effective doses from internal exposure from indoor radon and thoron and their progenies were larger than those from external exposure. This is contrary to the situation in Karunagappally in Kerala, where the internal exposure from indoor radon and thoron is one order of magnitude smaller than the external exposure. Internal exposure was not considered in risk analysis since the indoor radon and thoron survey covered only a small number of houses in the study area. However, radiation dose from internal exposure can increase lung cancer risk in HNBR areas. Nevertheless, the lung cancer mortality in HNBR areas was smaller than that in the control area, probably reflecting differences in smoking habits [T2].

151. Yukawa et al. measured the concentration of  $^{238}\text{U}$  and  $^{232}\text{Th}$  in the food samples collected in Yangjiang, using ICP-MS [Y3]. The annual effective doses from radionuclides from  $^{238}\text{U}$  and  $^{232}\text{Th}$  series through ingestion were estimated to be  $0.3$  and  $1.9 \mu\text{Sv a}^{-1}$ , respectively, in the HNBR area while the corresponding values were  $0.01$  and  $0.2 \mu\text{Sv a}^{-1}$ , respectively, in the control area [W6].

Table 17. Effective annual doses in houses from internal exposure (indoor radon and thoron) compared to external exposure in Yangjiang, China [K20, O2]

The conversion of indoor radon and thoron concentrations to effective doses was based on [U7]

Source of exposure		Effective annual doses (mSv)		
		Minimum	Maximum	Mean
External exposure <sup>a</sup>		0.6	1.8	1.2
Internal exposure <sup>b</sup> (inhalation)	Radon	0.7	12.0	3.1
	Thoron	0.2	10.1	2.2
	Total	1.5	16.4	5.3

<sup>a</sup> Doses were estimated from eight houses in four hamlets in Yangxi and Yangdong county.

<sup>b</sup> Doses were estimated from 59 houses in the four hamlets above. The average radon and thoron concentrations were used during the period between July 2013 and January 2014.

## (b) Biological dosimetry

152. Cytogenetic studies were performed as a validation of the physical dose assessment. In 1990, Wang et al. reported the results obtained from their thyroid study in Yangjiang [W5]. This study, conducted in collaboration between Chinese and United States researchers, examined chromosomes in lymphocytes obtained from residents, and revealed elevated frequencies of chromosomal aberrations in the HNBR area of Yangjiang. The frequency of stable chromosomal aberrations was  $0.29 \pm 0.06$  (mean and standard error per 100 metaphases) in the HNBR area and  $0.18 \pm 0.04$  in the control area. The difference was not significant ( $P=0.14$ ). In contrast, the frequencies of unstable chromosomal aberrations were  $0.16 \pm 0.04$  and  $0.06 \pm 0.02$  in HNBR and control areas, respectively, indicating a significant difference ( $P=0.04$ ).

153. Jiang et al. reported a dose-effect relationship of unstable chromosomal aberrations. Peripheral lymphocytes were taken from 22 inhabitants of different ages in the HNBR area and 17 inhabitants in the control area of the study [J7]. Cumulative dose from birth to the time of blood sampling ranged from 30.9–358.9 mGy and 6.0–59.2 mGy for HNBR and control areas, respectively. The variation of cumulative doses in controls was caused mainly by age because cumulative dose is a function of age. About 2,600 cells per subject on average were analysed. The average frequencies of dicentrics and centric rings were  $2.4 \pm 0.32$  per 1,000 cells for the HNBR-area residents and  $1.4 \pm 0.23$  per 1,000 for the control-area residents. The slope for age, reflecting also increasing cumulative dose, was steeper for the subjects from the HNBR area and there was also a significant effect of dose, but only when age was ignored.

154. When the frequency of dicentrics and rings per 1,000 cells was plotted against the age of each individual, the increase with age in the control group was not significant, but the slope was similar to the reported Japanese atomic bombing survivor data [T16]. In contrast, the increase with age in the HNBR-area was significant, and the slope was about three times steeper than that of the control group.

155. Concerning stable chromosomal aberrations, Zhang et al. analysed translocation frequencies in six children and 28 elderly persons in HNBR areas and in eight children and 24 elderly persons in control areas [Z5, Z6]. About 4,800 cells per subject were analysed on average. Except for two outliers in the elderly group due to medical radiological exposure by fluoroscopy for one and an unknown reason for the other, the mean frequencies in children were  $3.8 \pm 1.1$  per 1,000 cells in the HNBR area

and  $3.2 \pm 2.0$  in the control area. In elderly persons, the values were  $11.3 \pm 3.6$  in the HNBR area and  $10.0 \pm 3.8$  in the control area. Whether the two outliers were excluded or not, no significant difference was found between HNBR and control areas.

#### 4. Cancer mortality

156. The Yangjiang study examined cancer mortality only, and not cancer incidence. However, most cancers other than that of the thyroid and skin were fatal for local farmers, who could not afford expensive cancer treatment. In the most recent study, a cohort of 31,604 men and women aged 30–74 years living in the study area in Guangdong Province, China, was followed during the period 1979–1998 [T3]. The follow-up study accumulated 736,942 person-years at risk, and ascertained 6,005 deaths, including 956 cancer deaths (of which 15 were from leukaemia) and 4,525 non-cancer disease deaths. The number of cancer deaths did not increase in the latest update because the oldest age group (>75 years) was excluded, unlike in the earlier report [S28]. The mean cumulative radiation doses from background radiation in residents were 84.8 mGy in the HNBR and 21.6 mGy in the control areas [T3]. The data for those with attained ages below 30 years were excluded, as in the Indian HNBR study [N4].

157. Statistical analysis was based on the data in cross-tabulation by sex, attained age (five-year category) and follow-up interval. The entry into the cohort was 1 January 1979. The follow-up ended on the date of death or the date of attaining the age of 75 if either occurred before the end of follow-up. Cumulative external radiation dose, lagged by two years for leukaemia and ten years for all other cancers, was estimated for each individual on the basis of hamlet-specific indoor and outdoor air kerma rates, and sex- and age-specific house occupancy factors.

158. The ERR for all cancers, excluding leukaemia, was estimated to be  $-0.101$  per 100 mGy (95% CI:  $-0.253, 0.095$ ), consistent with, though lower than the estimate of  $-0.011$  per 100 mGy (95% CI:  $-0.067, 0.069$ ) reported in an earlier study [S28]. This study did not, however, exclude residents with attained ages below 30, and internal doses of  $4.273 \text{ mSv a}^{-1}$  and  $1.651 \text{ mSv a}^{-1}$  were added to annual doses of HNBR- and control-area residents, respectively.

159. Guangdong Province, including the Yangjiang area, is well known for a high frequency of liver cancer, which is due to a high prevalence of hepatitis B virus (HBV) infection in this area [L10]. The prevalence of the HBV antigen, a marker of HBV carrier state, was 17% in the HNBR area (Tongkou) and 14% in the control area (Enping in Taisha County) [L5]. In site-specific analysis, liver-cancer mortality was related inversely to the cumulative dose (ERR  $-0.338$  per 100 mGy; 95% CI:  $-0.516, -0.061$ ). However, accurate diagnosis of liver cancer is difficult as the distinction between liver cancer and liver cirrhosis, or primary liver cancer and metastasis from another cancer site can be challenging. Therefore, an analysis was conducted combining liver cancer and other liver diseases. No association with dose was observed and the ERR estimate was  $0.025$  per 100 mGy (95% CI:  $-0.203, 0.350$ ) for liver cancer and other liver diseases combined. The ERR for all cancers, excluding leukaemia and liver cancer, was  $0.019$  per 100 mGy (95% CI:  $-0.187, 0.304$ ). Non-cancer disease mortality was not related to cumulative radiation dose. The main characteristics and features of the Yangjiang cohort study are summarized in table 18.

Table 18. Summarized characteristics of the Yangjiang cohort study [T3]

<i>Characteristic</i>	<i>Description</i>
Study design	Prospective cohort study
Study population	The cohort consists of approximately 90 000 residents of the study area, including control areas, who were alive as of 1 January 1979
Outcome	Cancer mortality
Mortality follow-up	Deaths and migration of cohort members were ascertained by trained local census takers. The task group on the mortality follow-up survey then visited the study areas and reviewed the information recorded by census takers. In order to ascertain the cause of death, they visited the related hospitals in the study areas, reviewed medical records of deceased subjects and extracting relevant information. If necessary, the task group revisited the local village doctors and the family members or next of kin to collect further information on the cause of death
Exposure	Individual doses were estimated on the basis of outdoor and indoor doses and sex- and age-specific house occupancy factors. In every hamlet, indoor measurements were conducted in about one third of all households. Outdoor doses were measured on main roads, alleys, open recreational areas, rice paddies, areas adjacent to wells, dry land and the banks of ponds for each hamlet. Annual average dose from external radiation was approximately 2 mGy a <sup>-1</sup>
Confounding	No baseline survey was conducted to collect information on major risk factors for cancer (such as smoking) and, therefore, the study involved no control for confounders. Differences between the exposed and control area in some cancer rates suggest potential confounding
Medical exposure	Information on medical radiation exposure was not collected
Statistical power	The study does not have sufficient power to detect an ERR as large as what is expected from the Japanese LSS
Analysis	The main analysis was to estimate an ERR per unit dose, which was estimated using Poisson regression methods. Cumulative dose was lagged by 10 years for solid cancer risk analysis. Subjects used for analysis were those aged 30 years or older at the time of the baseline survey and attained ages of 30–74 during the follow-up period, which starts at the time of the baseline survey and ends at the time of migration, death, cancer development or the end of follow-up (the end of year 1998)
Main results	For incidence of cancers other than leukaemia, ERR: –0.10 per 100 mGy (95% CI: –0.25, 0.10). After exclusion of liver and nasopharyngeal cancers, the risk estimate was positive, though the confidence interval remained wide and still included negative values

160. The cancer mortality study in Yangjiang did not find increased cancer risk in relation to background radiation. However, the ERR estimate obtained from this study has a wide confidence interval because of the relatively small population size, and rather low cumulative doses, which contribute to low statistical power. These aspects reduce its potential to demonstrate an effect of the anticipated size, given exposure levels. Further, accuracy and completeness of ascertainment of cancer deaths are likely to be below those in highly developed areas. A major limitation of the study is the lack of data on confounders at individual level. The slightly higher rates of viral infections in the control area and differences in mortality from some cancer types suggest confounding, though risk factor surveys have not shown major differences between the regions. A substantial proportion (45%) of all cancer deaths were due to liver cancer and nasopharyngeal cancer, both associated with virus infections. Exclusion of these cancers from the overall analyses of all cancers reverses the direction of the association with background radiation (ERR=0.024; 95% CI: –0.053, 0.149, instead of –0.011 per

100 mSv; 95% CI: -0.067, 0.069) [S28]. Similarly, in the updated analysis, the ERR for solid cancer was positive after exclusion of liver cancer (ERR=0.19; 95% CI: -1.87, 3.04) [T3].

161. Advantages of the study include the minimal effect of migration from these areas during the period and also the reasonably good estimates of radiation dose, based on extensive outdoor dose measurements in each village and indoor dosimetry at selected houses (one third of houses in a village) supplemented by personal monitors, but the levels are too low to be able to discern possible radiation effects. There was also meaningful exposure to indoor radon and thoron in HNBR areas. Cytogenetic studies of blood lymphocytes have indicated higher levels of chromosomal aberrations in persons living in HNBR areas, confirming the difference in population exposure observed in physical dosimetry. The doses in the China HNBR areas (annual effective dose from external exposure  $2.1 \text{ mSv a}^{-1}$  and from internal exposure  $4.3 \text{ mSv a}^{-1}$ ) [Y1], however, appear too small and the dose distribution too narrow to provide convincing evidence of the presence or absence of radiation effects. At such low doses, even 80,000 subjects can be considered insufficient to detect an excess risk, given that one existed, i.e. the study has low statistical power.

162. In summary, while the strengths of this study include the relatively large population, the careful environmental dosimetry programme and low migration, there are limitations. The weaknesses include the uncertainties in dose estimates actually received by individuals, the low and narrow range of cumulative doses, and the possibility that key demographic and lifestyle factors might differ between the high background and control populations. Better access to medical care could mean more accurate and more frequent diagnosis of cancer and less misattribution of causes of death. Inaccuracies in assigning causes of death would be likely to dilute any differences, assuming that the quality of death certificates is similar for the exposed and control populations, while a difference in the quality between the areas could bias the results in either direction.

## C. Other studies

### 1. Guarapari, Brazil

163. *Environmental radiation and residents:* Guarapari, the coastal region of Espírito Santo State, is known for HNBR derived from monazite sands along the Atlantic coast [P7]. The principal radionuclides in monazite are from the  $^{232}\text{Th}$  series, but some uranium is also present. High levels of external radiation on beach sand and in some major streets of Guarapari were reported in the past [C6]. However, recent assessments found that radiation levels in Guarapari were near the average global level, except at hot spots on the beaches and in the fishing village of Meaipe [S1]. The decrease of radiation levels is due to urbanization, including the paving of streets and the construction of tall buildings in this area over the years, in addition to the removal of monazite-containing black sand from the beaches. Analysis of chromosomal aberrations was conducted using 13,242 lymphocytes from 202 persons in Guarapari and 9,001 lymphocytes from 147 persons in control areas. However, the culture period of lymphocytes in this study was too long (72 hours) for analysing aberrations specific to radiation [B6].

164. Other major HNBR areas in Brazil are Poços de Caldas and Araxá in the State of Minas Gerais. The HNBR area in Poços de Caldas is characterized by a huge alkaline intrusion of uranium and thorium anomalies [B2, P7]. Araxá in State of Minas Gerais is known for its spa area, where several

minerals rich in uranium and thorium are found [C1]. Six thousand people reside in the rural HNBR area in Poços de Caldas (population 120,000). The population size of Araxá is approximately 80,000.

165. The average annual effective dose in the rural residents in Poços de Caldas was estimated to be  $13 \text{ mSv a}^{-1}$ , with the range of  $6\text{--}16 \text{ mSv a}^{-1}$  [A14]. In the dose assessments conducted by Veiga et al. in the 2000s, the indoor air kerma rate was  $0.2 \text{ mSv a}^{-1}$  (geometric SD=1.3) in the rural area. The average indoor radon concentration in 41 houses was 220 (geometric SD=2.9) of  $\text{Bq m}^{-3}$  [V2]. A survey of patients in the Araxá spa estimated the mean annual effective dose due to natural sources. It was reported to be  $2.4 \text{ mSv a}^{-1}$ .

166. An ecological (geographical correlation) study was conducted of Guarapari and Araxá that showed no excess of cancer mortality compared with national rates [V3]. In contrast, increased mortality from cancer overall, from stomach, lung and breast cancer, and leukaemia was reported for Poço de Caldas. No cancer risk estimates per unit dose could be provided. Interpretation of this ecological study is limited by the lack of individual doses, the problem of migration not being addressed, and the inability to control for potential confounding factors. The SMR analysis does not allow inference on radiation-related cancer risk.

## 2. Ramsar, Islamic Republic of Iran

167. Ramsar is located 160 km northwest of Tehran on the coast of the Caspian Sea. It contains some HNBR areas of a few square kilometres, caused by  $^{226}\text{Ra}$  deposited from water flowing from hot springs. In addition, travertine with elevated levels of thorium was used as a building material inside the walls of some houses. Exceptionally high environmental dose rates are found in buildings with building material rich in travertine and in areas in close proximity to the hot springs [S21].

168. Dosimetry studies indicated that environmental measurements of ambient dose rate levels of gamma radiation, coupled with house occupancy factors gained by interview, would be inadequate to provide accurate estimates of dose for individuals unless they were supplemented with personal dosimetry measurements. The variation of doses in the homes and in the areas near the hot springs seemed too great for accurate estimation of individual doses. However, the size of the exposed population, only about a few thousand in the highest dose rate areas, is manageable and estimates of individual cumulative doses could be made using focused studies, such as screening for thyroid and possible cataract disorders.

169. A study examined chromosomal aberrations, using lymphocytes collected from 50 long-term inhabitants of Ramsar (with annual effective doses between 1.6 and 42 mSv) [G1]. The frequencies of both unstable and stable chromosomal aberrations in lymphocytes were compared with those in 30 age-matched inhabitants of a nearby control area where the mean annual effective dose was  $2.3 \pm 0.1 \text{ mSv}$ . Significantly increased frequencies of both aberration types were observed in the lymphocytes of Ramsar inhabitants as compared with the control area (mean frequencies for stable aberrations  $6.0\% \pm 2.1$  vs  $1.5\% \pm 0.95$  and unstable  $4.6\% \pm 2.0$  vs  $1.6\% \pm 1.2$ ). In order to further investigate the biological effects of exposure to low-dose radiation and to assess the dose-effect relationship in HNBR-area residents in Ramsar, unstable aberrations were examined, using lymphocytes collected from 15 healthy elderly women in Talesh mahalle, an HNBR area of Ramsar, and in 10 elderly women living in a nearby control area with normal background radiation [Z1]. In total, 77,714 cells were analysed with 48,819 cells from HNBR-area residents and 28,895 cells from control subjects. On average, 3,108 cells per subject were analysed (range 1,475–5,007 cells). Significant differences were found in the frequency per 100 cells of dicentric plus centric rings ( $0.207 \pm 0.103$  vs  $0.047 \pm 0.027$ ;  $P < 0.0005$ ), total

chromosome-type aberrations ( $0.86 \pm 0.44$  vs  $0.23 \pm 0.17$ ;  $P < 0.0005$ ), and chromatid-type aberrations ( $3.31 \pm 2.01$  vs  $1.66 \pm 0.63$ ;  $P = 0.01$ ) between HNBR- and control-area residents. No positive correlation was found between the frequency of dicentric plus centric ring aberrations and the cumulative dose of the inhabitants estimated by direct individual dosimetry.

170. An analysis of population-level cancer mortality rates showed no increase in about 3,000 people in the highest dose areas [M7]. Similar to studies in Brazil, this analysis cannot provide a quantitative estimate of radiation-related cancer risk, as such ecological studies cannot take possible confounding factors into account, including smoking, alcohol, dietary habits and exposure to various chemicals. The statistical power is also low due to the small sample size. Similar ecological studies have also been carried out in areas with lower background radiation level, but they are not covered here as they do not fulfil the inclusion criteria [A13, F1, K7].

## IV. STUDIES ON BACKGROUND RADIATION AND CHILDHOOD LEUKAEMIA

### A. Studies on natural background radiation

171. The association between environmental exposure to natural background radiation and leukaemia risk in children and young adults has not been addressed in HNBR studies in the past, mainly due to the small number of cases. However, recently, several studies have evaluated this association. In this chapter, the large-scale studies are reviewed.

#### 1. Studies in the United Kingdom

172. The United Kingdom Childhood Cancer Study (UKCCS) was a prospective, interview-based case-control study conducted to examine associations between childhood cancer risk and natural gamma-radiation exposure and other potential aetiological factors [U1]. Eligible children were those born in Great Britain (England, Scotland and Wales) who were not in local authority care. Subjects were ineligible if they themselves or their parents had lived outside Great Britain for the three months leading up to diagnosis. In England and Wales, the UKCCS population was defined as children (0–14 years) registered with one of the 98 family health services authorities (FHSAs). Note that, under the National Health Service, all general practitioners (GPs) and their patients are registered with their local FHSA. This comprises around 98% of the total population. In Scotland, where the system is similar but independent, the study population was defined as children registered with one of the 15 Health Boards (HBs) and has been described separately.

173. Case accrual was conducted during 1991–1994 in Scotland and 1992–1996 in England and Wales. The majority of cases were notified by paediatric oncologists belonging to the study group in regional treatment centres. Crosschecks were made against regional cancer registries and against the National Registry of Childhood Tumours. For leukaemia, the principal diagnostic sources were the Medical Research Council's treatment trials. Individual haematologists in participating centres diagnosed acute lymphocytic leukaemia (ALL) and acute myeloid leukaemia (AML) based on morphological, standard

staining and immunophenotyping. Central review was performed by a panel of three haematologists as part of the Medical Research Council's trial protocol. This panel ascribed individual patients to an appropriate French–American–British morphological classification type. To obtain reliable information about the diagnosis of cancers other than leukaemia, a histopathology review database was specially created for the purposes of the study.

174. Two age and sex matched controls were randomly selected from the same (former) FHSA/HB as the case child [U1]. The parents of 3,838 children with cancer (1,736 with leukaemia) and 7,629 children without cancer were interviewed, representing 87% of eligible cases and 64% of eligible controls. The UKCCS investigators found that there was a social class bias in those cases and controls who agreed to participate with more participants in higher socioeconomic groups [U1].

175. At interview, a full residential history for the child was collected with all dwellings inhabited for six months or more targeted for measurement. Indoor gamma-ray levels were measured for six months, using two TLDs, one placed in the main bedroom and one in the main living area. Investigators tried to obtain a complete set of measurements but this proved difficult and, in the final analysis, only the address at diagnosis was used. Measurements were obtained from the home at diagnosis of 2,165 cases (56% of the families interviewed) and 5,086 controls (67% of the families interviewed). Nearly all (97%) estimates were based on readings obtained from both the bedroom and the living room.

176. For the risk analysis, odds ratios (OR) were calculated, using conditional logistic regression modelling. The data were checked for confounding by SES and adjusted using a deprivation score. No evidence was found to support an association between higher background gamma radiation levels and risk of childhood ALL (OR=0.95; 95% CI: 0.66, 1.37 for the highest exposure category with  $>1 \text{ mGy a}^{-1}$ ) or other leukaemias (OR=0.68; 95% CI: 0.26, 1.82 for the highest exposure category), and no significant trends emerged across exposure categories. The investigators concluded that “it is unlikely that a relative risk of this magnitude predicted by modelling would be detectable in the present study after its statistical power, modest variations in dose rate and limitations of data collection are taken into account”.

177. The low participation rate of controls (64%) is a concern as are the low proportions of residences measured (49% of the originally eligible case and 43% of the originally eligible controls). Participation rates were affected by the deprivation score, a SES indicator, which was related to environmental dose. Medical exposure was not considered, nor birth weight or parental age as potential confounders. Exposure from radiation treatment is unlikely since children with prior malignancies were not eligible. Although this study found no association with measured values of gamma-ray exposure in homes, it does not have sufficient power to detect an ERR as large as what is expected from the LSS and the potential for serious participation bias must be considered.

178. A historical, record-based case-control study of childhood cancer examined associations with natural background radiation in Great Britain [K3]. The principal end point of interest in this study was leukaemia, but all types of cancer were included in the cases. This study examined a large number of cases (27,447, including 9,058 with leukaemia), comprising children born and living in Great Britain who were diagnosed before their 15th birthday, during the period 1980–2006. Lymphoid leukaemia accounted for more than 80% of all leukaemia cases. Those cases in children aged less than 15 years were ascertained through the National Registry of Childhood Tumours, which is an essentially complete population-based registry of cancer diagnosed in Great Britain from 1962 onwards. A control was selected for each case from the same birth register, matching on sex and date of birth (within six months). For cases diagnosed in 2000 and later years, a second control was selected in a similar way. Controls, which numbered 11,912 for leukaemia, were cancer-free at the time of diagnosis of their matched cases. There were no differences in SES between cases and controls.

179. Cumulative doses from gamma-ray exposure were calculated, using mean gamma-ray dose rates for county districts where the mothers of cases or controls lived at the time of the child's birth (generally defined to a few metres). Mean dose rates in county districts were obtained from the National Survey of natural background radiation based on 2,283 measurements of gamma radiation in houses [W10]. There are 459 county districts (or equivalent) in Great Britain with a mean surface area of 500 km<sup>2</sup> and the child population ranging from 300 to 213,000 (mean 24,000). About half the cases in the study had moved between birth and diagnosis. In an additional analysis, the effects of mobility on the association between leukaemia risk estimate and natural radiation dose were assessed as likely to be small [K4, K5]. Indoor radon levels were also estimated, using predictive maps based on domestic measurements grouped by geological boundaries, and cumulative radon exposure and RBM doses were calculated. The median gamma dose was 3 mGy among both cases and controls (interquartile range from 1 mGy to 5–6 mGy). ERRs per unit dose were estimated from ORs calculated using logistic models. SES was taken into account either through area-based deprivation measures or paternal occupation from the birth certificate. ERRs for all leukaemia and all cancers excluding leukaemia were 9 per 100 mGy (95% CI: 2, 17) and 2 per 100 mGy (95% CI: -2, 6), respectively. For bone marrow dose from gamma rays, the ERRs for all leukaemia, lymphoid leukaemia and acute myeloid leukaemia were 12 per 100 mGy (95% CI: 3, 22) and 13 per 100 mGy (95% CI: 2, 24) and 5 per 100 mGy (95% CI: -13, 28), respectively.

180. The information for this study was obtained by record linkage, so no interviews were used. The drawback was that neither individual residential histories nor direct radiation measurements of the homes of study subjects could be obtained. The leukaemia cases were identified through the National Registry of Childhood Tumours. The accuracy of leukaemia diagnosis can be considered high. Exposure estimates were based on mean dose rates in county districts, which are relatively large geographical units, of the residence at time of the birth. Interview of study subjects was not sought. The strength of this study is the large number of cases and controls, accurate and virtually complete case ascertainment, and also lack of participation bias. Of concern are uncertainties regarding dose estimates, which were area-based average dose rates at birth place obtained for large area units from a relatively small number of measurements, and lack of full residential history. This ignores house-to-house variability within a geographical unit, reducing the precision of exposure assessment, presumably in direct relation to the size of the unit used in the analysis. A previous report [L6] indicated that the sample of this study should provide reasonable power to detect the risk from natural background gamma radiation predicted by standard risk models. Hence, the study appears to have sufficient power to detect an ERR as large as that expected from the Japanese LSS. Although information on medical exposure is lacking, during the study period (1980–2006) medical exposure is unlikely to have been large enough to materially affect the results of risk analysis unless strongly correlated with natural background radiation. Departure from linearity was not formally examined.

## 2. The Swiss study

181. In a nationwide, record-based study of a cohort of children identified by the Swiss National Census in 1990 and in 2000, the relationship between the incidence of childhood cancer and background radiation exposure was examined [S25]. Study subjects were residents aged younger than 16 in Switzerland. Follow-up began at the first census in which a child was recorded (entry time) and ended on the earliest of following events: diagnosis, death, emigration, the child's 16th birthday and administrative censoring on the 31st December 2008. Cases diagnosed during the period 1990–2008 were ascertained by the record linkage through the Swiss Childhood Cancer Registry. From 2,093,660 children included at the census, 530 incident cases of leukaemia were identified.

182. In Switzerland, the central alpine massif has relatively high natural background radiation levels due to the relatively high radioactivity of crystalline rocks when compared to the sedimentary northern alpine foreland (Jura, Molasse Basin) [R8, R9]. Exposure was based on residential location at census. External background radiation levels in children's homes were estimated from a database of outdoor gamma radiation measurements, using a model which predicted dose rates for each cell of a  $2 \text{ km} \times 2 \text{ km}$  grid as the sum of cosmic radiation, natural terrestrial gamma radiation, and radiation from human-made sources [R8, R9]. For a child who was found to have lived at different locations in the 1990 and 2000 censuses, the 1990 exposure was updated in 1995 or 2000 depending on whether or not the child lived at the new location five years before the census in 2000 taking the information from census questionnaires. On average, the effective cumulative dose was approximately 9 mSv. Natural terrestrial radiation contributed most with  $54 \text{ nSv h}^{-1}$ , cosmic radiation  $45 \text{ nSv h}^{-1}$  and anthropogenic terrestrial radiation with only  $8 \text{ nSv h}^{-1}$ .

183. Several factors were considered as potential confounders, including traffic-related air pollution (distance to nearest highway as a proxy), electromagnetic fields from radio and TV transmitters, and from high voltage power lines (distance to nearest 380 kV or 220 kV power line), degree of urbanization of municipality (urban, suburban, rural), SES based on the Swiss neighbourhood index of socioeconomic position (Swiss-SEP), education of the household reference person (compulsory, secondary, tertiary, from the national census) and crowding (the number of persons per room), birth weight and birth order of the child. Information on education and crowding was obtained from national census data. Birth weight and birth order of the child, which were obtained from the birth registry, were available for approximately 60% the study subjects. The Swiss-SEP is an area-based measure of socioeconomic position [P1]. This index is defined for neighbourhoods of 50 households with overlapping boundaries using Census 2000 and road network data, and is based on median rent per square metre, proportion of households headed by a person with primary education or less, proportion headed by a person in manual or unskilled occupation and the mean number of persons per room were analysed in principle component analysis.

184. Cox regression models were used to assess associations of cancer risk with dose rates and cumulative dose since birth. The hazard ratio for the cumulative dose of external radiation was 1.04 per mSv (95% CI: 1.00, 1.08) for leukaemia, corresponding approximately to an ERR per 100 mSv of 4 (95% CI: 0, 8). In this study, the excess leukaemia risk was virtually restricted to children exposed to  $>200 \text{ nGy h}^{-1}$ . Adjustment for a range of potential confounders had little effect on the results.

185. Interview of study subjects was not sought. Information necessary for follow-up and exposure assessment, and on SES was obtained by record linkage. Area-based measures of exposure were used instead of individual estimates and they were estimated for the dwelling of the child at the census. Migration was at least partially taken into account and an analysis restricted to children with stable residence gave higher hazard ratios. Internal exposure was not considered in this analysis (though evaluated in a parallel publication). Besides leukaemia, a similar positive relationship was also found for several other tumour types and it was close to significance for CNS tumours and other CNS and lympho-haematological malignant tumours, unlike in the UKCCS [K3]. The increased risks were largely due to a high risk in the highest exposure category, with little indication of excess in the intermediate exposure groups. The strengths of this study include virtually complete case ascertainment, lack of participation bias and the availability of information on several potential confounders. However, the number of leukaemia cases was relatively small, given the anticipated effect size (and smaller than in some other studies). Of concern are uncertainties regarding area-based dose estimates related to a single dwelling. Information on medical radiation exposure was not collected. The statistical power was not sufficient for detecting an effect of similar size to the LSS.

### 3. The Finnish study

186. A nationwide register-based case-control study was conducted to examine childhood leukaemia risk associated with background radiation [N10]. Subjects were children aged 2–15 years in Finland (the entire nation). Cases (N=1,093) were identified through the Finnish Cancer Registry (known for its high quality). Three controls were selected for each case matching on sex and year of birth from the database at the Population Register Centre (N=3,279).

187. Complete residential histories and previously collected survey data of the background gamma radiation in Finland were used to assess the exposure of the study subjects to indoor and outdoor gamma radiation. Outdoor dose was from the data encoded in a map of 8 km × 8 km grids based on a nationwide mobile survey carried out in 1978–1980 obtained from Radiation and Nuclear Safety Authority [A16]. The nationwide average dose rate outdoors was 51 nSv h<sup>-1</sup>. For the residencies abroad (N=63, 0.8% of all residencies), the world's average natural background radiation value reported by UNSCEAR (55.3 nSv h<sup>-1</sup> effective dose rate) was used [U10]. The indoor doses of gamma radiation were based on measurements in 346 randomly chosen dwellings. The national average dose rate in houses was 41 nSv h<sup>-1</sup> and in flats/apartments 70 nSv h<sup>-1</sup> [A16]. The difference is due mainly to the concrete used as the building material in blocks of flats. The indoor rates were correlated with local outdoor gamma-radiation levels. These correlations were used for converting local outdoor dose rates to indoor dose rates. The percentage of time spent indoors (indoor occupancy) was modelled according to a Finnish study providing age group specific estimates [M1].

188. The mean annual effective dose from medical radiation in Finland is 0.45 mSv in 2012, but for children it is markedly lower due to strict imaging guidelines especially with CT scans, which constitute the largest contribution to the annual dose from medical exposure [M8, U10]. Furthermore, CT use in Finland is less frequent than in many other industrialized countries and only 1.7% of CT scans in Finland were performed on children [H3]. Since average population doses from medical procedures are relatively small compared to annual doses from background radiation (0.59 mSv to RBM) in this study and no correlation with background radiation was anticipated, medical radiation exposure was judged unlikely to cause confounding.

189. Data on diagnosis of Down's syndrome were obtained from the Register of Congenital Malformations by the National Institute of Health and Welfare. Data on gestational weeks and birth weights were obtained from the Medical Birth Register for all but 184 (18.6%) cases and 511 (15.6%) controls. Maternal smoking data were obtained from the Medical Birth Register and data were missing for 200 cases (18.3%) and 563 controls (17.2%).

190. Conditional logistic regression analyses were adjusted for Down's syndrome, birth weight (large for gestational age) and maternal smoking. Investigators stated that this study has sufficient power (≥80%) to detect a linear dose response with OR of 1.06 or greater per 10 nSv h<sup>-1</sup> increase in dose rate. This study reported ORs per unit dose rate and ORs per unit cumulative dose. Investigators did not clearly state which leukaemia subtype was the main target of the risk estimate. Regarding dose rate, the overall OR for leukaemia was 1.01 (95% CI: 0.97, 1.05) for each 10 nSv h<sup>-1</sup> increase in the equivalent dose rate to RBM. Regarding cumulative dose, the OR was 0.97 (95% CI: 0.89, 1.06) for a 1 mSv increase in cumulative equivalent dose to RBM. In subtype-specific analysis, only the relationship between ALL and dose rate gave an OR larger than 1, which was 1.02 (95% CI: 0.98, 1.07). Cumulative dose was not positively associated with any of the leukaemia subtypes. In age-specific analysis, ORs per 10 nSv h<sup>-1</sup> were 1.05 (95% CI: 1.00, 1.10) for ages 2–6 years and 0.93 (95% CI: 0.86, 1.00) for ages 7–15. For cumulative dose, the ORs were 1.27 (95% CI: 1.01, 1.60) and 0.93 (95% CI: 0.85, 1.02) per 1 mSv, respectively. The OR for the younger age group approximately corresponds to ERR per 100 mSv of 27 (95% CI: 1, 60). The increased risk is significant for ages 2–6 years, however,

it may still be a chance finding, given the wide confidence interval. The statistical power presented in the study was low for the effect sizes predicted from LSS.

191. In this study, cases were ascertained through the Finnish Cancer registry, which covers the entire nation, and is known to be of high quality [D1, T8]. Investigators estimated lifetime cumulative doses and average dose rates to RBM from background gamma radiation using information on indoor and outdoor survey data and housing types during the lifespan of the children. One of the advantages of this study in dose estimation is the fact that the residential history of every study subject was collected. A disadvantage was the lack of residential dose rate measurements. Information on medical exposure is also lacking but, as the investigators concluded, medical exposure is unlikely to distort the risk estimate substantially in a country where CT use has been strictly controlled. Information on SES was not obtained (and therefore not adjusted for) in this study.

#### 4. The French study

192. A study combining small-area-based incidence analysis and a case-control study investigated the association between acute leukaemia and location-based estimated exposure to natural background radiation in France [D18]. The incidence study identified 9,056 acute leukaemia cases during the period 1990–2009 through the French National Registry of Childhood Cancer. Complementary analyses used the data obtained from the so-called “GEOlocalisation des Cancers Pédiatriques (GEOCAP) study, which examined 2,763 acute leukaemia cases diagnosed during the subperiod 2002–2007, and 30,000 control children with geocoded addresses randomly sampled by the French National Institute for Statistics and Economic Studies, using the income and council tax databases for households.

193. Since residential history was not available in this study, cumulative exposure to radon or gamma radiation were calculated on the basis of residence at diagnosis or inclusion and the assumption that the same exposure had prevailed since birth. According to an interview-based study [R7], 66% of the children had been living in the same municipality since birth. The correlations between exposure estimates at birth and at diagnosis/inclusion were 0.86 for radon exposure and 0.89 for gamma-radiation exposure.

194. Dose from environmental radiation exposure was estimated on the basis of the 36,326 municipalities in France and geocoded addresses of the residences, which were available at the time of diagnosis (cases, 1990–2009) or inclusion (controls, 2002–2007). Natural background exposure was determined at the town centre for radon, and as the mean exposure over the municipality territory for gamma radiation, in the incidence study, and at the residence address and the town centre, respectively, in the case-control study. The radon domestic exposure was estimated from two datasets: (a) 10,843 measurement results of indoor radon concentration performed by the Institute for Radiological Protection and Nuclear Safety and Health Ministry during a national campaign (1982–2003), and (b) the French map of the geogenic radon potential. A mathematical model using both datasets was developed, enabling estimates of the indoor radon concentration measured in a 1 km × 1 km grid. Exposure to natural background gamma radiation was calculated as the sum of exposures to cosmic gamma radiation and terrestrial gamma radiation. The determination was based on 97,595 measurement results of indoor gamma dose rate conducted by the Institute for Radiological Protection and Nuclear Safety in 17,404 dental surgeries and veterinary clinics throughout France, using radio photoluminescent dosimeters, exposed for several months in 2011–2012. To estimate the indoor telluric gamma dose rate, multicollocated co-kriging was conducted on 1 km × 1 km grid in a geostatistical model that used two datasets: the indoor terrestrial gamma radiation dose-rate measurement results and the French map of geogenic uranium potential. For the 30,000 GEOCAP controls, the arithmetic mean radon exposure estimated at the place of residence was 67.8 Bq m<sup>-3</sup> (SD=45.5), the 5th percentile was

24.9 Bq m<sup>-3</sup> and the 95th percentile was 145.3 Bq m<sup>-3</sup>. The arithmetic mean gamma radiation exposure was 98.2 nSv h<sup>-1</sup> (SD=24.9), the 5th percentile was 70.1 nSv h<sup>-1</sup> and the 95th percentile was 148.5 nSv h<sup>-1</sup>.

195. The potential for confounding by SES was taken into account by stratification on the quintiles of the first component in a principal component analysis of four census variables: median income and percentages of baccalaureate holders, labourers and unemployed. This was based on the 1999 census and was strongly correlated with the indicators based on the 1990 and 2006 censuses. In addition, the GEOCAP case-control study was used to evaluate potential confounding by environmental factors available at the address of residence by exclusion (vicinity of nuclear power plants or proximity to high-voltage power lines) or by adjustment (proximity of high-traffic roads). There was no confounding effect of census-based socio-demographic indicators, or environmental factors (road traffic, high voltage power lines, vicinity of nuclear plants) related to acute leukaemia in the GEOCAP study.

196. The power to detect an association between acute leukaemia and dose to RBM in the incidence analysis based on the UNSCEAR 2006 Report [U8] exponential multiplicative model assuming ERR 20 per Gy was 92% for exposure to natural gamma radiation (using simulation with the observed exposure distribution). A standardized incidence ratio (SIR) was calculated as a ratio between the observed and expected numbers of cases by exposure category; the expected number of cases was calculated on the basis of the age-specific incidence rate and number of person-years in that stratum. The power calculation did not consider any attenuation due to exposure misclassification from use of aggregate data instead of individual measurements.

197. Acute leukaemia, irrespective of subtype and age group, was not significantly associated with the municipality-specific gamma radiation exposure level in terms of annual dose at age reached and the cumulative exposure to RBM dose. In the incidence analysis, acute leukaemia risk showed a small increase with gamma dose rate (SIR=1.01 per nSv h<sup>-1</sup>; 95% CI: 1.00, 1.02), but no association with cumulative gamma dose (SIR=1.00 per mSv; 95% CI: 0.99, 1.01). The results were not changed by incorporating a time lag of 24 months in the analysis. In the case-control analysis, no association with background gamma radiation dose rate was found (OR=1.00 per 10 nSv h<sup>-1</sup>; 95% CI: 0.98, 1.01).

198. This is a large record-based study using a reliable source of childhood acute leukaemia cases, and the power to detect the predicted effect is high. The number of indoor dose-rate measurements is also large although the exposure range appears quite narrow for evaluating the association between childhood leukaemia risk and background radiation as the third quartile of the cumulative dose was only 50% higher than the first quartile. Municipality-level estimates of radiation exposure and lack of full residential history (a third of the subjects had moved at least once) were other potential weaknesses.

## B. Studies of environmental exposure from human-made sources

### 1. The case-control study in Belarus, the Russian Federation and Ukraine

199. A population-based case-control study of acute leukaemia was conducted in the areas of the former Soviet Union that were contaminated by radioactivity from the Chernobyl accident [18]. Eligible subjects (cases and controls) were children who were in utero or <6 years of age at the time of the Chernobyl accident and were in contaminated regions of Belarus, the Russian Federation and Ukraine, which were the Gomel'skaya and Mogilevskaya Oblasts in Belarus, the Bryanskaya Oblast in the

Russian Federation (the most contaminated oblast), and the Rovenskaya, Zhytomirskaya, Chernigovskaya, and Cherkasskaya Oblasts in Ukraine (Chernigovskaya and Cherkasskaya Oblasts were on average significantly less contaminated than the Rovenskaya and Zhytomirskaya Oblasts).

200. Eligible for the study were acute leukaemia cases diagnosed in these geographic regions during 26 April 1986 and 31 December 2000. They were identified from records of the Pediatric Oncology Centre in Belarus, the national Belarus Tumour Registry and the Bryansk Oncology Registry in the Russian Federation. In Ukraine, case ascertainment was based on the archival records of regional cancer hospitals. A group of haematological morphologists and haematologists from Belarus, Israel, the Russian Federation, Ukraine and the United States verified the diagnosis of leukaemia on the basis of haematology slide review. In 67 cases, diagnosis was made on the basis of other information, such as the results of laboratory tests, medical records from the diagnosing institution, and patient therapy data. Of 463 identified potential acute leukaemia cases, a diagnosis was made in 95% (442 cases).

201. A total of 20 potential controls were selected from the clinical records for each case and interviews were scheduled for the first two. If the first or second potential controls could not be reached, the next individuals on the list were contacted. Controls were matched to each case on sex, birth year and residence. Eligible controls were those who were alive at the reference date, which was the date of diagnosis of the corresponding case. The protocol of matching on residence differed between republics. Investigators described it as follows: “In Russia, controls were matched to cases on raion of residence of the case at the time of accident. In Ukraine, controls were initially matched on raion of residence of the case at the time of accident (118 or 22% of the controls), and subsequently were to be randomly selected from a raion different from that of the case, but within the same oblast. In Belarus, controls were matched to cases on raion of residence on the reference date and randomly selected from any raion of residence at the time of accident with the selection weighted by raion population”.

202. Trained physicians and dosimetry specialists interviewed the cases and controls to collect information on demography, general health interview, leukaemia risk factors, maternal and paternal occupational history and radiation exposure, using questionnaires. For deceased cases, the interview was administered to substitutes, preferably the subject’s mother or another close relative. The dosimetry questionnaire included questions on the sources, types and consumption of milk; sources and consumption of food; residence and occupation; relocation and migration; personal protective measures after the accident; type of housing; and time spent indoors and outdoors after the accident.

203. Cumulated radiation dose absorbed by the bone marrow was estimated for cases and controls from the time of the accident until the reference date, taking account of dose changes over time. External dose for a particular residence was calculated on the basis of field measurements. Internal dose estimates relied on food, water and milk consumption. For study subjects who were possibly exposed in utero (61 cases), the mother’s residence and dietary history were also obtained in order to estimate the dose received in utero. The uncertainties of individual doses were estimated by Monte-Carlo simulation of the variability of each of the input parameters used for dose calculations. Median estimated radiation dose of participants was 10 mGy.

204. In statistical analysis, logistic analysis adjusted for matching was conducted. A log-linear model used by investigators gave an ERR of 32 per Gy (95% CI: 8.8, 84). An increase in leukaemia risk with increasing radiation dose to the bone marrow was found only in Ukraine (ERR=79 per Gy; 95% CI: 22, 213). Investigators admitted that “the large and statistically significant dose response might be accounted for, at least in part, by an overestimate of risk in Ukraine”.

205. The risk estimate reported is very large and mainly driven by the Ukrainian data (particularly Cherkasskaya Oblast), with a different matching from the other countries. Whether the control series represents the catchment population of the case series or not is unclear. Medical exposure was not considered. The general conclusions of the Committee thus remain that there is little convincing evidence to suggest a measurable increase in the risk of leukaemia among those exposed as children to the radiation resulting from the accident at Chernobyl [U11]. This conclusion is consistent with the earlier cancer registry studies of childhood cancer risk in Europe following the Chernobyl accident [A18, H6, P3, P5].

## V. BIOLOGICAL DOSIMETRY

206. In the TRC study, two methods were used for the validation of estimates of external absorbed dose: EPR on human teeth and stable-type chromosomal aberrations in human lymphocytes [D11, V9]. The results of these studies were generally correlated with the estimates of the external absorbed dose calculated for the residents of Metlino. As this is the closest settlement to the discharge point, the residents there received the highest levels of external exposure. In the Yangjiang and Karunagappally studies, the analysis of chromosomal aberrations was also performed in order to validate the physical estimates of absorbed dose. In both areas, increased frequency of unstable chromosomal aberrations (dicentric and rings) has been demonstrated, but no excess of stable aberrations (translocations) has been shown compared with inhabitants from areas with lower levels of background radiation.

207. While analysis of chromosomal aberrations has contributed to the estimation of absorbed dose, uncertainties and limitations are, nevertheless, involved in their application to the estimation of dose from prolonged low-level radiation exposure [V5], especially from internal emitters [A3]. One of the reasons for the uncertainty is the low number of aberrations induced by chronic low-level radiation exposure and the low cumulative dose. Though unstable chromosomal aberrations are recognized as a sensitive and specific marker for exposure to ionizing radiation, a large number of cells must be scored to minimize the uncertainty when the dose is low. The frequencies of spontaneous translocation were reported to be of the order of one per hundred cells [S17], higher than those of dicentric and rings, of the order of one per thousand cells [I9]. This is because translocations can be induced by many clastogens in contrast to dicentric and rings, where induction is relatively specific for radiation exposure. Therefore, this makes it difficult to distinguish translocations induced by radiation from those induced by other clastogens. An increased frequency of dicentric and centric rings has been reported in vitro at an acute dose of about 20 mGy, but for human biological dosimetry, in practice a detection limit of approximately 0.1 Gy is realistic [I9, L8, S31].

208. The complexity of the elimination rate of aberrant lymphocytes in vivo is another reason for the uncertainty. The elimination of lymphocytes with unstable chromosomal aberrations might be affected by other factors, such as age and elapsed time between exposure (or end of chronic exposure) and blood sampling [S2]. The information available from biological dosimetry studies in the assessment of health effects from low doses of radiation is currently limited because of the low detection limits, the resources required for large studies and incomplete participation. They are, nonetheless, useful markers of exposure and provide some assurance that the estimates of dose are generally consistent. Furthermore, several of the studies are difficult to interpret because of the lack of understanding of the influence of internal radiation on chromosomal aberrations.

209. For stable chromosomal aberrations, which are considered to persist for longer than the unstable type, a significant dose–response relationship has been observed in studies of radiology technologists [B12] and radiation workers [T7]. Because translocations can be introduced by many clastogens other than ionizing radiation, they increase with age [S17], and individual variation is large. This makes it difficult to demonstrate the difference between radiation-induced translocations and those caused by other factors, such as smoking or chemicals. In spite of these uncertainties and limitations, cytogenetic methods could be successful in validating relatively high cumulative doses.

210. The detection threshold for FISH-based analysis of translocations depends on the type of exposure (uniform whole-body vs partial body, radiation quality), number of cells scored, age, and co-exposure such as smoking. Estimates of detection limit have ranged 200–500 mGy and lower doses are detectable for exposed groups (population average) than at individual level. Chromosomal aberrations have been shown to predict subsequent cancer risk, which seems to reflect partly innate DNA repair capacity and partly the influence of external exposure [B14, B16]. Further studies to validate their capacity for predicting cancer risk from low-dose radiation exposure would be important.

211. Unstable and stable aberrations are produced in equal proportions and the latter could lead to cancer [H1]. However, despite an excess of unstable aberrations in the residents of HNBR areas in Yangjiang and Karunagappally, no increase was observed in cancer mortality (Yangjiang, China) or cancer incidence (Karunagappally, India). Studies of newborns do not appear informative, despite the advantage of being free from influence of other exposure. It seems that the potential higher sensitivity of infants is offset by the low in utero exposure levels in HNBR.

## VI. COMPARATIVE EVALUATIONS OF SELECTED STUDIES

212. In this chapter, studies on solid cancer and childhood leukaemia will be compared and evaluated further. In addition, the TRC study, unlike other studies reviewed here, has provided reasonably precise and valid risk estimates for adult leukaemia. The main focus here will be to reach a synthesis of available evidence, with assessment of the methodological features of the studies, applying the quality criteria of annex A. The main outcomes of different studies were analysed by all cancer types (except all leukaemia combined) and by childhood leukaemia separately. Combining a variety of cancer types into a single category can result in poor comparability of the findings, which is discussed below. Further, specific cancer types pose less of a problem in this respect, but statistical power is substantially lower. Several studies assigned environmental exposure estimates based on area of residence linked with dose-rate measurements instead of strictly individual measurements. Even in the LSS, individual radiation dose was not measured but estimated retrospectively on the basis of location and shielding. Aggregate level studies without individual data (ecological studies or geographical correlation studies) are not addressed here, as they were judged as not informative enough for risk assessment.

213. Statistical power is an important point for consideration. Most epidemiological studies on low-dose-rate exposure ( $<0.1 \text{ mGy min}^{-1}$ ) have relatively low cumulative doses ( $<200 \text{ mGy}$ ). The potential cancer risk from such low doses is very small, and can be easily missed or, alternatively, spuriously produced by bias and confounding. In the most recent LSS report on cancer incidence in Japanese atomic bombing survivors, exposure to 1 Gy of gamma radiation at age 30 increased solid cancer incidence at age 70 by 47% [G7]. If we can assume that the ERR per unit dose is proportional to the dose, a radiation dose of 200 mGy increases solid cancer risk in men by approximately 9% ( $=47/5$ ), which corresponds to a RR of 1.09 and an ERR of 0.09.

## A. Studies in areas with elevated environmental radiation levels

### 1. Review of selected studies

214. In this section, studies will be compared that provided a quantitative estimate of cancer risk per unit dose of environmental radiation for general population. Table 19 summarizes the main features of radiation exposure and its sources in those studies. Associations between environmental radiation and cancer risk observed in those studies vary in degree but they are not inconsistent because of large confidence intervals. They have the potential to provide new knowledge on the magnitude of excess risk from low-dose-rate radiation exposure and to some extent too on modifiers of such risk and risk related to specific cancer sites. Tables 20–23 summarize methodological features of those studies.

215. The Karunagappally study and the Yangjiang study are prospective cohort studies. The TRC was established mainly in the late 1960s through 1980 (the majority of subjects were identified in the late 1960s), and follow-up was conducted partly retrospectively, partly prospectively. Case ascertainment for cancer incidence and mortality is a major factor in epidemiological studies, and comprehensive and high-quality case ascertainment is particularly important for the interpretation of low-dose/low-dose-rate studies. Ascertainment in the studies of high-background radiation areas may not be adequate for addressing the effects of low-dose radiation, particularly in the early follow-up period.

216. In the TRC study, the follow-up of cancer was started for mortality in the 1950s and for cancer incidence in 1956 and is still continued up to now. There was no national cancer registry in the Soviet Union and follow-up of cancer incidence in TRC members started only from 1956. In the TRC study, the proportion of cases identified solely through death certificate notification decreased throughout the follow-up period from 35% for 1956–1969 to 9% for 1990–2007, while the proportion of cases with morphological or radiological confirmation (e.g. based on X-rays, ultrasound) increased from 33% to 82% between the above time periods. The investigators of the TRC cancer incidence study [D5] concluded that for the studied period “the ascertainment of solid cancers is thought to be largely complete for cohort members residing in the study regions”.

217. In the early follow-up of the study, the cancer registry in Karunagappally had approximately 10% of cases based on death certificate only, which is higher than desirable, particularly in a low-dose study. In the Yangjiang study, with only mortality follow-up, the ascertainment of deceased cases was virtually complete except for subjects who moved out of the study area permanently. That is particularly so for old residents, who tend not to migrate. However, the accuracy of cause-of-death data can be a problem and it will be discussed later.

Table 19. Main features of radiation exposure in cohort studies on cancer risk from low doses of radiation from environmental sources

Feature	<i>Techa River study [D5, K18, S3]</i>	<i>Karunagappally study [N4]</i>	<i>Yangjiang study [T3]</i>
Main sources of external exposure	$^{137}\text{Cs}$ and shorter-lived fission products	$^{232}\text{Th}$ and its decay products	$^{232}\text{Th}$ and its decay products
Sources of internal radiation exposure	$^{90}\text{Sr}$ , $^{89}\text{Sr}$ , $^{137}\text{Cs}$	Negligible	Negligible
- Ingestion			
- Inhalation	Negligible	Radon: $<10 \text{ Bq m}^{-3}$	Radon: $10\text{--}100 \text{ Bq m}^{-3}$
Period of exposure	Lifetime; highest exposure: 1950–1956	Lifetime	Lifetime
Dose rate	Mean RBM dose: $135 \text{ mGy a}^{-1}$ in 1951, $10\text{--}60 \text{ mGy a}^{-1}$ in 1952–1960, $<10 \text{ mGy a}^{-1}$ afterwards Mean stomach dose: $28 \text{ mGy a}^{-1}$ in 1951, $0.3\text{--}15$ to $15 \text{ mGy a}^{-1}$ in 1952–1960, $<1 \text{ mGy a}^{-1}$ afterwards	$1\text{--}15 \text{ mGy a}^{-1}$ (colon dose from external exposure)	$1\text{--}5 \text{ mGy a}^{-1}$ (colon dose from external exposure)
Mean cumulative doses	RBM dose: 430 mGy; Stomach dose: 43 mGy	188 mGy (colon dose from external exposure)	85 mGy (colon dose from external exposure)

Table 20. Features related to study populations in cohort studies on cancer risk from low doses of radiation from environmental sources

Feature	<i>Techa River study [D5, K18, S3]</i>	<i>Karunagappally study [N4]</i>	<i>Yangjiang study [T3]</i>
Study design and study population	A cohort study of rural residents (mainly farmers), 12 558 men and 17 172 women of all ages. Cancer incidence study is based on a subcohort (N=17 435) consisting of residents in Chelyabinsk Oblast	A cohort study of rural residents, 32 085 men and 37 873 women, aged 30–84 years	A cohort study of rural residents (mainly farmers), 16 045 men and 15 559 women, aged 30–74 years
Eligible subjects	All residents born before 1950 who lived in 41 villages along the Techa River in 1950–1960	All residents whose information was collected at the time of baseline survey (1990–1997)	All residents of the study area, including control areas, who were alive as of 1 January 1979
Selection bias of study subjects	It is unlikely that there could be selection bias since, according to the Soviet law in the 1950s, the list of residents of any village was constantly updated by the local administration. All persons were members of collective farms and could not leave a workplace without official permission. Residents of villages had no passports till the 1960s. Moreover, all residents were listed in tax books, which were updated for each farm. Loss to follow-up was relatively high, but unrelated to exposure levels	Selection bias is unlikely since it is a prospective cohort study, in which incident cancer cases were identified in a prospective follow-up after a baseline survey	Selection bias is unlikely as there is no reason to suspect that the identification of study subjects is affected by vital status and exposure status
Comparability of the exposed and control/comparison groups	Lower dose groups tend to be located in more remote places	Some highly exposed areas are located near the major fishery ports	The control areas are closer to metropolitan areas

Table 21. Features related to exposure and exposure assessment in cohort studies on cancer risk from low doses of radiation from environmental sources

<i>Feature</i>	<i>Techa River study</i> [D13, D14, D16, S10, S12]	<i>Karunagappally study</i> [N3, N4, O3]	<i>Yangjiang study</i> [K20, M6, O2, T3, Y1]
Ages at exposure / exposure periods	Lifetime exposure since 1949. The main exposure took place in the early 1950s	Lifetime exposure from birth time for those without migration	Lifetime exposure from the birth time for those without migration
Individual dosimetry	Individual external dose estimates were based on exposure rate measurements along the banks of the river and on the shore within a few hundred metres from the water in specified areas of settlements. The estimates for each settlement were calculated as a weighted sum of the dose rates at locations with high occupancy, including houses. Individual internal dose estimates were based on measurements of <sup>90</sup> Sr in the subjects (post-mortem concentrations in bone samples, in vivo measurements of surface activity of anterior teeth, body-burden measurements)	Individual external dose estimates were calculated as a weighted sum of the average ambient dose rates at locations with high occupancy, including homes. The time spent at the corresponding location is used as the statistical weight	
External dosimetry (outdoors)	Measurements conducted periodically at 25 monitoring posts along the shoreline of the river	Measurements conducted at the front gate of all the houses in the study area	Measurements conducted at major activity areas (e.g. roads, open recreational areas, rice paddies) in all the hamlets in the study area
External dosimetry (indoors)	The ratios between indoor and outdoor air kerma rates were obtained from a survey of 10 houses conducted in 1954	Indoor air kerma rate measurements were made in the room with maximum occupancy at every house at the time of the baseline survey during 1990–1997	Indoor dosimetry was conducted in the main bedroom, the sitting room and the kitchen in one third of houses in each hamlet
External dosimetry (indoors, non-residential)	Measurements were conducted in the areas within 400 m all along the Techa River (about 200 km long), including farmland	Not conducted. Air kerma rates at school or at work were not measured	Air kerma rates in schools and also at farmland in each village were conducted
Occupancy factors	Took into account only the age-dependent variation in the hours spent at the shoreline, outdoors and indoors. Ignored possible sex and ethnic differences	Sex- and age-specific house occupancy factors obtained from a survey of 7 711 residents in 2002. Only information on occupancy in homes	Used sex-and age-specific population average obtained from a survey of 5 291 subjects in over 88 hamlets conducted in 1991–1993
Residential history	Lifetime migration history was taken into account in dose accumulation		
Internal dosimetry (ingestion)	Mainly through ingestion of water and milk contaminated primarily by <sup>89</sup> Sr, <sup>90</sup> Sr and <sup>137</sup> Cs	Considered negligible	Through inhalation of radon and its progenies
Internal dosimetry (inhalation)	Doses from radon progeny substantial in some areas including Muslyumovo but ignored	Measurements of radon and thoron progeny were made in 259 dwellings. The mean equivalent dose to lung is similar to that from external irradiation, but ignored	The mean equivalent dose to the lung due to inhalation of radon and thoron progenies was found to be greater than the corresponding value for external irradiation

<i>Feature</i>	<i>Techa River study [D13, D14, D16, S10, S12]</i>	<i>Karunagappally study [N3, N4, O3]</i>	<i>Yangjiang study [K20, M6, O2, T3, Y1]</i>
Medical radiation exposure and others	Individual medical doses received at the URCRM clinic for special surveys were reconstructed. Medical doses deemed not to be large enough to affect cancer risk estimate	Medical exposure is considered infrequent	Medical exposure is considered infrequent
Organs considered in dose calculation	Twenty-three organs and tissues, including RBM and stomach wall, are considered in the dose calculation. Air kerma rates, occupancy factors and age-dependent conversion factors were used to calculate external dose. Age-dependent radionuclide intake and dose coefficients per unit intake were used to calculate internal dose	Colon dose for solid cancer, calculated using air kerma and ICRP 74 organ dose conversion coefficient [15]	Colon dose from external radiation for solid cancer, calculated using air kerma rate and ICRP 74 organ dose conversion coefficient. Effective dose (instead of lung equivalent dose) for intakes of radon and thoron progenies
Dose validation	EPR- and FISH-based dose estimates, carried out on a limited number of subjects, agreed well with the dose estimates derived from the use of the TRDS. Luminescence measurements of anthropogenic dose in bricks from old buildings located on the Techa River banks were also found to be consistent with calculations performed using the TRDS parameters	TLD measurements and scintillometer spot readings were conducted for one year in 800 houses, randomly selected. The estimated annual doses derived from the spot readings correlated well with the TLD-measured annual doses. Also, the frequency of chromosomal aberrations was found to increase in proportion to the cumulative dose in adult females	Individual dose estimates obtained from measured indoor and outdoor air kerma rates (indirect method) were compared with individual dose estimates measured using pocket dosimeters and TLDs (direct method) (N<100). There was a good correlation between the results obtained with the two methods
Dose uncertainties	Substantial efforts have been made to evaluate the uncertainties in the individual dose estimates. Preliminary results, dating back to 2000, indicated that the uncertainties in external doses ranged in about a factor of 4 to 5 and that the ratios of the 97.5 and 2.5 percentiles for the internal dose estimates were in the range of 20–30 and could reach 100 or more. Since 2000, major work has been performed to reduce these uncertainties and to separate the shared and the unshared uncertainties. The first results for internal dose to the RBM showed that the uncertainties in the individual dose estimates appeared to be log-normally distributed with a geometric standard deviation of about 2 to 2.5. The complete results of this thorough uncertainty analysis have yet to be published	Uncertainties in the individual dose estimates were not quantified. It is likely that the contribution of the unshared errors is larger than that of the shared errors because the individual dose estimates are based on measured indoor and outdoor dose rates in each dwelling	Uncertainties in the individual dose estimates were not quantified. It is likely that the contribution of the shared errors is larger than that of the unshared errors because most of the individual dose estimates are based on village-averaged parameter values

Table 22. Features related to outcomes in cohort studies on cancer risk from low doses of radiation from environmental sources

MV: morphologically verified; IM: Instrumental Methods (X-rays, CT, ultrasound, bronchoscopy etc.)

<i>Feature</i>	<i>Techa River study on cancer mortality [S3]</i>	<i>Techa River study on cancer incidence [D5, K18]</i>	<i>Karunagappally study [N4]</i>	<i>Yangjiang study [T3]</i>
Outcome	Cancer deaths in Chelyabinsk and Kurgan Oblast	Incident cancer case in Chelyabinsk Oblast	Incident cancer case	Cancer death
Case ascertainment	Death certificates from regional ZAGS and Regional Statistical Bureau Office	Through mandatory cancer registration since the mid-1950s. Own additional systematic efforts	Case ascertainment, which was through regional cancer registry established in 1990, may be affected by SES	Own systematic efforts to identify deceased subjects and to determine cause of death
Completeness of case ascertainment	Some incompleteness	The completeness may not be satisfactory in early years	Completeness in the 1990s may be unsatisfactory	Some under-ascertainment likely due to low level of health-care use and quality
Accuracy of diagnosis	91% with defined cause of death confirmed by death certificates, generally 10–30% of deceased cases underwent autopsy	During 1990–2009, MV% was 67% and IM% was 19%. During 1956–2009, MV% was 55% and IM% 14%. No pathological panel review for diagnostic verification	MV%>65%. May be affected by SES. No pathological panel review for diagnostic verification. Proportion of cases with unknown primary site high	MV 26%. Probably unsatisfactory, considering the quality of medical care. No pathological panel review for diagnostic verification
Most common site of cancer	For men, cancers of the lung and stomach; and for women, cancers of the uterus, stomach and breast		For men, cancers of the lung and head and neck; for women, cancers of the breast and head and neck	Hepatocellular carcinomas and nasopharyngeal cancers are the most common cancers
Migration	At the end of follow-up, approximately 16% of the cohort had migrated out of the catchment area (i.e. distal migrants)	<20%	<10% during the follow-up	<10% during the follow-up

Table 23. Statistical analysis, information bias, and confounding in cohort studies on cancer risk from low doses of radiation from environmental sources

<i>Feature</i>	<i>Techa River study on cancer mortality [S3]</i>	<i>Techa River study on cancer incidence [D5, K18]</i>	<i>Karunagappally study [N4]</i>	<i>Yangjiang study [T3]</i>
Information bias	Information on exposure levels is unlikely to be affected by vital status			
Confounders	No baseline survey was conducted. Only demographic information is available. Social conditions for rural populations in the Soviet years were very similar in study areas	Data on smoking recorded at the URCRM clinic were collected (smoker and unknown smoking status). Social conditions for rural populations in the Soviet years were very similar in study areas	Data on SES and lifestyles were collected by the baseline survey conducted during 1990–1997	No baseline survey was conducted and therefore no adjustment for confounders
Adjustment for confounders	A recent cancer incidence study was adjusted for smoking		Adjusted for smoking and SES	Not conducted
Risk factors similar across exposure levels	Smoking was not positively related to exposure levels. Most TRC members were poor collective-farmers in the Soviet era. Demographic factors including ethnicity, were adjusted in risk analysis. Number of migrants and loss to follow-up, methods of confirmation of cancer diagnosis do not correlate with radiation exposure		Smoking and SES, which can be related to exposure levels, were adjusted in risk analysis	Prevalence of smoking and alcohol use, medical exposure and SES were found to be similar in HNBR and control areas in small-scale surveys on potential confounders
Lag time	Cumulative dose was lagged by 5 years		Cumulative dose was lagged by 10 years	Cumulative dose was lagged by 10 years
Statistical model	Poisson regression analysis was conducted			

218. In the Yangjiang study, extensive surveys were conducted periodically to identify deceased cohort members. Although no effort was made to evaluate the completeness of cancer death ascertainment, it was not difficult to enumerate deceased cases in the countryside, where residents knew each other well, and permanent migration was infrequent. However, the accuracy of cause of death could be far from ideal since farmers could not afford expensive treatment for cancer or other serious diseases. In the mortality study [T3], of the 941 deaths of cancer, excluding leukaemia, the underlying causes of death were determined on the basis of pathological information for 26% of the deaths, and on radiological or ultrasonographic diagnosis for 62%. Particularly of concern is the diagnosis of liver cancer, which is difficult to diagnose accurately due to difficulties in distinction between liver cancer, liver cirrhosis and hepatic metastases of other cancers.

219. The TRC study examined not only cancer incidence but also cancer mortality. The catchment area of cancer mortality follow-up was larger than that of cancer incidence, covering the entire territories of the Chelyabinsk and Kurgan Oblasts. The mortality follow-up was virtually complete. However, it is difficult to evaluate the accuracy of cause of death, particularly those that occurred at home.

220. It is often easier to obtain data on cancer mortality than on cancer incidence, because death certification tends to be more widely available and more complete than cancer registration. In addition, cancer incidence studies are more likely to be affected by loss to follow-up because of migration, unless there is a high-quality nationwide cancer registry. Nevertheless, cancer is often more accurately reported than most other causes of death [R5]. However, cancer deaths are fewer than incident cases, though depending on prognosis.

221. Since the ratio between cancer incidence and mortality rates is usually in the range 1.5–2, a mortality study cannot identify the 33–50% of cancer cases that are non-fatal, even if the data are complete and the information on the death certificates is accurate. As mortality depends on both incidence and prognosis, variation between populations also reflects availability and effectiveness of treatment. Inclusion of contributing causes of death improves the coverage, but not substantially [S4].

222. In the TRC study, almost 25% of the cohort members are known to have left the study area during 1949–1989. Roughly 80% of the cohort members who left the area moved to nearby cities and towns in Chelyabinsk, Yekaterinburg (formerly Sverdlovsk) and Kurgan Oblasts. Therefore, the proportion of emigrants who were lost to follow-up is not exceedingly large. Furthermore, emigration was unrelated to exposure level. Generally speaking, permanent migration is infrequent in rural areas of India and China. The cohort members of the Karunagappally study were mainly farmers, fishermen and blue-collar workers [N4]. The survey conducted in 2001 showed that migration outside Karunagappally was 6% in the 13-year survey period. The populations in the Yangjiang study were mainly farmers working on collective farms in rural areas. Their families had lived in the area for generations [H5]. Although Yangjiang is close to areas that have witnessed rapid economic development, it is difficult for local farmers to change their family registration to city areas and settle there.

223. In all the studies reviewed in this chapter, individual dose estimates from external exposure were calculated as a weighted sum of the average ambient dose rates at locations with high occupancy, including homes. The time spent at the corresponding location is used as the statistical weight. This approach requires information on indoor and outdoor air kerma in the places—such as residences, schools and workplaces—where a subject spent a significant amount of time. In addition, it is necessary to collect information on time spent in those places.

224. Collection of exposure information throughout lifetime is challenging. Exposure to natural background radiation already starts before birth. Data on possible changes over time in indoor and

outdoor air kerma and occupancy factors is difficult to obtain. In the TRC study, residents had shorter periods of exposure than residents in HNBR areas, but more variability in exposure over time. Their occupancy during the early years was also reported retrospectively, relying on recall, which adds uncertainty. Even so, it is practically impossible to measure radiation doses comprehensively that were received by residents throughout the study period.

225. In the TRC study, external exposure was the main contributor to organ doses other than RBM dose. For RBM dose, internal exposure from ingestion is a major component of exposure. Dose estimation in the TRC has been improved over the years [D7]. Few measurements were made in 1951, when the highest release levels occurred and, thus, short-lived fission products that contributed to organ dose had to be estimated on the basis of surveys conducted later. Uncertainties are related to mixing data on internal and external doses and to measurements made years after the intake of internal doses. Biokinetic models also contain uncertainty with regard to key assumptions related to isotope depositions and detection decay after intake.

226. In the Karunagappally and the Yangjiang studies, the evaluation of internal exposure has not been conducted systematically. In Karunagappally, the radionuclide concentration in local food was not high. The results from a meal survey suggest that internal exposure from radium intake in meals is negligible in comparison with that of  $^{40}\text{K}$ . The activity concentration of radium in meals did not show any difference between HNBR and other areas as only a minor proportion of the food commonly consumed by the residents was grown locally. Therefore, it is unlikely that lifetime radiation dose from internal exposure was significantly different in the high and low exposure areas within Karunagappally [T12]. In the Yangjiang study, local foods did not have high concentrations of radionuclides [Y3].

227. In the two natural HNBR areas, thorium can be a possible source of internal exposure. The thorium burden of 87 residents in Karunagappally was determined by a thoron-in-breath analysis, indicating ingested level of thorium [N3, N5]. These results showed that the subjects from high and medium indoor radiation level areas had a significantly elevated thorium body burden compared to those from low indoor radiation level areas. No such evaluation has been conducted in the Yangjiang study.

228. Internal exposure from inhalation is another potential problem. In the TRC study, doses from radon and its daughters in the Techa River region were reported to be  $1.7\text{--}6.2\text{ mSv a}^{-1}$  [Z8], and were ignored in risk analysis. Exposure to radon and its progenies in the Karunagappally study can be ignored because their indoor concentrations were low [T11]. In the Yangjiang study, indoor radon levels were higher (close to  $50\text{ Bq m}^{-3}$ ) but still too small to substantially increase lung cancer risk [T10]. Further, lung cancer risk in the HNBR area of Yangjiang is similar to that in the control area [T2]. Both the Karunagappally and Yangjiang studies ignored internal exposure from ingestion.

229. It is possible to measure individual doses from HNBR during a short period (e.g. a few months). In all the studies reviewed in this annex, individual dosimetry using selected subjects was conducted for a short period and the measured doses were compared with estimated doses. However, the correlation between such a dose and the “real” cumulative dose up to the time of measurement is practically impossible to evaluate. Moreover, the accuracy of the dosimetry is sometimes questionable because it is not possible to tell whether the dosimeters were properly worn by residents.

230. Another possible approach to evaluating HNBR doses received by residents is to examine chromosomal aberrations. However, unstable aberrations, which are almost exclusively induced by ionizing radiation, do not reflect long-term cumulative doses as cells with such aberrations are eliminated relatively quickly. Stable chromosomal aberrations are related to cumulative radiation doses. Yet, because they are also caused by factors other than radiation [S17], their association with cumulative doses is weak at best, and require relatively large cumulative doses for an increase to be

detectable. There is evidence that chronic exposure produces increased chromosomal aberrations in radiation workers at a lower rate than acute exposure [T7, T17]. Given that the half-life of human lymphocytes is considered to be about three years [I1], frequencies of unstable chromosomal aberrations induced by chronic irradiation could be expected to reach a plateau after several years [S2]. However, unstable chromosomal aberrations accumulate over the periods of half-lives of lymphocytes in mice, according to dose rate in the range of one to hundreds  $\text{mGy d}^{-1}$  [T1]. Even in humans, there is a report suggesting that unstable-type aberrations could accumulate during longer periods than the half-life of lymphocytes [B3]. The kinetics of turnover of lymphocytes could become slower at low dose [R2] and low dose rate [A15]. In most studies in HNBR areas, an increased frequency of chromosomal aberrations has been found, despite some inconsistencies. The dose response is comparable with studies of higher dose levels, but one has to keep in mind that the precision of chromosomal aberration studies in the low dose range is poor, in particular, when the number of metaphases scored is low.

231. All the studies have limitations in dose assessment despite extensive efforts. The uncertainties are related to use of area-based measurements instead of individual data, and assumptions on occupancy and exposure outside home over long periods. Even if the uncertainties cause non-differential misclassifications, in the comparison between the exposed and unexposed groups, non-differential misclassifications typically bias ERRs and RRs toward the null value (0 and 1, respectively). However, if the exposure categories are divided into three or more groups, non-differential misclassification may bias the dose response away from the null value [D19]. Dosimetric uncertainties shared among subgroups of a study population can bias dose response, either masking or exaggerating a true effect [G2, L1]. It is desirable to evaluate dosimetric uncertainties shared by subgroups, as is being done in the TRC study, and to conduct dose–response analysis to account for those uncertainties [S19].

232. Since women in the HNBR study areas tend to stay at home, annual dose is more easily estimated for women. However, residential stability is lower for women, as a considerable number of women moved into their current residence after marriage. Doses at the houses before marriage are more likely to be missed in the dosimetry survey, which was conducted at the time of the baseline survey during the period 1990–1997 in the Karunagappally study. This problem can be more serious if women moved from high-dose areas to low-dose areas before the baseline survey.

233. Medical exposure was infrequent in Karunagappally and Yangjiang, because the areas are mainly rural and access to medical facilities was neither easy nor affordable. On the other hand, in the TRC study, subjects underwent X-ray diagnostic procedures as part of their medical examinations. No attempt was made to examine the correlation between cumulative doses from medical exposure and HNBR in the Indian and Chinese studies. However, the contribution of medical exposure was small compared to the environmental doses, with the average doses to major organs ranging between 11 and 33  $\text{mGy}$  [D15].

234. Several risk factors have a stronger effect on solid cancer risk than low-dose radiation. As a result, even a weak association of radiation exposure with such a factor can confound the relationship between radiation exposure and cancer risk. In HNBR and Techa River areas, radiation levels are determined mainly by geography, which can be associated with lifestyle factors related to cancer risk and indicators of such factors including SES, religion, ethnicity and occupation.

235. Information on several lifestyle factors such as smoking and alcohol use and also SES was more comprehensive in the Karunagappally study than in the TRC study or Yangjiang study. The lack of detailed information on confounders is a major drawback. The TRC study could not collect information on lifestyles and socioeconomic factors from the entire cohort. However, because the TRC study populations consist mainly of farmers working in collective farms in rural areas, their lifestyles were

relatively homogeneous, particularly during the Soviet era. Differences in smoking habits and alcohol use are, however, very likely. On the other hand, lifestyle can be correlated with sex and ethnicity. Adjustment for these proxy indicators of behavioural risk factors in risk analysis should diminish confounding to some degree.

236. The TRC cancer incidence study [D5] used data on smoking that were recorded during interviews for TRC members of the cohort who visited the URCRM clinic. Individual information on smoking intensity and duration were not available for risk analysis.

237. The Karunagappally study collected information on lifestyle and SES in the baseline survey, and the collected information was used in the cancer risk analysis. However, the study reported by Nair et al. [N4] was, for unclear reasons, not adjusted for tobacco chewing, which is a major cancer risk factor in the study area for cancers of the upper digestive tract organs, even if the information were available.

238. One of the main concerns in the Yangjiang study is the comparability of lifestyles and other potential confounders in HNBR and control areas. It has been criticized that a slightly low cancer mortality rate in the HNBR area reported by the first international publication [H5] might be due to differences in living standards and lifestyles in HNBR and control areas. The Yangjiang study collected information on those factors for only a small portion of the cohort members. On the basis of those surveys on the selected residents, it has been concluded that the distributions of several potential confounding factors – including diet and nutrition, drinking water, pesticide residue and aflatoxin B1 in food, medical exposure, tobacco smoking and alcohol consumption in HNBR areas – were not substantially different from those in the control area [T4, Z4]. Differences were noted, however, for infections such as tuberculosis.

239. The cumulative dose was lagged by five years in the TRC study, and was lagged by 10 years in the Karunagappally and the Yangjiang studies, assuming that cancer risk is not increased during the lag time, i.e. before a minimum latency\* has elapsed. If cancer risk is already increased during the excluded lag time, absolute risk due to radiation, such as lifetime risk, will be underestimated though the ERR estimates may be either underestimated or unaffected [R6].

240. Statistical power is calculated before a study is conducted to assess whether there is sufficient likelihood of finding an effect of a given size, provided that it exists. The number of cases attributable to exposure is a good indicator of the amount of information from a study, as it reflects both effect size and number of cases. Effect magnitude depends on exposure level (and potential modifiers of risk), and the number of cases on baseline risk. After a study is conducted, confidence intervals indicate the range of risks consistent with the observed results. Of the studies on environmental radiation exposure resulting from human activities, the TRC study has a statistical power higher than 80% for showing a risk estimate similar to the LSS, while the Taiwanese study does not. Of the HNBR studies, the Yangjiang study had fewer cases and lower average doses in the exposed group than the Karunagappally study and, therefore, also lower statistical power.

241. Even studies of low statistical power, such as several of the natural background radiation studies presented here, are informative if they can indicate levels of risk that are unlikely, given the observations. If an expected estimate of ERR per unit dose and its standard errors are available, the statistical power of a given study to find this expected ERR per unit dose can be calculated in retrospect. In the Karunagappally study, the ERR estimate per 100 mGy for solid cancer was  $-0.013$  per 100 mGy (95% CI:  $-0.058, 0.046$ ). After adjustment for attained age, the LSS estimate was  $0.062$  at 100 mGy (95% CI:  $0.053, 0.071$ ). The statistical power to detect an ERR per unit dose similar to the LSS with an alpha of 10% is  $>80\%$  for the Karunagappally study. The lack of overlap in the confidence interval in the risk estimates per unit dose,

suggest influence by some of numerous differences between the two studies in exposure (e.g. dose rate and distribution of cancer sites and age at exposure) and/or conduct of the studies.

242. In the evaluation of results from individual studies, consistency of results with previous epidemiological literature is needed for proper interpretation. Validity\* requires solid study design and appropriate data analysis, and credibility can be assessed also by comparing reported patterns of risk with earlier studies. In the TRC study, the reported excess risk was largely driven by two cancer sites, cancer of the cervix and uterus and the oesophagus. Uterine and cervical cancer have not been convincingly linked to ionizing radiation, and the association with oesophageal cancer in the TRC was found only in women and not in men. Further, the oesophageal cancer risk was concentrated only in one ethnic group. Moreover, in the TRC study the ERR tends to increase with age at exposure, whereas in the LSS and other studies, relative risk has decreased with age at exposure. Likewise, the TRC indicated a tendency of relative risk increasing with attained age, whereas in other studies it decreased with attained age. The differences between age groups in the TRC were, however, not significant. The differences between the TRC study and the LSS should not be overemphasized since they can be due to statistical imprecision. The number of excess cancer cases in the TRC study [S3] is around 50 and, therefore, its statistical power to evaluate risk modification or risk by cancer site is much lower than that of the LSS. Variability\* in risk within the study population also tends to decrease the statistical power (precision) [L6].

## 2. Summary

243. The epidemiological cancer studies reviewed here have advantages and drawbacks in various aspects. Dosimetry is always a challenge in studies of environmental exposure, as it is practically always based on retrospective reconstruction of spatial distribution of dose rates, with efforts to account for factors such as shielding and occupancy. For internal exposure, information is also needed for past intake and sources of food and water. The case ascertainment is suboptimal, especially in comparison with other cancer incidence studies such as the LSS, and studies of workers and patients. The risk estimates in studies of environmental exposure can be distorted by biases and confounding. However, the magnitude of those biases and confounding are difficult to evaluate without extensive sensitivity analysis. Fewer major risk factors are known for leukaemia than for various solid cancers and, therefore, the findings on leukaemia are less likely to be influenced by confounding. Some heterogeneity in solid cancer risk may also stem from the fact that even if all studies excluded leukaemia from analyses of other cancers, exclusion of other lympho-haematological malignancies was not entirely consistent in various studies. The limitations need to be considered when drawing inference about radiation-induced risks from the observed rates reported in the studies evaluated here (see also annex A and the glossary).

244. The LSS reported for solid cancer mortality an ERR of 0.042 per 100 mGy for those with attained age 70 and exposed at age 30 (the male-female ratio is assumed to be 1:1). In the TRC study, the ERR for mortality from all solid cancers was 0.061 per 100 mGy (95% CI: 0.004, 0.127), which is close to, though slightly higher, the reported value in the LSS.

245. Using the solid cancer risk model given in the recent analysis of cancer incidence in the LSS, the sex-averaged estimate of ERR per Gy at age 65 for a person exposed at age 25 (which corresponds roughly to the mean age at initial exposure and age at diagnosis in the current TRC data) is about 0.06 per 100 mGy, which is very close to the LSS results. The direction of the estimated sex, age and age at initial exposure effects on the ERR in the TRC are different from those in the Japanese survivors of the atomic bombings [G7, H9]. However, these effect modification parameters are imprecise, and their confidence intervals are wide and therefore, cautious interpretation is needed, as it is unclear

whether they reflect methodological shortcomings or differences between the effects of protracted low-dose-rate exposure compared with acute radiation exposure.

246. The mean RBM dose in the TRC was 0.42 Gy and there were 99 incident leukaemia cases in the cohort (82% microscopically verified diagnoses). The ERR per 100 mGy was 0.22 (95% CI: 0.08, 0.54) for non-CLL leukaemia. This is higher than reported from the LSS, with more than 300 non-CLL cases (ERR 0.08 at 100 mGy based on the linear component which predominated at doses <1 Gy), but comparable to, for example, the recent results from the INWORKS study of radiation workers (with >500 non-CLL cases but very low average doses) showing ERR 0.3 at 100 mGy [L4]. Of leukaemia subtypes, the combined group of acute leukaemias and chronic myelocytic leukaemias showed a dose response, while CLL and lymphomas were not associated with radiation exposure. Attrition due to emigration and loss to follow-up, as well as unknown causes of death and possible under-ascertainment of cases in the early follow-up reduced the precision of the results as for other analyses, but nevertheless the leukaemia findings are the most robust results from the TRC study.

247. The ERR of solid cancer obtained from the TRC cancer mortality study was 0.061 (95% CI: 0.004, 0.127) [S3] and the TRC cancer incidence study gave 0.077 (95% CI: 0.013, 0.150) [D5]. The corresponding estimate from the Karunagappally study [N4] was -0.013 (95% CI: -0.058, 0.046) and from the Yangjiang study [T3] was 0.019 (95% CI: -0.187, 0.304, excluding liver cancer). The study of the residents of <sup>60</sup>Co-contaminated buildings from Taiwan, China, showed an ERR 0.03 (90% CI: -0.04, 0.09) but it is substantially smaller than the other studies and has some unresolved methodological issues. In the TRC incidence study, the ERR per 100 mGy became 0.063 (95% CI: 0.00, 0.14) after the exclusion of oesophageal cancer. The ERR estimates obtained from those studies have wide confidence intervals and overlap each other. Continued follow-up of these relatively low-dose cohorts, in particular the Karunagappally study, can potentially improve the precision, better characterize the uncertainties in these risk estimates, and provide some insight into effect modification and dose-rate effects on the magnitude of the risk.

248. When making comparisons between those ERRs per unit dose in those studies, it should be noted that cancer patterns differ. In the TRC, the most common cancers are cancers of the stomach and lung. On the other hand, in the Yangjiang study, hepatocellular carcinoma and nasopharyngeal cancers accounts for nearly 50% of all cancers, known to be aetiologically associated with HBV and Epstein-Barr virus. In the Karunagappally study, lung cancer was the most common site, as was the case in the TRC. However, the second most common cancer in men is head and neck cancers. These different cancer patterns may be an explanation for differences in ERR estimates per unit dose, as the risk coefficients are likely to vary by site. Ideally, assessment of radiation-induced risk should be evaluated by specific cancer site, but this is limited by low statistical power.

249. Further improvement in the quality of HNBR studies would make them more valuable. This could be done by improving cancer registries in that they provide long-term follow-up of residents, enhancing cause of death assignment and data on non-radiation risk factors, and refining risk estimates for subgroups of the population. Additional follow-up is likely to enhance the power of the Karunagappally study more quickly than that of the Yangjiang study, because the cancer incidence rate in the former is higher than the cancer mortality rate in the latter. In the interpretation of the findings from the HNBR studies, there is also the fact that the study populations have resided and received the constant exposure levels often for several generations. Hence, if the adaptive responses shown in laboratory studies have relevance for cancer risk in human populations, such potential adaptive responses may reduce the effect magnitude.

250. An alternative source of information for risks from protracted exposure to low doses of radiation is through studies of occupationally exposed groups. Large studies have been conducted, a three-country analysis of nuclear workers (INWORKS) as a recent example [L4, R3]. Occupational studies

also have strengths and weaknesses (e.g. lack of data on confounders, and study populations restricted to working-age population, mostly men). Studies of anthropogenic radiation in the environment, including those on the effects of the Chernobyl and Fukushima accidents, will also provide important information about cancer risk from low doses of radiation. A third opportunity for studying low-dose risks is from diagnostic uses of radiation. The exposed subjects are, however, examined for a disease or suspicion of disease, which makes it difficult to disentangle the effect of the indication for the examination from that of the radiation exposure from the examination, unless similar patients can be identified who were not examined radiologically.

## B. Childhood leukaemia studies

### 1. Review of selected studies

251. The association between leukaemia and environmental radiation exposure observed in the studies is not consistent. However, all studies reported childhood leukaemia risk in relation to unit RBM dose or dose estimate have the potential to provide new knowledge on the dose response, the magnitude of excess risk and modifiers of the relationship between childhood leukaemia risk and low-dose-rate radiation exposure. Based on the quality criteria for the Committee's reviews on epidemiological studies elaborated in annex A, the main quality features of studies presented here (Finland, France Switzerland and the United Kingdom as well as the Chernobyl study conducted in Belarus, the Russian Federation and Ukraine) are summarized in tables 24 and 25.

252. In a population-based control study, controls are so selected from the population that they represent distribution of the exposure of interest and relevant co-variables, including potential confounders, of the base population (usually, they are randomly selected from a comprehensive population registry or a representative population roster). In the Chernobyl childhood leukaemia study, two controls were selected from hospital records in each study raion, matching to each case on sex, birth year and residence. In this case, it is difficult to tell whether the catchment population of cases is the same as the population that controls are supposed to represent and from which the cases arise. In the other studies the base population or the control series was more clearly defined. The controls were selected from the census record or family and birth registers.

253. Dependence of case ascertainment rate on exposure results can distort the association between risk and exposure. The studies conducted in Finland, France, Switzerland and the United Kingdom identified leukaemia cases through nationwide cancer registries. The quality of those registries was shown to be good [B7, D1, T8] and therefore, such a concern is not warranted.

254. There are several subtypes of leukaemia, outlined in detail by the WHO classifications [V1]. In epidemiological studies, however, classification as detailed as for selection of treatment is not used and the emphasis is not on the prognosis. The main types include acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML), acute lymphocytic leukaemia (ALL) and chronic lymphocytic leukaemia (CLL) [B5]. CLL is considered aetiologically unrelated to ionizing radiation exposure even though some recent studies have suggested otherwise [G6]. The possible differences between leukaemia subtypes in terms of radiation-induced risk are not entirely clear, i.e. it is not well established which subtypes are more strongly related to radiation. ALL has an incidence peak at age 3–5 years [B5]. In myelocytic leukaemia, the peak incidence is already at age one year and in infant leukaemia the predominance of ALL is not as clear as in childhood leukaemia at older ages [B5].

Table 24. Main quality features of childhood leukaemia studies in Belarus, the Russian Federation and Ukraine (Chernobyl study) and in the United Kingdom

<i>Criteria</i>	<i>Chernobyl case-control study [I8]</i>	<i>UKCC study [U1]</i>	<i>2nd UK study [K3]</i>
<b>1. STUDY POPULATION/PARTICIPANTS</b>			
Age at exposure (years)	0–20	0–15	0–15
Study design	Case-control study	Nationwide population-based case-control study	Nationwide population-based case-control study
Eligible subjects	421 cases, inclusion criteria unclear	2 165 cases selected on the basis of family register	Cases (N=27 447) were collected from multiple sources and cross-checked against birth registers. Controls (N=36 793) were selected from birth registers
Controls	835 hospital-based controls, matched by year of birth, sex and residence	Family health service authority or GP list or health board matched by date of birth, sex and region of residence (N=3 637)	Cases and controls were matched on sex and date of birth (to within six months)
Selection bias	Considerable, as the population represented by the control series is unclear	A serious participation bias is a concern	Unlikely
<b>2. EXPOSURE</b>			
Individual dosimetry (assessed for accuracy)	Not directly measured	Indoor dose was measured at the current residence	Record-based (taken as the mean for the county district); no data on building characteristics
Residential history	Collected	Collected	Not collected
Effect of migration on dose estimation			Investigated separately with indications that doses at successive addresses are strongly correlated
Radon exposure	Not measured	Measured	Examined
Other internal exposure	Mainly through milk consumption	Not examined	Not examined
Organ doses calculated	RBM	RBM	RBM
Dose range	Median cumulative dose <10 mGy	0–20 mSv a <sup>-1</sup> (average 0.8 mSv a <sup>-1</sup> )	Mean: 109 mSv; median: 103 mSv; range: 55–383 nSv h <sup>-1</sup>
Medical exposure	Not examined	Not examined	Not examined
Effect of other exposure on dose estimate	Unclear	Probably negligible	Negligible in early years

<i>Criteria</i>	<i>Chernobyl case-control study [I8]</i>	<i>UKCC study [U1]</i>	<i>2nd UK study [K3]</i>
<b>3. OUTCOME</b>			
Number of leukaemia cases	421	Not reported (total number of all childhood cancers 2 165)	9 058
Leukaemia subtypes	Acute leukaemia was the end point	ALL is distinguished from the others	Leukaemia subtypes available
Case identification	Hospital records and cancer registry	Hospital records and cancer registry	Through the nationwide cancer registry
Complete case ascertainment	Unclear	Considered almost complete for leukaemia	Considered to be very high
Pathological review of cases for diagnostic verification	A review was conducted for most cases	A central review was performed	No re-evaluation
Years of diagnosis	1986–2000	1992–1996 (1991–1994 in Scotland)	1980–2006
<b>4. BIAS AND 5. CONFOUNDING</b>			
Information on confounders	Collected, but not on SES	Collected	Sex, age, county and SES (both individual measures of SES and averages for Census wards with a mean population of ~5 000)
Risk factors similar across exposure levels		SES is related to exposure	SES is related to exposure
<b>6. STATISTICAL METHODS/ANALYSIS</b>			
Adjustment for confounders	Statistical analysis was adjusted for matching factors. SES not considered	SES (area-based level of deprivation)	Adjustment for SES (county-level deprivation index) did not affect the results
Statistical analysis	Conditional logistic analysis (matched factors taken into account)	Conditional logistic analysis (matched factors taken into account)	Conditional logistic analysis (matched factors taken into account)
Latency period	No latency period was assumed	No latency period was assumed	9 or 12 months
Sensitivity analyses	Done	Done	
<b>7. REPORTING</b>			
ERR or equivalent (95% CI) for all leukaemias	Not reported	Not reported	12 (3, 22) per 100 mGy
ERR or equivalent (95% CI) for leukaemia subtypes	ERR: 3(1, 8) per 100 mGy for acute leukaemia	No estimate per unit dose (or dose rate) reported. For ALL, in the highest exposure category OR=0.95 (95% CI: 0.66, 1.37); trend p=0.11	10 (2, 19) per 100 mGy for lymphoid leukaemia

Table 25. Main quality features of childhood leukaemia studies in Finland, France and Switzerland

<i>Criteria</i>	<i>Finnish case-control study [N10]</i>	<i>French case-control study [D18]</i>	<i>Swiss cohort study [S25]</i>
<b>1. STUDY POPULATION/PARTICIPANTS</b>			
Age at exposure (years)	0–15	0–14	0–15
Study design	Nationwide case-control study	Nationwide population-based case-control study	Nationwide population-based cohort study
Eligible subjects	Cases (N=1 093) from national cancer registry, controls (N=3 279) selected from national population register	2 763 cases were diagnosed during 2002–2007, collected through the National Registry of Childhood Cancers	Selected from census records, with 530 incident leukaemia cases
Controls	Cases and controls were matched on gender and year of birth	30 000 controls were randomly selected from income and council tax databases of households	No matching
Selection bias	Unlikely	Unlikely	Unlikely
<b>2. EXPOSURE</b>			
Individual dosimetry (assessed for accuracy)	Record-based (mainly based on 8×8 km <sup>2</sup> grid average), also using building characteristics of the child's residence	Record-based (1×1 km <sup>2</sup> grid) for residence and town centre; building characteristics not considered	Record-based (based on 2×2 km <sup>2</sup> grid average); no data on building characteristics
Residential history	Complete residential history was obtained from the Population Register Centre	Not collected. Doses at diagnosis or inclusion were used to estimate lifetime exposure	Residential address histories of patients were obtained from the Childhood Cancer Registry
Effect of migration on dose estimation	Collected and utilized	Unclear	Available; stronger association among those with stable residence
Radon exposure	Considered ignorable	Estimated	Considered ignorable
Other internal exposure	Fallout of the Chernobyl accident was taken into account (the data were collected by a nationwide mobile survey in 1986–1987)	Not examined	Unclear
Organ doses calculated	RBM	RBM	RBM
Dose range	Cumulative dose: <12 mSv	Mean annual dose: 1 mSv a <sup>-1</sup> (95% CI: 0.8, 1.7)	Cumulative dose: mean 9.06 mSv; median 9.12 mSv; range 0.03–49.4 mSv
Medical exposure	Not examined	Not examined	Not examined
Effect of other exposure on dose estimate	Negligible, as postulated	Negligible in early years	Negligible in early years

<i>Criteria</i>	<i>Finnish case-control study [N10]</i>	<i>French case-control study [D18]</i>	<i>Swiss cohort study [S25]</i>
<b>3. OUTCOME</b>			
Number of leukaemia cases	1 093	9 056 in incidence analysis, 2 763 in case-control analysis	530
Leukaemia subtypes	ALL, AML and others	Leukaemia subtypes available	ALL is distinguished from the others
Case identification	Through the nationwide cancer registry	Nationwide cancer registry	Through the nationwide cancer registry
Complete case ascertainment	Considered to be very high	Considered very high	Considered to be very high
Pathological review of cases for diagnostic verification	No re-evaluation	No re-evaluation	No re-evaluation
Years of diagnosis	1990–2011	2002–2007	1990–2008
<b>4. BIAS AND 5. CONFOUNDING</b>			
Information on confounders	Sex, age and other risk factors (Down's syndrome, birth weight, gestational age, maternal smoking)	Sex, age and SES (individual measures) – excluded were subjects living in the vicinity of nuclear power plants and proximity high-voltage power line at the time of diagnosis or inclusion of SES and averages for Census wards with a mean population of ~5 000	Sex, age, SES and other risk factor (birth weight, birth order, traffic density, environmental EMF)
Risk factors similar across exposure levels		SES is related to exposure	SES and others are related to exposure
<b>6. STATISTICAL METHODS/ANALYSIS</b>			
Adjustment for confounders	Adjustment for Down's syndrome, birth weight, maternal smoking did not affect the results; no adjustment for SES	Adjusted for SES (county average)	Adjustment for SES, proximity to highways or powerlines, urbanization or crowding did not affect the results
Statistical analysis	Conditional logistic analysis (matched factors taken into account)	Unconditional logistic analysis, adjusting for age	Cox regression analysis
Latency period	Two years in the main analysis	No latency period was assumed	No latency period was considered
Sensitivity analysis			
<b>7. REPORTING</b>			
ERR or equivalent (95% CI) for all leukaemias	Overall –3 (–11, 6) per 100 mSv; 27 (1, 60) for ages 2–7	Cohort analysis SIR=0 per 100 mGy (–2, +1); results from case-control analysis reported only for dose rate	Approximately 4 (0, 8) per 100 mGy
ERR or equivalent (95% CI) for leukaemia subtypes	–1 (–10, 9) per 100 mSv for ALL	Cohort analysis: ALL SIR=1 per 100 mGy (–1, +2)	

255. A problem in case-control studies with interview/dosimetry is the collection of information on the exposure of interest (radiation) and other co-variables after the development of the disease of interest. Even for indoor dosimetry that does not involve interview, it is too naive to assume that behaviour and conditions, including occupancy, did not change after detection of symptoms and diagnosis. However, in the case of gamma-radiation measurements, such a problem is unlikely to be serious. If an interview is involved, the impact of the disease may be more pronounced. If case subjects are too ill to be interviewed or deceased, surrogates, including family members, will be interviewed for information on occupancy, lifestyle and other factors. However, this kind of retrospective approach may introduce inaccuracy and bias to the information, and may distort the relationship between leukaemia risk and radiation exposure.

256. Children commonly spend most of their time in the home in their early childhood. However, as they get older, they tend to spend a relatively longer time outside home, for instance in day care. Therefore, a study to estimate individual dose would ideally need to measure not only exposure at home, but also cover exposure at nurseries and schools, playgrounds, shopping centres, parks, greenspaces and so on. However, comprehensive dosimetry including exposure outside the home is difficult and unlikely to be feasible in a large-scale epidemiological study. In recent years, increased unwillingness to participate in research for various reasons, including increased awareness of privacy issues, has decreased coverage for population studies in many countries. Generally, participation is higher among those concerned about the exposure/disease of interest.

257. In record-based studies, radiation dose estimates are not based on information obtained from each study subject, but on area-based or other group-level dose estimates. The validity of such estimates hinges on the homogeneity of dose distribution within the child's everyday sphere, including occupancy and variability of exposure within an area. Exposure can vary substantially in a child's environment. Systematic differences due not only to residential location, but also to other features such as shielding by building structures/material as a source of background radiation should also be considered for accurate exposure assessment. A key problem with area-based dose estimates is that they cannot take account of inter-house variation in the way that direct measurements do. Unfortunately, the feasibility of individual measurements in thousands of houses is limited by prohibitive cost and, furthermore, incomplete participation tends to introduce bias.

258. In the United Kingdom record-based study, if dose distribution is fairly uniform within a county district (a county consists of up to seven county districts), and the child's sphere of daily life corresponds to that of the district, individual dose represented by county-district-specific average doses can be reasonably accurate. In the Swiss study, investigators used 2 km × 2 km grids to represent the sphere of children's everyday life. Although a smaller area is more likely to have more homogeneous dose distribution, the actual sphere of everyday life is likely to extend beyond the specified area.

259. Theoretically, if the frequency of medical exposure such as CT imaging is associated with natural background gamma-radiation exposure, medical exposure would cause exposure misclassification. However, such associations seem unlikely, and medical exposure of RBM is unlikely to be large enough to affect risk per dose unit in the studies reviewed here.

260. Studies of childhood leukaemia relied largely on area-based measurements for exposure assessment. The size of the area varied (mapped grid data with 2 km × 2 km in the Swiss study and 8 km × 8 km in the Finnish study to administrative units of varying sizes in the United Kingdom and French studies), with presumably larger errors for larger area units. The measurement data included outdoor dose-rate measurements (Swiss and Finnish studies) and surveys of residential (UKCCS, N=2,283) or other buildings (France, N>17,000). The coverage of residential history also ranged from

only the place of residence at diagnosis (France) or birth (UKCCS) to the entire residential history (Finland). In several studies, approximately half of the children had lived in more than one dwelling. The details of the type of building affecting shielding and also building material as a source of radiation were incorporated only in the Finnish study. The directly ionizing component of cosmic radiation was incorporated in the measurements, but only terrestrial radiation was used in the analyses in some studies. In addition, fallout from Chernobyl was taken into account in the Swiss and Finnish studies (the exposure levels from Chernobyl were lower in France and in the UKCCS). All studies with area-based measures assumed a similar occupancy for all subjects and ignored exposure at other places such as kindergartens and schools. No data on medical exposure were obtained in these studies though, overall, the dose from CT and other diagnostic procedures is likely to be substantially lower than that from environmental gamma radiation. Radon causes also some dose to the RBM but it was evaluated only in the UKCCS and the Swiss study. Other sources of radiation exposure (missed doses) are likely to result in some non-differential exposure misclassification with possibly minor bias toward the null, assuming that other exposure is uncorrelated with background gamma radiation. For radon, this is, however, questionable, as radon tends to be correlated with other geogenic radionuclides but RBM doses are substantially lower than those from background gamma radiation. Only one study (UKCCS) was able to obtain direct measurements of natural background gamma radiation at individual level (with only one residence measured per subject, the residence at diagnosis or equivalent for controls), but participation was incomplete and compliance was lower among controls than cases, which raised concerns of possible selection bias.

261. Potential confounding factors include the well-established risk factors for childhood leukaemia such as some congenital conditions, including Down's syndrome (21 trisomy) and some rare hereditary diseases (ataxia telangiectasia, Fanconi anaemia, Bloom syndrome) [B10, M2]. Boys have slightly higher rates than girls, heavy birth weight is associated with a slightly increased risk for Caucasian than children of other ethnicities [M3, R4]. In addition, older parental age is associated with higher risk [S7]. Parental benzene and insecticide exposure and child's exposure to pesticides are also suspected risk factors [B1, C2, Z7]. Extremely low frequency electromagnetic fields have also been consistently associated with elevated risk in epidemiological studies [A2, K6]. Higher SES has been associated with higher childhood leukaemia risk in several studies, though the results have not been consistent across countries and study types [P9]. Furthermore, the effects of several risk factors differ between lymphocytic and myelocytic leukaemia.

262. The Finnish and Swiss record-based studies obtained individual information from birth registries, population census, and other sources, enabling them to adjust for potential confounders such as birth order and maternal smoking. Several studies had area-based measures of SES and the Swiss and French studies included data on some environmental exposure, such as residential proximity to major traffic arteries, power lines and nuclear installations. However, none of the studies had information on parental occupational exposures or children's day breast feeding, allergies or care attendance or pesticide exposure. Lack of comprehensive adjustment for potential confounders indicates possibility of confounding, assuming that other exposure sources are correlated with natural background radiation.

263. The importance of adjustment for deprivation as an area-based measure of SES is frequently pointed out. In the UKCCS, similar to the Swiss study [R8, R9], mean dose rates were higher in children classified in lower socioeconomic categories [K4, K5]. In the UKCCS, deprivation was also positively related to annual dose [U1].

264. The direction of bias is difficult to predict in a particular study, as it depends on the correlation between the confounder and radiation exposure. Nevertheless, it is important to collect information on confounding factors and adjust for them in the risk analysis if needed. Other key issues in evaluation of confounding are the effect magnitude of the confounder and its frequency of occurrence (or

prevalence). The maximal extent of bias is equal to the effect of the confounder (when there is a perfect correlation between the exposure of interest and the confounder). The effect of a rare but strong confounder is most effectively dealt with by excluding subjects with the confounder. A good example of this is Down's syndrome, which is associated with 20- to 50-fold risk of leukaemia, but only approximately 1 in 800 newborns are affected. Even if most recognized risk factors have small to modest effects and are relatively uncommon, they remain a concern as the expected effect range is below OR 1.2–1.3 because of the low exposure levels and modest exposure contrasts between subjects in studies of natural background radiation and risk of childhood leukaemia.

265. The potential confounding factors were addressed to some degree in the childhood leukaemia studies. The UKCCS was adjusted for SES only; the Swiss study for SES, electromagnetic fields and air pollution from traffic; the Finnish study for birth weight, Down's syndrome and maternal smoking; and the French study for traffic density and power lines.

266. All studies of childhood leukaemia conducted in Europe had comparable exposure levels and, therefore, comparison of statistical power between them is based largely on sample size. A case-control study with multiple controls per case is likely to approach the power of a cohort study with similar numbers of cases. Misclassification of exposure can also decrease power, so studies with full residential history or measured doses have some advantage. The UKCCS investigators wrote: "It is unlikely that a relative risk of this magnitude would be detectable in the present study after its statistical power, modest variations in dose rate and limitations of data collection are taken into account". It is a matter of debate whether or not the relatively low statistical power and possible participation bias in the UKCCS can be offset by the superiority of measurements made on actual residents and not area-wide-based estimates used in the record-based study and other recent studies. However, the subgroup analyses do not have sufficient statistical power. An example is the analysis of ALL in children aged 2–7 years in the Finnish study [N10], with an OR of 1.27 (95% CI: 1.01, 1.60) per 1 mSv, which approximately corresponds to an ERR of 27 per 100 mSv. This estimate is an order of magnitude larger than the LSS estimate and, therefore, does not appear highly plausible. Furthermore, the studies are not adequately powered for assessing the shape of the dose response (departure from linearity).

## 2. Summary

267. In studies of natural background radiation and childhood leukaemia, radiation exposure may be assessed by direct measurement in the homes of the study subjects or estimated using models or small area averages. The former has the advantage of being better able to take inter-house variation into account, i.e. the fact that radiation exposure in adjacent residences may vary considerably. Exposure assessment relying on models or area-based estimates can provide only mean expected values and typically have substantial uncertainty, which reduces statistical power and can bias results. Nevertheless, direct measurements are often affected by low compliance, making them prone to selection bias. Also, residential measurements do not cover other exposure circumstances, such as day care or schools.

268. The first UKCCS has the advantage of individual measurements instead of area-based estimates. However, the dosimetry does not cover the entire sphere of children's everyday life. Studies based on interview and individual dosimetry may, however, be limited by low participation. In the UKCCS, the participation of cases and controls in the interviews was 87% and 64%, respectively, and for radiation monitoring among participants, 55% and 67% (48% of the cases and 43% of the controls with both). If the participation rates are differential and related to radiation dose, selection bias can occur, potentially distorting the results.

269. Recently, several studies using area-based dose estimates have been conducted. In such studies, statistical power can be increased by large sample size since, in the absence of any need for empirical measurements, exposure estimates can easily be generated for large numbers of residences. A clear disadvantage is uncertainties involved in estimation of individual dose based on area-based approaches. However, the magnitude of dose measurement errors\* in this approach depends on the variability of exposure within an area. Comprehensive evaluation of radiation exposure throughout a child's lifetime is also a challenge and requires the construction of residential history, with exposure assessment in each dwelling. In several studies, about half the cases in the study had moved between birth and diagnosis. Overall, the uncertainties in dosimetry in the childhood leukaemia studies are larger than in the TRC or Karunagappally studies. An advantage of the register-based studies is the nearly complete enrolment of study subjects, when no contribution from the subjects is required. In countries and areas with high medical standards, the accuracy of leukaemia diagnosis is not of concern, either, even if diagnosis cannot be confirmed by expert panel review.

270. Residual confounding is another concern. In some countries, information on possible confounders including SES and birth weight for each study subject can be obtained comprehensively through record linkage with census and other register data. All the recent studies of natural background gamma radiation and childhood leukaemia have been able to adjust for some of the other established or suspected risk factors, but none comprehensively. Also, adjustment for area-based measures of potential confounders is likely to result in some residual confounding, due to misclassification from variability within an area unit. The extent of confounding depends on the strength of the effect of the confounder, and its prevalence and degree of correlation with the exposure under study, which are likely to vary between populations and study settings. The lack of individual information on medical exposure is also an issue, particularly in populations with high standards of health care. The degree of confounder control by adjustment depends on how well the effect is captured by the measurement and any imperfection in validity or accuracy reduces the effectiveness of control. However, unless the magnitude of risk is large and the confounder closely correlated with radiation exposure, the extent of distortion by confounding can be assumed to be small, even though it needs to be related to the anticipated true effect magnitude of radiation exposure. More efforts to collect information on all sources of radiation exposure and accurate confounder data are necessary for future studies to improve the risk estimates.

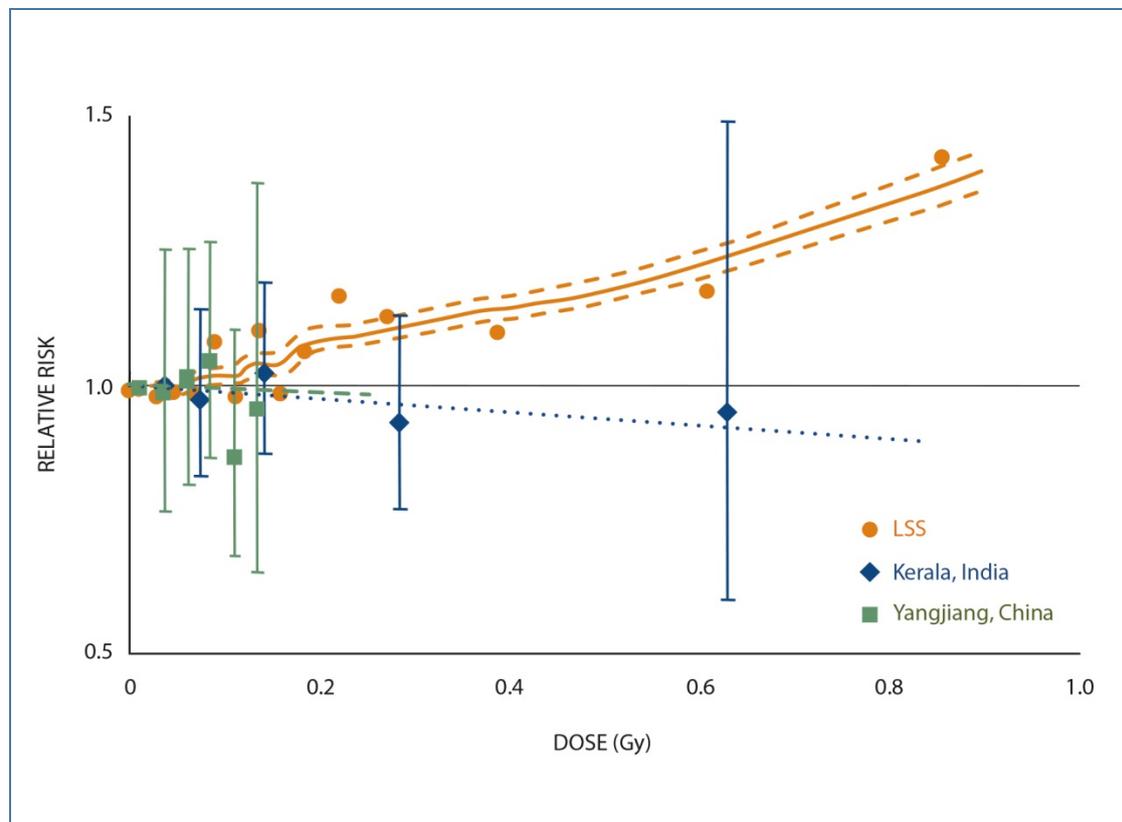
## C. Comparison with studies of acute exposure

271. It is of interest to compare cancer risk estimates obtained from high-dose-rate studies such as the LSS with those obtained from studies of low-dose-rate radiation from environmental sources. However, valid comparisons of the risk estimates are difficult because of differences in methodological approaches, and uncertainties in the studies. A major difficulty in comparing solid cancer risks is the extreme variation in background cancer rates between populations and over time. China, India, Japan and the Russian Federation have differing cancer rates and distributions by primary site, and changes from the 1950s to the current time. Combining all cancers, including those not convincingly linked to radiation, is problematic and could distort the validity of any comparisons. The studies also differ in epidemiological design and methodological quality, including differences in case ascertainment, dosimetry, and the handling of other sources of exposure such as diagnostic radiography and internal exposure. Any residual confounding may also distort the comparison of results. Further, the risk estimates from studies of environmental exposure are rarely precise enough to allow assessment of the shape of the dose response and, for most analyses, a linear no-threshold model is applied. Further, they do have sufficient power or precision to empirically evaluate the latency but have generally applied assumptions of a minimum latency of two years for leukaemia and ten years for solid cancers.

272. Cancer risk from radiation is not consistent across population subgroups, but depends on sex, age at exposure and other factors. Such patterns of variation (effect modification) provide an opportunity to examine the consistency of findings across studies and this is particularly important for studies of low doses, where the extent of effects is small and results can be unstable due to statistical uncertainty reflecting small numbers of radiation-induced cancers. However, expecting complete consistency may not be justified, because risk patterns may depend on dose or dose rate (differences may reflect real variation of effect). The complexity is further increased by the fact that such patterns of variation in risk may differ across cancer sites and types. Even if the cancer types most easily induced by radiation may be consistent across populations, differences in the underlying risk and demographic features may affect the sites for which an excess can be observed. Results based on different cancer types combined into a single category such as solid cancers are not always comparable because, in different studies, the aggregate risk estimate is composed of different proportions of specific cancer sites (reflecting variation in baseline risks). As pointed out earlier in the Committee's UNSCEAR 2000 Report [U6], comparison across studies can be difficult if background rates and modifying factors such as demographic factors differ between studies.

273. Studies on residents in HNBR areas provide opportunities to examine health risks in relation to low-dose-rate exposure to low-LET radiation. For example, despite lack of significant excess risk, the risk estimates from the Karunagappally in Kerala, India and the Yangjiang, China studies are compatible with the LSS results, although they can exclude only very high risks or strong protective effects due to their wide margin of uncertainty (figure VIII).

Figure VIII. Relative risks comparison of the LSS [P16] with the Karunagappally [N4] and the Yangjiang [T3] studies



274. On the other hand, in the TRC, the ERR of solid cancer mortality was 0.061 per 100 mGy (95% CI: 0.004, 0.127), which is somewhat higher than that reported for solid cancer mortality in the LSS of the Japanese atomic bombing survivors. The LSS reported an ERR of 0.042 per 100 mGy for those with attained age 70 and exposed at age 30. However, the wide 95% CI of the TRC estimate includes the LSS estimate. The differences between results of studies on natural background radiation may reflect differences in study design, in dose assessment, in methodology, and in case ascertainment; or be due to combining all solid cancers and making comparisons from different countries, and also the inability to adjust for confounding influences.

275. The ERR estimate for non-CLL leukaemia in the TRC was comparable to that seen in the atomic bombing survivors [P13, P15], who received acute high-dose-rate exposure. However, the dose response for the Japanese atomic bombing survivors had a significant upward curvature at high doses, higher risk for those exposed at young age, and the ERR estimates were somewhat smaller than the ones observed in the TRC. These differences may be related to different situations of exposure: acute (LSS) vs chronic exposure (TRC), external only (LSS) vs external and internal exposure through intake of water and food (TRC), and differences in baseline rates. The main criteria and results of the studies are summarized in table 26.

276. As noted above, the age structure of the study population may affect the results owing to the modifying effect of age (dependence of risk on age at exposure and age at observation). Another challenge is handling age at exposure in continuous exposure. These features complicate the assessment of consistency between the results of studies of low-dose environmental radiation and those assessing effects of acute exposure, as comparability in terms of various age parameters (age at exposure, age attained) is needed. Because radiation exposure is continuous in HNBR studies (and long-term in TRC), age at exposure is not a single value but can be crudely summarized as the mean age (at a specific time or during a given period). In the LSS, age at exposure shows an approximately inverse relation to ERRs per unit dose for ages below 50 years [P16]. Therefore, the use of an arithmetic mean to represent the age at exposure during an exposure period of below 50 years seems a reasonable approach.

277. The average attained age of the TRC population is approximately 45 years, whereas the average age at diagnosis of solid cancer is approximately 65 years [S3]. At an average attained age of 45 years in the TRC study, the ERR per unit dose from the recent mortality analysis (0.061 at 100 mGy) is approximately two thirds of the LSS estimate. Furthermore, the analysis of modification of ERR by attained age in the TRC study showed a tendency of increasing ERR values with increasing attained age. However, the observed risk modification was not significant. A recent analysis evaluated the solid cancer and leukaemia risk estimates from the LSS and TRC, and it showed that the results from the two studies are compatible, when the average attained age and average age at initial exposure are taken into account [P17]. In the TRC study, the ERR for solid cancer incidence was 0.08 (95% CI: 0.01, 0.15) compared to 0.06 (95% CI: 0.05, 0.07) for LSS; and the ERR for leukaemia was 0.22 (95% CI: 0.08, 0.54) and 0.15 (95% CI: 0.03, 0.32), respectively.

278. An extensive analysis of 22 epidemiological low-dose-rate studies on risk of solid cancer with more than 800,000 subjects and 30,000 cancers was published after the literature review for this report [S16]. A large majority of the data were from studies of occupational radiation exposure, but also the four cohort studies of environmental radiation exposure evaluated here were included. The findings suggested materially lower risk estimates per unit dose (by a factor of three) for solid cancers compared with the LSS results, but the findings were heavily influenced by the Mayak worker cohort with very low risk estimates (accounting for 91% of the total variance for cancer mortality and 80% for cancer incidence). If that study were excluded, the pooled risk estimate would be consistent with the LSS results. Restricting the analysis to studies with mean doses <100 mGy gave yield coefficients similar to LSS in analyses of mortality, though incidence results of those studies yielded a lower point estimate.

Table 26. Summary of the main criteria of studies on cancer risk from low dose and dose rate from environmental sources in comparison with the LSS

<i>Criteria</i>	<i>Techa River Cohort [D5, K18, S3]</i>	<i>Taiwan, China <sup>60</sup>Co-contaminated buildings [H8, H10, H11]</i>	<i>Yangjiang, China [T3]</i>	<i>Karunagappally, India [N4]</i>	<i>Atomic bombing survivors study, LSS [G7, H9]</i>
Size of study population	29 730 (mortality), 17 435 (incidence)	6 242	31 604	69 958	80 205 (incidence)
Median dose, mGy	43 (stomach)	6.3	85 (colon)	161 (colon)	230 (colon)
Typical annual dose	Peak 10–20 mGy a <sup>-1</sup> , <10 mGy a <sup>-1</sup> after 1955 (stomach)	<5 mGy a <sup>-1</sup>	~2 mGy a <sup>-1</sup> external	2–5 mGy a <sup>-1</sup>	Instantaneous exposure
Solid cancer cases	1 933 incident cases, 2 303 deaths	106 incident cases	956 deaths	1 349 incident cases	22 538 incident cases
Solid cancer ERR/100 mGy (95% CI)	Incidence 0.08 (0.01, 0.15) Mortality 0.06 (0.004, 0.12)	0.03 (–0.04, 0.09)	–0.10 (–0.25, 0.10)	–0.01 (–0.06, 0.05)	Incidence 0.047 (0.039, 0.055)
Leukaemia cases (non-CLL)	99 (72) incident cases	6 incident cases	15 deaths	30 (20) incident cases	416 incident cases (other than CLL or adult T-cell leukaemia)
Mean RBM dose, mGy	420	48 (whole-body dose, not RBM)	107	163	100
Leukaemia ERR/100 mGy	0.12 (0.04, 0.25) all leukaemias, 0.22 (0.08, 0.54) non-CLL	0.19 (0.01, 0.31)	1.1 (<0, ∞)	0.6 (not defined, 34)	0.08 (0.003, 0.18) linear component, 0.01 (0.03, 0.18) quadratic component, incidence

## VII. FUTURE RESEARCH NEEDS

279. Epidemiological studies use observations from populations with contrasting exposure to the exposure of interest. There are few major opportunities for studies of cancer risk from low-dose-rate exposure to environmental radiation, because large (or very large) studies are required to achieve sufficient statistical power for detecting the predicted excess risks of modest size. Ideally, such studies would be conducted in populations that are otherwise highly comparable, but with a stark contrast in radiation exposure. Similarities should include major risk factors for cancer, and a comprehensive source of high-quality cancer diagnoses, and also deaths and migration (with minimal loss to follow-up). Accurate and detailed dosimetry for all major sources of radiation (including diagnostic radiography and radon where appropriate) and repeated surveys of smoking behaviour, alcohol consumption and other major non-radiation risk factors for cancer would be important. Assuming that it is not practicable to obtain individual dose measurements for large groups of study subjects over long periods in an unselective fashion, constructing accurate prediction models with detailed data on each residence of the study subjects (and exposure levels outside) based on dose-rate surveys with large numbers of measurements may be the optimal approach for radiation exposure assessment. A more comprehensive account of the factors influencing quality of epidemiological studies is given in annex A.

280. Cohort studies are typically established by constructing an exposed group and then finding a reference group that is not exposed or has a materially lower level of exposure. Few dose measurement databases exist where individual doses would be comprehensively recorded though such data sources would be ideal. Dose monitoring of occupationally exposed radiation workers is the only setting where such measurements are systematically available. Very large population-based cohort studies aimed at representative population samples have been initiated in several countries recently—such as the United Kingdom Biobank, and German and Danish national cohort studies—to assess the role of genetic and other factors in common diseases.

281. The Swiss study of childhood leukaemia and background radiation used a nationwide cohort, and illustrates the limitations of such an approach. The exposure levels were low and differences in exposure within the study population narrow, limiting the power of the study. Information on several possible (but not all) confounding factors was available but information on medical radiological exposure could not be obtained. These features suggest that cohort studies may not be ideal research strategies. There are a few populations with radiation doses from natural background radiation several times higher than the global average but such high exposure levels occur in relatively small areas that do not have high-quality data available on cancer incidence and mortality. Thus, large sample sizes would be needed, with a thousand cancer cases or more for accurate risk estimates at low dose levels.

282. Continued follow-up of existing studies, particularly Karunagappally, with cancer incidence data and baseline survey on behavioural risk factors, is likely to yield improved estimates of cancer risk from low-dose-rate radiation from natural sources. Future analyses should focus on individual cancer types, such as leukaemia, for which estimated relative risks are large and for which residual confounding may not be as serious an issue as for other cancers. Childhood leukaemia is an obvious choice, as it has a high relative risk coefficient, and residual confounding is likely to be a lesser issue than for other cancers due to both few well-established major risk factors and to the limited range of exposure of children compared with that of adults.

283. Pooling data from several studies conducted using comparable methods and data sources provides one possibility of improving the precision of risk estimates. As stated in annex A, pooling data in a meta-analysis requires compatibility of the studies, which is best ensured by using a joint protocol or, at the very least, being able to construct a minimum set of key data that are comparable across studies. Pooled analysis\* of individual-level data often provides the best comparability and, hence, most uniform synthesis of study results with evaluation of dose response, which is a key objective in any study aimed at radiation risk estimation.

284. Taking this information into account, the Committee concluded that key challenges for future research could be summarized as:

- Improving individual dose estimates from all sources of exposure;
- Ensuring comprehensive and high-quality cancer registration;
- Enhancing tracing of loss to follow-up through death or migration in cohort studies;
- Improving control of confounding by key non-radiation risk factors;
- Developing and implementing improved methods (with user-friendly software) for accommodating the impact of non-sampling errors, such as dosimetric uncertainties and residual confounding, in risk estimates and hypothesis testing results.

## VIII. CONCLUSIONS

285. This annex evaluated epidemiological studies reporting cancer risk per unit dose on the basis of individual cumulative doses from exposure to low-LET radiation from environmental sources. Inherent limitations of epidemiological studies impede the precision of direct estimates in the very low dose range. Nonetheless, studies of populations exposed to low-dose-rate radiation accumulating to levels, where observable effects are anticipated, are highly valuable. The TRC study has demonstrated dose-dependent increases in occurrence of solid cancer and leukaemia, though associations with radiation exposure were also found for cancer types that have not been commonly increased following radiation exposure in other studies. No discernible increases were reported for solid cancer or leukaemia in the Karunagappally or Yangjiang HNBR studies, though the low precision of the risk estimates does not rule out either absence of an excess risk of cancer or substantially higher risks per dose unit than those reported in high-dose and dose-rate studies.

286. The five childhood leukaemia studies, except for the French GEOCAP-study, give largely consistent, though not highly precise estimates of ERR per unit dose in the low dose range. However, since the confidence intervals are wide, it is difficult to confirm whether the ERR per unit dose is similar to estimates obtained from studies of acute exposure such as the LSS.

287. Overall, the results of the studies of cancer risk due to radiation exposure at low dose rates from environmental radiation do not provide strong evidence for materially lower risks per unit exposure than in studies of high radiation doses and dose rates, though the findings are consistent with a range of risk estimates. The current results warrant a cautious interpretation of the magnitude of cancer risk per unit radiation exposure at low dose rates from environmental sources. The studies reviewed here have shortcomings, such as small sample size and methodological weaknesses that limit the conjectures/conclusions that can be drawn from their results. In the future, nested case-control studies within these

cohorts may be able to overcome some of the limitations. Longer follow-up with larger numbers of cases can be expected to improve the precision of the results.

288. For solid cancer, the risk estimates from the three major studies in China, India and the Russian Federation can be regarded as consistent with each other due to large uncertainty partly related to statistical imprecision, even if no increases in cancer rates could be demonstrated in HNBR studies, unlike the TRC study. Dose estimation is always a major challenge in studies of environmental radiation exposure, because it often requires retrospective reconstruction of residential history, occupancy, and for internal exposure, amounts and sources of food and water intake. This is particularly demanding when exposure levels have changed markedly over time, as in the Techa River region. Hence, in addition to low statistical power due to the limited sample size relative to the anticipated magnitude of effect, further uncertainty stems from exposure measurement error that is often not accounted for in the analysis. This can distort the results and, therefore, realistic estimation of the amount of measurement error is important, particularly when it can be assumed to be substantial. The TRC study is the only one that has yielded a precise estimate also for adult leukaemia and incorporated information on the health effects from internal exposure. It should be noted that the nature of exposure in the TRC study is different from that of the Karunagappally and Yangjiang studies. In the TRC study, maximum internal and external exposure took place over one to two decades and decreased materially with time, while the exposure in the two other studies was mainly external and lifelong.

289. Previous studies—including those on the Japanese survivors of the atomic bombings, and also medical and occupational exposures—show that some cancer types are more strongly associated with radiation exposure than others. In the LSS, for example, the ERR per unit dose after childhood exposure is materially higher for leukaemia than for solid cancers. Similarly, the ERR per unit dose for thyroid cancer in those exposed in childhood is materially higher than for other solid cancers. Although the differences in risk estimates between solid cancer types are less striking in those exposed in adulthood, there is major uncertainty in using a single estimates for all solid cancers combined for comparisons across studies, because the background rates of various cancer types differ strongly across populations (for instance China, India and the Russian Federation) and the proportion of a cancer site of all cancers affects the weight it has in the risk estimate for all cancers combined. Therefore, combining all cancer types could result in mixing differing dose responses for various cancer types, with dissimilar composition of the combined category of all cancer types between the study populations. All solid cancers combined comprise malignancies with different aetiology and risk coefficients per unit radiation dose (including some that are not consistently linked to radiation) and, therefore, the estimates obtained for risk coefficients of all solid cancers can differ between studies for these reasons alone. Differences in radiation-related risk estimates across studies may also be due to the variations in risk modifiers such as age, sex, and behavioural (e.g. tobacco and alcohol use) and genetic factors. Focusing on specific cancer types would result in better comparability between studies and should be pursued, although small numbers are likely to pose problems of interpretation.

290. Radiation exposure at low dose rates typically, although not necessarily, results in low doses and, therefore, risk estimation can be readily affected by confounding from other cancer risk factors. This is an essential challenge in trying to detect a very small radiation effect from low doses against a sizable background rate. This may add to the differences between study results, because the prevalence of confounders and their association with radiation exposure can vary. Also, inaccuracy in assessing confounders leads to poorer ability to control for their effects. An analysis accounting for the effects of confounders also sets requirements for sample size in a study, which in itself might be constrained when the entire exposed population is studied and cannot be increased. Precise and valid risk estimates require sufficient follow-up, case ascertainment through high-quality cancer registry systems, and accurate information on risk factors other than radiation exposure. This emphasizes the need for prospective long-term follow-up studies with high-quality dosimetry and accurate outcome data.

291. In conclusion, the Committee recognizes that studies of low-dose-rate exposure from environmental sources have potential to make a contribution to understanding radiation-induced cancer risk. Direct evidence from such studies would be valuable because most radiation exposure in the general population is obtained from low doses received over extended periods. However, improvements would be needed to overcome the key limitations of these studies including low statistical power, dosimetric uncertainties, imperfections in control of confounding, and any other biases. Studies of low-dose-rate exposure are more susceptible to such limitations than studies of high dose exposure. Differences in results of environmental radiation exposure studies may be due to problems in study quality, including bias from under-ascertainment of cases (deaths or diagnoses), inaccurate cancer diagnosis, imprecise dose assessment, and residual confounding. Further improvement in the quality of such epidemiological studies could be achieved by improving the quality of clinical cancer diagnoses and cancer registries, collecting accurate data on risk factors for specific cancer types and causes of death, and improving dose estimation, to obtain reliable ERR estimates for specific cancer types and population subgroups.

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## GLOSSARY

*Note: The glossary is based on the glossary included in the UNSCEAR 2012 Report to ensure consistency of terms and definitions [U3]*

**Absorbed dose, D:** The fundamental dose quantity given by

$$D = \frac{d\bar{\epsilon}}{dm}$$

where  $d\bar{\epsilon}$  is the mean energy imparted to matter of mass  $dm$  by ionizing radiation. The SI unit for absorbed dose is joule per kilogram (J/kg) and its special name is gray (Gy).

**Adjustment:** the process of statistically accounting for effects of differences between groups or populations under comparison in order to control confounding. Adjustment is frequently performed when estimating effect measures from epidemiological data, for example by stratification or multivariate regression analysis.

**Assigned share:** Assigned share is the probability that an observed health effect in an individual was caused by a specific radiation exposure. It is equal to the fraction of the total number of cases of a specific type of cancer diagnosed among individuals which is in excess to the baseline number of cases for persons who share the same attributes, such as absorbed organ dose, age, time since last exposure, sex, smoking history, etc. The assigned share (AS) is quantified as

$$AS = \frac{\text{excess relative risk}}{\text{relative risk}}$$

The AS is often referred to as the “attributable fraction” or “probability of causation” assuming that the calculated excess relative risk represents the net consequences of mechanisms of disease manifestation for a given individual diagnosed with disease.

**Assignment error (“Berkson error”):** Assignment error is relevant in situations where the difference (or ratio) of the assigned and true values of quantity of interest (e.g. a radiation dose) is independent of the assigned value. Such errors typically arise as the result of some sort of grouping in which all members of a defined subgroup are assigned a single representative value (e.g. an unbiased expected value of dose for each member of a subgroup, where the subgroup is identified by exposure characteristics, such as age, sex, location, diet, residence history and shielding). A fundamental characteristic of assignment error is that true values vary at random about the assigned value. Thus, the variance of true values will be larger than the variance of assigned values. Furthermore, the assigned value will equal (or closely approximate) the true mean value for the subgroup. In linear regression, the presence of additive assignment error in the independent variable does not lead to bias in the estimate of the regression slope. Assignment error can be contrasted with “measurement error” and “shared error”.

**Baseline (hazard) rate (frequency):** disease rates for a population of interest in the absence of exposure or at some reference exposure level, allowing to calculate e.g. expected case numbers in a reference population without exposure. See also “Hazard rate (function)” and “Excess (absolute) rate”.

**Bayesian inference:** The method of inference that quantifies the degree of belief (or the analyst's state of knowledge) of a true value or sets of values of a quantity of interest by combining their prior knowledge about these quantities with recent measurements, observations, or estimates. The degree of belief of the quantity of interest is often described by a subjective probability distribution representing possibly true values for that quantity. The distribution resulting from Bayesian inference is called a posterior distribution which combines the prior and observed data.

**Berkson error:** See "Assignment error".

**Bias:** Systematic deviation of results or inferences from the truth [P1]. A statistical estimation procedure is "biased" if the expected value of the estimate of the quantity of interest is not equal to the true value of the quantity. The "bias" of the procedure is the difference between the expected and true values (see also "Selection bias", "information bias", survivor bias).

**Biodosimetry:** the use of biological (or chemical, physiological) markers of exposure to reconstruct acute or protracted radiation doses.

**Causation:** The relationship between cause (here, radiation exposure) and effect (radiogenic health effect or associated disease/mortality risk). The term can also mean the action of causing something.

**Classical error:** Classical error, or more precisely classical measurement error, applies in situations in which the difference between the measured or estimated value and the true value of a quantity of interest (e.g. a radiation dose) is independent of the true value. Classical measurement error is a type of random error; it arises when measured or estimated values of a quantity of interest are determined by imprecise measurements or by estimates of quantities used as independent variables in a regression analysis. A fundamental characteristic of classical measurement error is that the variance of measured or estimated values is larger than the variance of true values. The mean of the measured or estimated values is unbiased with respect to the true mean. In linear regression, the presence of classical measurement error in the independent variable biases the estimate of the regression slope toward zero. Classical measurement error can be contrasted with "assignment error" and with "shared error".

**Confidence interval:** In "frequentist inference", a confidence interval is an interval defined in terms of the sampling distribution of a statistic of interest (i.e. the distribution of estimates of the statistic that would arise from repeated—generally hypothetical—realizations of data generated from the same underlying distribution as the observed data) such that, for example, the probability that a 95% confidence interval for a given parameter contains the true value of that parameter is 0.95. (Compare this with "Credible intervals" used in "Bayesian inference".)

**Confounding factor or confounder:** A confounding factor is a variable that is correlated with both the exposure (e.g. radiation exposure or dose) and the outcome variable (e.g. risk of lung cancer) and, if not controlled for analytically, may distort the conclusions. For example, occupation may be a confounding factor in a study of the relation between lung cancer incidence among non-smokers (dependent variable) and medical radiation exposure (independent variable). For instance, air crew are exposed to higher levels of radiation due to their employment (correlation with radiation exposure) while staff working in certain recreation industries are often occupationally exposed to cigarette smoke (correlation with outcome lung cancer). This confounding might be controlled by introducing into the analysis an indicator for the occupational group.

**Dose rate:** Dose relative to time during which the dose is received. In experimental studies dose rate is often expressed per minute, while in epidemiological studies of long-term exposure dose per year is frequently used.

**Effect modification:** Effect modification (also called statistical “interaction”) occurs when the magnitude of the influence of the dependent variable of interest (e.g. radiation dose or exposure) on an independent (outcome) variable (e.g. lung cancer) depends upon the magnitude of some other factor (the effect modifier). For example, analyses of the atomic bombings survivors suggest that the magnitude of the outcome of ionizing radiation exposure on the excess relative risk of lung cancer depends on smoking intensity, with a larger outcome from unit dose among moderate smokers and much smaller outcome among heavy smokers. An effect modifier may or may not be a *confounding factor*, depending on whether or not there is a correlation between the dependent variable of interest and the effect modifying factor.

**Excess absolute risk/rate (EAR):** The difference between the disease rate in an exposed population and the baseline rate in that population. This is often a function of dose, age (or some other measure of time) and other factors (effect modifiers). Excess absolute rate is often called “excess absolute risk” or “excess rate”.

**Excess relative risk/rate (ERR):** The excess relative risk is the proportional increase above the baseline rate of the disease or condition under study. Numerically, it is the “relative risk/rate” minus one. The excess relative rate is strictly a statistic calculated from observed frequencies/rates, while the excess relative risk is a prospective estimate inferred from the data and reasoning. The ERR is often considered as a function of dose and other factors.

**Frequency (of occurrence of disease):** The number of new cases of the disease under study divided by the number of people in a population over a defined time period.

**Frequentist inference:** A method of inference in which parameter estimates, hypothesis tests, and confidence intervals for some quantities of interest are based on the chances of obtaining the observed data in repeated (hypothetical) realizations of the data given an assumed state of nature. The main alternative approach to frequentist inference is “Bayesian inference”.

**Hazard:** In epidemiology and statistics, a measure of occurrence obtained as time integral of risk and interpreted as risk intensity. With respect to aspect of health and safety, the term “hazard” refers to any source of potential damage, harm or adverse health effects.

**Health effects (of radiation)** (also radiogenic health effects):

**Deterministic (health) effect:** A health effect of radiation for which generally a threshold level of dose exists, which varies with person and circumstance, above which the severity of the health effect is greater for a higher dose. The ICRP has introduced a term “tissue reactions” to describe a group of health effects comprising deterministic effects and some health effects (such as cataracts and fibrosis) that are not determined solely at the time of irradiation but can be modified after radiation exposure [I1, I2].

**Stochastic (health) effect:** A radiation-related health effect, the probability of occurrence of which depends on radiation dose and the severity of which (if it occurs) is independent of dose. In radiation protection the so-called LNT-model is used (linear non-threshold) meaning that the assumption is made that one can linearly extrapolate from moderate/high doses to low and very low doses without a threshold. Note that this should not be confused with the stochastic actions or processes of radiation interaction at the molecular or cellular level.

**Information bias:** this type of bias occurs when there are systematic information differences between different groups that are being compared in an epidemiological study. Recall bias is a type of information bias where cases with the disease of interest are likely to recall past exposures differently

no control persons without disease. Information bias also occurs when there are differences in disease ascertainment between exposed and non-exposed groups in an epidemiological study.

**Interaction:** Refers to the situation in which the magnitude of the influence of one risk factor on disease rates depends upon the magnitude of one or more other risk factors (see “Effect modification”).

**Latency (period):** The period between exposure and manifestation of a health effect. This is also the period after which statistically significant increases in frequency of occurrence of the health effect in a population have been seen; theoretically, there might be an undetectable increased frequency of occurrence of the health effect in an exposed population during the presumed latency period, but this possibility becomes vanishingly small in the period shortly after exposure because there is a finite time required for damaged cells to replicate in an uncontrolled manner and manifest as a cancerous growth.

**Likelihood:** Generally, the state or fact of being likely or probable. The term may also be used to express a defined statistical concept. Specifically, given a set of data and a statistical model that describes the distribution of the data in terms of some parameters, the statistical concept of “likelihood” is a function of the model parameters that is proportional to the probability density function for the data (given the parameter values). For independent observations, the likelihood of the data is the product of the likelihood values for each observation. Likelihood functions play a central role in both “frequentist inference” and “Bayesian inference” (albeit with different interpretations). Frequentist inference often proceeds by finding parameters that maximize the likelihood given the data (maximum likelihood estimation) and using (asymptotic) properties of the maximized (log-) likelihood as the basis for inference.

**Loss to follow-up:** In cohort studies lost to follow-up means failure to trace a subject, resulting in loss of information on the outcome such as death or disease occurrence. This can be due to non-compliance in active follow-up (e.g. non-response or missing contact information) or emigration in registry-based follow-up (e.g. moving to other countries or regions not covered by the study). Loss to follow-up reduces the statistical power of a study. If loss to follow-up differs by exposure status, it can lead to information bias.

**Low dose:** Doses below 100 mGy are called low doses [U3], though the threshold value is necessarily arbitrary.

**Low dose rate:** The Committee has defined “low dose rate” as 0.1 mGy per minute, averaged over one hour or less, for radiations such as external X-rays and gamma rays [U1, U2].

**Measurement error:** The difference between the true value of a quantity of interest and a measurement of that value. Measurement error can be random (see “Assignment error” and “Classical error”) or systematic (see “Shared error”).

**Meta-analysis:** In statistics, a meta-analysis combines the results of two or more studies that address a set of related research hypotheses, for example by estimating a certain unknown parameter or parametric function common to two or more data sets, while controlling or adjusting for differences in other parameters unrelated to those of immediate interest. The purpose is to obtain an estimate that is more informative than any obtainable from a single study, while ensuring that other data do not corrupt or bias the result. The term “meta-analysis” is also used for statistical pooling of summary results available in published form, in contrast with a *pooled analysis* of original individual-level data from two or more studies.

**Misclassification:** measurement error for discrete variables (sex, ethnicity etc.) where individuals are wrongly classified into a group to which they do not belong. If the classification error depends on the

value of other variables (e.g. it differs by exposure group), it is called differential misclassification. If it is independent of the value of other variables, the term non-differential misclassification is used. The latter generally introduces a bias towards the null value, but there are exceptions.

**Model:** An analytical or physical representation or quantification of a real system and the ways in which phenomena occur within that system, used to predict or assess the behaviour of the real system under specified (often hypothetical) conditions. This is in contrast to a relationship, which is simply the way two or more factors are connected or related (i.e. relationships include causal relationships, those based on models, and those that simply fit the observed data).

**Model uncertainty:** The value of a quantity of interest derived from a data set of observations depends in general on the model that has been assumed to analyse the data. The related uncertainty of that value (i.e. the range of values for a quantity of interest that is obtained from analysing the data with different assumed models) is called model uncertainty.

**Multi-model inference:** Multi-model inference derives the probability density function of a quantity of interest by accounting for results of more than one model applied to the same set of data.

**Odds ratio:** the effect measure used in case-control studies. Its interpretation is similar to that of a risk ratio or rate ratio, but its numerical value is more extreme (further from the null), particularly when the studied disease is common. An odds ratio is obtained as the ratio of the number of exposed cases to non-exposed cases relative to the ratio of exposed controls to non-exposed controls. It can also be computed from studies using other designs, with slightly different interpretation. For ubiquitous exposures such as indoor radon or natural background radiation, a lower level is used as reference instead of no exposure

**Point estimate:** the most supported single value of the property estimated from the observed data, e.g. rate ratio or odds ratio in an epidemiological study. The results of a study are, however, best interpreted as consistent with a range of values, e.g. that in the confidence interval or supported range, though the data generally lend more support to the central values within that range.

**Pooled analysis:** A combined analysis of original individual-level data from two or more data sets bearing on a common question of interest. The analysis may include parameters that distinguish between the different data sets. (Contrast with “*meta-analysis*”.)

**Radiogenic health effects:** See “Health effects (of radiation)”.

**Random error:** An error in which the difference between the true value and an estimated value occurs at random. Random error implies the absence of systematic bias in the central or mean value. Random error gives rise to classical measurement errors if each individual’s true dose is estimated using information obtained independently from each individual in a cohort. Random error gives rise to assignment errors when expected values of dose estimates are assigned to every individual having the same exposure characteristics, such as age, gender, occupation, residence history, and diet, and when the assigned dose to an individual is equal to the true mean dose for the exposure subgroup. An estimate is considered precise if there is little random error.

**Rate:** In general, the ratio of two quantities, where the denominator is usually a function of the period of time at risk. Rates of interest in epidemiology (and radiation risk estimation) are of the form  $\frac{e}{PY}$ , where  $e$  is the number of events (e.g. incident cases, deaths) over some time period of interest in a study population and PY (expressed as person-years) is the sum of time at risk during this time period for each person in the study population. Rates for an event of interest can vary with such factors as age,

sex, and dose. Characterization of how rates depend on dose (or exposure) is central to radiation risk estimation. See also “Hazard function”, “Risk”, “Relative risk”, “Excess rate”, and “Relative risk”, and “Excess relative risk”.

**Regression calibration:** Usually refers to a method used to adjust quantities measured with (classical) measurement error to reduce the bias in dose–response estimates derived from the estimated doses. More generally, regression calibration involves replacing the estimated dose by its expected value given the estimated dose, and using what is known about the magnitude of the measurement error and the distribution of true doses in the population of interest. As a further generalization, samples from the conditional distribution of dose given the estimated dose, and what is known about the measurement error and the distribution of true doses in the population could be used. In principle, complex (Monte Carlo) simulation systems are intended to provide such sets of dose realizations.

**Relative risk/rate ratio:** The ratio of disease rates in different groups (e.g. an exposed and unexposed group) or for different exposure levels (e.g. people exposed at high dose rates and people exposed at low dose rates). It is often useful to view the relative risk as a function of variables, such as dose, sex, or age. In epidemiology, the term relative risk is commonly used as synonym for rate ratio, which should be the preferred term.

**Risk:** In the context of (radiation-related) health effects, risk refers to the probability that an event of interest (e.g. onset of cancer) will occur (i.e. it is prospective) during a given time period (e.g. the rest of life following an exposure). Risks can be estimated using evidence from epidemiological investigations of disease rates in previously exposed populations (i.e. based on past observations). The results from such retrospective analyses often are used, with appropriate modifying and adjustment factors, to make inferences about the risk for other exposure situations involving different populations for which direct epidemiological data on the dose–response relationship are not available.

**Selection bias:** This bias occurs when the group of persons actually under study differs from the intended target group, and this difference affects (biases) the study results. An example is selective enrolment of volunteers into a study, which will lead to biased results.

**Shared error:** An error common to some or all members of a cohort or cohort subgroup. Shared error is a form of systematic error, which influences the direction and magnitude of the difference between the estimated value of the true value of a quantity of interest for individual members of a cohort or cohort subgroup. Uncertainty in the estimate of a true value for a model parameter used to quantify dose to a group of individuals is a common source of shared errors in dosimetry. Being a form of systematic error, shared errors should be distinguished from independent random errors such as “assignment errors” and “classical errors”. This distinction is especially important when estimates of the dose to an individual dose are used in an analysis of the dose–response relationship.

**Statistical significance:** Statistical significance testing is a technique originally developed for decision making, where the compatibility of the observations is contrasted with that expected in the absence of any difference (null hypothesis). An alternative or study hypothesis needs to be specified positing a difference, usually evaluating difference to any direction (called two-sided test), or to a specific direction (one-sided test). Conventionally, 0.05 has been used as the limit (critical value, alpha level or type I error) for significance, corresponding to a frequency of 1/20 for occurrence of a difference equally large or larger as observed in the absence of any true difference (under the null hypothesis). The choice of the cut-off level is, however, arbitrary and statistical significance should not be seen as the sole criterion for interpretation of the findings.

**Stratification:** The process of stratification leads to the separation or grouping of a sample into several subsamples defined by stratification variables such as socioeconomic status, age group or sex. Stratification is the basic principle of confounder control in the analysis of epidemiological data.

**Stochastic (health) effect:** See “Health effects”.

**Survivor bias:** A type of selection bias which occurs in an epidemiological study when participants with a higher survival probability are preferentially included in the study. This occurs for example when cancer cases are studied, but only those who have survived up to a certain date are included. Surviving cases, however, may differ systematically from those with more severe forms of cancer, who have a higher early mortality.

**Systematic error:** A systematic error affects bias in a group of measurements or in estimates of a quantity of interest. This bias will be in a given direction, but may apply to varying degrees for different cohort subgroups. As mentioned above, systematic error is related to “Shared error”. The three main types of systematic error in epidemiological studies are selection bias, information bias and confounding.

**True dose:** The true but unknown value of dose for a specific individual. The state of knowledge about this unknown true value can be characterized by measurements and estimates that produce a distribution representing state of knowledge about possibly true values. In an epidemiological cohort, there will be a unique set of unknown true doses.

**Uncertainty:** Expression of having doubt, or being unsure about study results, hypotheses, model-based estimations or results of measurements, and specifically the true value of a quantity of interest. This may be due to lack of complete knowledge about true values for an individual or to a lack of complete knowledge of factors explaining the inter-individual variability of true values in a defined subgroup or population. Unlike error, uncertainties can be quantified. Estimates of uncertainty represent the amount or percentage by which an observed or calculated value might differ from its true value. For a quantity of interest that has a true fixed value, uncertainty is defined here as a degree of belief probability distribution comprising many realizations of possibly true values. For a quantity of interest that is a group or population of true values, uncertainty can be characterized as many alternative realizations of sets of true values.

**Validity, internal:** The extent to which the study accurately reflects the true situation within the study population, i.e. the degree to which the study is free from systematic error.

**Validity, external:** The extent to which the study results are applicable to other populations that have not been studied (i.e. generalizability).

**Variability:** Heterogeneity, diversity or a range which characterizes variation in estimated, measured, or true values of a quantity of interest. The term variability is often used to describe differences in measured or true values among individuals in a population or cohort. Examples include inter-individual differences in body weight and/or dose or inter-cohort differences in exposure–response due to differences in sensitivity to a hazardous agent. Further study cannot reduce variability, but may provide additional information to explain reasons why some of this variability occurs. This additional information can reduce the fraction of inter-individual variability initially treated as stochastic.

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This publication contains:

REPORT OF THE UNITED NATIONS SCIENTIFIC COMMITTEE ON THE EFFECTS  
OF ATOMIC RADIATION TO THE GENERAL ASSEMBLY

**Scientific Annexes**

- Annex A: Principles and criteria for ensuring the quality of the Committee's reviews of epidemiological studies of radiation exposure
- Annex B: Epidemiological studies of cancer risk due to low-dose-rate radiation from environmental sources



EVALUATING RADIATION SCIENCE FOR INFORMED DECISION-MAKING

In 1955 the United Nations General Assembly established the Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) in response to concerns about the effects of ionizing radiation on human health and the environment. At that time fallout from atmospheric nuclear weapons tests was reaching people through air, water and food. UNSCEAR was to collect and evaluate information on the levels and effects of ionizing radiation. Its first reports laid the scientific grounds on which the Partial Test Ban Treaty prohibiting atmospheric nuclear weapons testing was negotiated in 1963.

Over the decades, UNSCEAR has evolved to become the world authority on the global level and effects of atomic radiation. UNSCEAR's independent and objective evaluation of the science are to provide for—but not address—informed policymaking and decision-making related to radiation risks and protection.

