United Nations Scientific Committee on the Effects of Atomic Radiation

SOURCES, EFFECTS AND RISKS OF IONIZING RADIATION

UNSCEAR 2013 Report

Volume II

SCIENTIFIC ANNEX B:
Effects of radiation exposure of children

UNITED NATIONS

SOURCES, EFFECTS AND RISKS OF IONIZING RADIATION

United Nations Scientific Committee on the Effects of Atomic Radiation

UNSCEAR 2013
Report to the General Assembly with Scientific Annexes

VOLUME II
Scientific Annex B

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NOTE

The report of the Committee without its annexes appears as *Official Records of the General Assembly*, Sixty-eighth Session, Supplement No. 46.

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

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CONTENTS

Scientific findings on effects of radiation exposure of children

Note: The findings and conclusion, together with information on members of delegations to UNSCEAR and scientific staff and consultants, presented here are based on scientific annex B of the UNSCEAR 2013 report and are extracted from the Official Records of the General Assembly at its Sixty-eighth session, Supplement No. 46.

[…]

45. Epidemiological studies reported in the literature vary with regard to the specific age groups they consider. For the purposes of the Committee's evaluation of the effects of radiation exposure on children, the term "children", in contrast to "adults", included those exposed as infants, children and adolescents. The evaluation did not specifically address effects of in utero exposure to radiation because such information is contained in other comprehensive reports. The evaluation also did not address the many beneficial uses of radiation exposure for children, such as in medical diagnosis and therapy, which are outside the mandate of the Committee.

46. Sources of exposure to children that are of particular interest include accidental exposures, and specific regions with enhanced levels of natural background radiation, as well as diagnostic and therapeutic procedures. The data reviewed by the Committee were derived from studies covering a wide range of doses, variable dose rates, whole and partial body exposure and children of different ages. The effects described in the annex are often very specific to a given exposure scenario.

47. At its sixtieth session the Committee considered the effects of radiation exposure of children and reached the following conclusions:

(a) For a given radiation dose, children are generally at more risk of tumour induction than are adults. Cancers potentially induced by exposure to ionizing radiation at young ages may occur within a few years, but also decades later. In its report on its fifty-fourth session, the Committee stated that estimates of lifetime cancer risk for those exposed as children were uncertain and might be a factor of 2 to 3 times as high as estimates for a population exposed at all ages.[*] That conclusion was based on a lifetime risk projection model combining the risks of all tumour types together;

(b) The Committee has reviewed evolving scientific material and notes that radiogenic tumour incidence in children is more variable than in adults and depends on the tumour type, age and gender. The term "radiation sensitivity" with regard to cancer induction refers to the rate of radiogenic tumour induction. The Committee reviewed 23 different cancer types. Broadly, for about 25 per cent of these cancer types, including leukaemia and thyroid, skin, breast and brain cancer, children were clearly more radiosensitive. For some of these types, depending on the circumstances, the risks can be considerably higher for children than for adults. Some of these cancer types are highly relevant for evaluating the radiological consequences of accidents and of some medical procedures;

[*] *Official Records of the General Assembly, Sixty-first Session, Supplement No. 46* and corrigendum (A/61/46 and Corr.1) paras. 21-22.

(c) For about 15 per cent of the cancer types (e.g. colon cancer), children appear to have about the same radiosensitivity as adults. For about 10 per cent of cancer types (e.g. lung cancer), children appear less sensitive to external radiation exposure than adults. For about 20 per cent of cancer types (e.g. oesophagus cancer), the data are too weak to draw a conclusion regarding any differences in risk. Finally, for about 30 per cent of cancer types (e.g. Hodgkin's disease and prostate, rectum and uterus cancer), there is only a weak relationship or none at all between radiation exposure and risk at any age of exposure;

(d) At present, projections of lifetime risk for specific cancer types following exposure at young ages are statistically insufficient. Estimates currently do not adequately capture the known variations, and additional studies are needed;

(e) For direct effects that occur after high (either acute or fractionated) doses (so-called deterministic health effects), the differences in outcome between exposure in childhood and in adulthood are complex and can be explained by the interaction of different tissues and mechanisms. These effects may be seen after radiation therapy or following high exposures in accidents. The difference between the radiation sensitivity of children and that of adults for deterministic effects in a specific organ is often not the same as the difference for cancer induction. There are some instances in which childhood exposure poses more risk than adulthood exposure (e.g. risk of cognitive defects, cataracts and thyroid nodules). There are other instances where the risk appears to be about the same (e.g. risk of neuroendocrine abnormalities), and there are a few instances where children's tissues are more resistant (e.g. lungs and ovaries);

(f) Because of all the above considerations, the Committee recommends that generalizations on the risks of effects of radiation exposure during childhood should be avoided. Attention should be directed to specifics of the exposure, age at exposure, absorbed dose to certain tissues and the particular effects of interest;

(g) There have been many studies of possible heritable effects following radiation exposure; such studies were reviewed by the Committee in 2001. It has been generally concluded that no heritable effects in humans due to radiation exposure have been explicitly identified (specifically in studies of offspring of survivors of the atomic bombings). Over the past decade, there have been additional studies that have focused on survivors of childhood and adolescent cancer following radiotherapy, where gonadal doses are often very high. There is essentially no evidence of an increase in chromosomal instability, minisatellite mutations, transgenerational genomic instability, change in sex ratio of offspring, congenital anomalies or increased cancer risk in the offspring of parents exposed to radiation. One reason for this is the large fluctuation in the spontaneous incidence of these effects;

(h) Health effects and risks are dependent on a number of physical factors. Because children have smaller body diameters and there is less shielding by overlying tissues, the dose to their internal organs will be larger than for an adult for a given external exposure. Because they are also shorter than adults, children may receive a higher dose from radioactivity distributed in and deposited on the ground. These factors are important when considering doses to populations in some areas with high levels of radionuclides in and on the ground. In diagnostic medical exposure, children may receive significantly higher doses than adults for the same

examination if the technical parameters for delivering the dose are not specifically adapted;

(i) Regarding internal exposure, because of the smaller size of infants and children, and thus because their organs are closer together, radionuclides concentrated in one organ irradiate other organs of children's bodies more than occurs in adults. There are also many other age-related factors involving metabolism and physiology that make a substantial difference in dose at different ages. Several radionuclides are of particular concern regarding internal exposure of children. Accidents involving releases of radioactive iodines (for example, in a nuclear power plant accident) can be significant sources of exposure of the thyroid gland, and thus have the potential to induce thyroid cancer. For a given intake, the dose to the thyroid for infants is eight or nine as large as that for adults. For intakes of caesium-137, there is very little difference in dose between children and adults. Internal exposure of children also occurs in the medical use of radionuclides. The spectrum of procedures normally performed on children is different from that performed on adults. Potentially higher doses in children are offset in practice by the use of a lower amount of administered radioactive material.

48. The Committee recognizes that continued research is needed to identify the full scope and expression of the differences in effects, mechanisms and risk from exposure to ionizing radiation for children and for adults. This is necessary because for a number of studies (such as of the atomic bombing survivors, children exposed to radioiodine after the Chernobyl accident and those who have had computed tomography scans), the lifetime results remain incomplete. Future long-term studies following childhood exposure will face significant difficulties owing to unlinked health records, administrative and political barriers and ethical and privacy considerations.

49. Important areas of future research and work also include evaluation of potential radiation effects for children: (a) in areas of high natural background exposure; (b) after high-dose medical procedures involving interventional fluoroscopy; and (c) after cancer radiotherapy (including evaluation of potential interactions with other therapies). The Committee has identified the following areas for future research as well: development of databases on radiation doses for children who can be tracked in the long term; and evaluation of effects following whole and partial irradiation of juvenile organs. Studies at the molecular, cellular, tissue and juvenile animal level are potentially informative.

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ANNEX B

EFFECTS OF RADIATION EXPOSURE OF CHILDREN

CONTENTS

I. INTRODUCTION

1. The Committee—in its 2000 Report (annex F), 2001 Report and 2006 Report (annex A)—has previously considered the effects, and associated risks, of ionizing radiation exposure on vulnerable populations [U10, U11, U12]. Several population groups are specifically identifiable as being more vulnerable to radiation exposure than the population as a whole. These include embryos/foetuses, children, and those persons with abnormalities of DNA repair, co-morbid conditions or concomitant insults or stresses. Children are clearly the largest and most easily recognizable vulnerable population group.

2. Knowledge of the effects of radiation exposure on children is, and will continue to be, of great social, public health, scientific, and clinical importance. Exposures range from those due to fallout from atmospheric nuclear weapon testing to exposures from accidents, natural radiation and medical procedures such as computed tomography (CT) and radiotherapy. Radiation effects have been studied for over a century, and many of the large epidemiological studies and reports of the sources and effects of ionizing radiation exposure have included children as part of the groups studied. Therefore, there is already a large amount of scientific literature on the topic. To date, however, there have been no comprehensive reports specifically addressing all aspects of radiation exposure of children and the consequent health effects and associated risks. Information is often buried in epidemiological reports on general population exposure. Scientific investigations and radiation protection efforts have occasionally focused on “critical” or “most exposed” individuals and “vulnerable” or “radiosensitive” populations.

3. The general perception that children are more vulnerable to radiation exposure than are adults is only partly true. The susceptibility of children to the effects of ionizing radiation has been a focus of interest for over half a century. There is a loosely stated notion that children might be two–three times more sensitive to radiation than adults. Is this really true? In the broad spectrum of adverse health effects, children are at greater risk for some but not all effects. For a few effects, children may be more resistant than adults. For example, while there are clear instances of an increased risk for children, compared to adults, of the radiation-induction of some types of cancer, children actually have a decreased risk or no difference in risk for other types. There are similar examples with regard to non-cancer (deterministic) effects.

II. SCOPE AND METHODOLOGY

4. This annex includes information on adverse effects following radiation exposure of children. Although the medical benefits of using radiation for diagnosis and therapy of illnesses such as cancer are well recognized, the assessment of the beneficial effects is not included within the scope of this report. The annex aims to present a detailed review of the current scientific literature that will highlight the differences in radiation effects and associated risks between children and adults. The objective is to include information on the magnitude of the doses from various radiation sources to which children are exposed, the relevant aspects in the development of the anatomy and physiology of children, dosimetry and the health effects of radiation exposures (including cancer, benign tumours, tissue reactions and heritable effects). It will answer the following questions:

- What are the most important sources of ionizing radiation exposure of children and the levels of exposure, both now and potentially in the future?
- What are the dosimetric differences between children and adults?
- How does ionizing radiation affect children differently from adults?
- How sensitive are children to radiation exposure in comparison with adults?
- What are the factors that make children more sensitive to radiation exposure?
- Are children more sensitive to all radiation sources and effects or just to some?
- What gaps exist in our knowledge on radiation effects following childhood exposure that may guide future research?

5. This annex is intended to provide a reference for specialists in radiation protection, radiation biology, epidemiology and other health sciences, and regulatory authorities. It provides a review of the health effects in children arising from exposure to sources of ionizing radiation.

6. The definitions of "child" and its derivative "childhood" are not consistent in scientific and legal literature. The most common understanding is that childhood ceases with the completion of development, usually between the age of 18 and 19, even though neurocognitive development continues through the twenties. However, some of the epidemiological literature considered in this report includes groups of up to only age 16; other papers have involved studies of different age groups. In this report, the term "child" is used in contrast with that for "adult". Therefore, the scientific literature the Committee reviewed is for those <20 years of age and includes infants, children and adolescents.

7. Data on the risks of radiation exposure in childhood and possible differences with those in adulthood come from studies of exposure to radiation due to accidents, medical diagnostic radiology, radiotherapy, the atomic bombings in Japan, fallout from nuclear weapon testing, and potential radioactive discharges from nuclear installations. All the various studies have some limitations. One of the major difficulties in the assessment of the effects of exposure in childhood is that it takes many decades to be sure that all the effects have become manifest. Almost all the epidemiological studies remain incomplete in terms of lifetime follow-up. Thus, for risk assessment, there is a need for lifetime projection models.

8. Accidental exposures involving high doses to children are quite rare but when they do occur, the subjects often have early and late severe injuries. Medical diagnostic exposure typically involves low doses (<100 mSv) and a very large population would be required in order to be able to observe a statistically significant number of effects. Studies have now begun to assess possible neoplastic effects in children who have had CT scans. Studies of survivors of childhood cancer who have had radiotherapy are useful in that they involve high doses and follow-up has been carried out for a few decades. These studies are complicated by the disease process and the administration of other types of therapy (e.g. chemotherapy). The survivors of the atomic bombings received relatively low doses and follow-up has been carried out for over 60 years. Even with this long follow-up, there are many still alive who were exposed as children. Studies of those exposed to fallout from nuclear weapon testing and of those living near nuclear installations have usually involved even lower doses and are thus subject to great statistical uncertainty and more potential bias. Useful information on thyroid cancer has been gained from the studies of children exposed as a consequence of the Chernobyl accident, but even with 25 years of follow-up, the long-term nature of the risk of thyroid cancer as a result of the

Chernobyl accident is not known. Juvenile animals and in utero exposure of the embryo and foetus are not part of this review. These are covered, respectively, in relatively comprehensive reports by the Committee in its UNSCEAR 2008 Report [U14], by the International Commission on Radiological Protection (ICRP) [I23] and recently by the National Council on Radiation Protection (NCRP) [N20].

9. This annex and accompanying appendices examine the potential differences in sources of exposure and differences in developmental anatomy and physiology that affect the doses received by various organs in children compared to adults. The review of the scientific literature elucidates differences by age at exposure for stochastic and deterministic responses in various organs and tissues.

10. The subject of this annex potentially affects a number of the Committee's activities. For example, it will:

- Provide a basis for the evaluation of the potential effects of the marked increase in medical radiation exposure of the largest vulnerable population as outlined in the UNSCEAR 2008 Report;
- Provide information for the possible update of age-group classification—e.g. on infants, children and young adults—to be used in future surveys of the Committee;
- Provide a basis for the follow-up of children and adolescents exposed as a result of the Fukushima Daiichi nuclear power plant accident;
- Enhance development of a knowledge base on the levels of radiation exposure and effects specific to children;
- Imply that future reports will need to highlight those sources that are important for this large vulnerable population.

III. SOURCES OF EXPOSURE

11. Ionizing radiation exposure of children comes from a wide variety of sources. Some sources are widespread while others are local. Some sources expose children and adults almost equally while others expose children to a greater or lesser extent than adults. Worldwide, children typically receive less exposure than adults since they are not occupationally exposed and undergo fewer medical procedures. Annex B of the UNSCEAR 2008 Report [U14] has detailed information on exposure of the public from various sources of radiation.

12. Sources of childhood exposure that are of concern include radiation accidents, regions of high natural background radiation and also diagnostic and therapeutic procedures. The data is derived from a wide range of doses, variable dose rates, whole and partial body exposure and children of different ages. The effects described in this annex are sometimes specific to a given exposure scenario.

A. Background radiation

13. Natural background is the largest worldwide source of ionizing radiation exposure of children. There is significant geographical variation in the doses received. Doses from cosmic radiation increase with altitude and geomagnetic latitude, but there is little or no difference between the doses received by children and adults who are in the same location. Terrestrial radiation exposure varies as a result of a number of factors, including the concentration of radionuclides in soil and diet. Radon is the largest contributor to natural background radiation exposure, but there is little variation in dose with age. The average annual effective dose to an individual resulting from natural background radiation is approximately 2.4 mSv [U2, U14]. There are rare circumstances in which adolescents have been exposed to elevated levels of radon as a result of occupational exposure in tin mines [L34, X1].

B. Medical radiation uses

14. Medical exposure represents the second largest source of ionizing radiation exposure of the world population, and was recently summarized in the UNSCEAR 2008 Report (annex A) [U14]. Limited data on the frequency of medical diagnostic radiation procedures on children are available. Those data are shown in table 1. While there is some variation among countries, approximately 3–10% of all such procedures are performed on children. There is a higher percentage of some particular examinations performed on children (e.g. X-rays of the head, abdomen and extremities). Fluoroscopically-guided interventional procedures can deliver high doses to various organs of children (particularly to the brain, lens of the eye and the heart) [T16].

15. Additional data from some European countries on the age and sex distributions of various radiographic examinations are presented in table 2.

16. Very few data are available on the number of children exposed as patients during nuclear medicine procedures. Nevertheless, there is little doubt that the percentage of various types of examination for children differs widely from those for adults. Most nuclear medicine procedures in adults are related to cardiac problems or cancer (both of which are rare in children). Renal examinations constitute the majority of nuclear medicine procedures performed on children in some countries. Typically, in clinical practice, children receive lower administered activities of radiopharmaceuticals compared to adults [J7].

17. Children can also be exposed as a consequence of mothers having had nuclear medicine examinations if the radiopharmaceutical is excreted in the breast milk and breast feeding continues. Children can also be exposed if they are in the vicinity of a patient treated with radioiodine.

18. Data on the number of children receiving radiotherapy are also very sparse. The percentages are low since childhood cancer is rare. In the United States of America, 1 in 600 children develop a malignancy and this represents only 1% of patients with cancer. It is estimated that the number of children treated with radiotherapy in the United States is about 2,500 annually out of a total of about 870,000 radiotherapy patients. For most medical procedures, the situation regarding children is likely to be very different from country to country owing to differences in resources and in the health-care delivery system.

Table 1. Percentage of various types of medical examination performed on infants and children (0-15 years old) in well-developed countries

Adapted from UNSCEAR 2008 Report (annex A, table B47) [U14]

Examination	*Percentage performed on children (%)*	*Examination*	*Percentage performed on children (%)*
RADIOGRAPHY		CT SCANNING	
Chest (posterior-anterior)	9	CT head	8
Chest (lateral)	10	CT abdomen	4
Limbs and joints	15	CT thorax	5
Lumbar spine (anterior–posterior)	7	CT spine	3
Thoracic spine (anterior–posterior)	12	ANGIOGRAPHY	
Cervical spine (anterior–posterior)	9	Non-cardiac angiography	2
Head	19	Cardiac angiography	4
Abdomen	13	Cerebral angiography	2
Upper gastrointestinal	3		
Lower gastrointestinal	3	NUCLEAR MEDICINE	Not available
Cholecystography	2		
Pelvis/hip	9	RADIOTHERAPY	Not available
Urography	7		

Table 2. Percentage distributions of averaged European age and sex for some radiographic and CT examinations

Adapted from EC Radiation Protection N° 154 (table A3.1) [E5]

Distribution (%)										
Age	*Males*	*Females*	*Males*	*Females*	*Males*	*Females*	*Males*	*Females*	*Males*	*Females*
RADIOGRAPHIC EXAMINATIONS										
	Chest		Lumbar spine		Abdomen		Pelvis and hips		IVU[a]	
0–4	2.30	1.82	0.23	0.21	2.82	2.27	1.39	2.10	0.53	0.35
5–9	0.55	0.44	0.32	0.38	1.18	1.02	1.11	0.68	0.38	0.31
10–14	0.42	0.37	0.92	1.25	0.97	0.97	1.07	0.78	0.38	0.26
15–19	0.78	0.62	1.74	1.81	0.94	1.46	1.10	0.96	0.67	1.13
20–24	1.05	0.87	2.03	1.80	1.27	2.01	1.12	0.79	1.44	2.05
25–29	1.38	1.15	2.58	2.47	1.85	2.21	1.23	1.17	2.34	2.44
30–34	1.80	1.55	3.57	3.29	2.49	2.68	1.50	1.45	3.38	3.47
35–39	2.14	1.79	4.03	3.94	2.81	2.76	1.81	1.72	4.00	3.86
40–44	2.47	2.19	3.83	4.21	2.95	2.84	1.89	2.08	4.51	3.69
45–49	3.05	2.64	3.65	4.67	3.15	2.92	2.11	2.67	4.79	3.92

Distribution (%)										
Age	*Males*	*Females*	*Males*	*Females*	*Males*	*Females*	*Males*	*Females*	*Males*	*Females*
RADIOGRAPHIC EXAMINATIONS										
	Chest		Lumbar spine		Abdomen		Pelvis and hips		IVU[a]	
50–54	3.85	3.26	3.97	5.02	3.72	3.22	2.83	3.53	5.76	3.81
55–59	4.67	3.57	3.42	4.75	3.67	3.11	3.14	4.07	5.64	3.66
60–64	5.25	3.91	2.85	4.21	3.92	3.17	3.35	4.59	5.47	3.55
65–69	5.81	4.42	2.48	4.36	4.25	3.45	3.41	5.71	5.50	2.99
70–74	6.25	5.15	2.41	4.74	4.40	3.99	3.67	6.87	5.50	2.93
75–79	5.39	5.23	2.04	4.50	3.91	4.10	3.16	7.43	4.00	2.17
80–84	3.24	4.25	1.26	3.36	2.66	3.99	2.34	6.77	2.05	1.44
85–89	1.65	2.66	0.59	2.06	1.54	3.00	1.37	5.01	0.75	0.54
>90	0.60	1.43	0.22	0.81	0.70	1.62	0.76	3.25	0.17	0.15
Total	52.65	47.32	42.14	57.84	49.20	50.79	38.36	61.63	57.26	42.72
COMPUTED TOMOGRAPHY EXAMINATIONS										
	CT head		CT neck		CT chest		CT spine		CT abdomen	
0–4	0.75	0.53	0.25	0.29	0.32	0.16	0.10	0.06	0.09	0.07
5–9	0.76	0.46	0.49	0.20	0.28	0.21	0.22	0.16	0.12	0.08
10–14	0.84	0.70	0.34	0.26	0.22	0.21	0.30	0.30	0.21	0.18
15–19	1.29	1.24	1.08	0.71	0.75	0.47	1.15	0.90	0.63	0.50
20–24	1.62	1.55	1.43	1.09	1.13	0.75	1.76	1.49	0.82	0.83
25–29	1.75	1.94	2.04	1.34	1.45	0.91	2.57	2.10	1.48	1.24
30–34	2.48	2.61	2.68	2.50	2.09	1.31	4.12	2.90	1.94	1.61
35–39	3.01	2.77	4.06	3.41	2.44	1.99	5.26	4.36	2.37	2.06
40–44	2.84	3.08	3.89	4.09	2.84	2.11	5.55	5.13	2.84	2.56
45–49	3.06	3.25	4.64	4.50	3.45	3.07	5.25	5.48	3.27	3.29
50–54	3.79	3.68	6.08	4.70	5.07	3.97	5.43	5.17	4.45	4.32
55–59	4.15	3.45	6.17	4.67	6.02	4.73	4.74	4.59	5.65	4.76
60–64	4.08	3.64	5.77	3.77	7.25	4.88	3.65	3.96	6.03	4.87
65–69	4.27	3.99	4.66	3.38	7.53	4.78	3.08	3.93	7.20	5.07
70–74	4.80	4.53	4.10	3.29	7.42	5.25	2.72	3.72	6.95	5.55
75–79	4.45	4.96	3.03	2.85	5.52	4.01	2.02	3.27	5.49	4.57
80–84	2.99	4.41	1.99	2.54	2.47	2.32	1.10	1.91	2.47	3.16
85–89	1.62	3.02	1.10	1.63	0.95	1.08	0.45	0.80	0.97	1.42
>90	0.56	1.07	0.31	0.67	0.28	0.31	0.06	0.21	0.26	0.61
Total	49.11	50.88	54.11	45.89	57.48	42.52	49.53	50.44	53.24	46.75

[a] *Intravenous urogram.*

C. Nuclear weapons

19. The largest database concerning age-at-exposure effects is on the survivors of the atomic bombings in Japan. The Life Span Study (LSS) includes 86,611 persons. Of these, 17,833 were 0–9 years old at exposure and 17,563 were 10–19 years old at exposure [O25]. The radiation dose was predominantly from external acute penetrating radiation. In addition, populations that include children have been exposed to fallout from the testing of nuclear weapons. Prior to 1958, 66 nuclear tests were carried out in the Marshall Islands. The Bravo test contaminated the inhabited Rongelap, Alinginae and Utirik atolls. There were 239 inhabitants—of whom 93 (39%) were children under 10 years of age—who received severe exposure from the fallout [C43]. Although the number of children exposed locally as a result of fallout from the testing of nuclear weapons has not been quantified at several sites, a cohort of about 4,500 under age 20 downwind of the Semipalatinsk nuclear testing has been followed up [B7], and a leukaemia case-control study of Utah children and adults downwind of the Nevada atomic bomb testing has been conducted [S114]. With regard to the accident at the Mayak nuclear complex, there is a Russian "Children's Registry", covering the period 1934–2008, which includes more than 90,000 people who were either born in Ozyorsk (the city nearest the Mayak site) or moved there before their 15th birthday.

D. Accidents and incidents

1. Radiotherapeutic and radiographic sources

20. There have been a number of tragic incidents involving exposure of children to industrial radiography sources [I1, I3, M33]. Due to the limited populations exposed, the details of these accidents are not very helpful in ascertaining differences in radiosensitivity between children and adults. Similarly, therapeutic misadministration is rare and thus the resulting information is largely anecdotal.

2. Nuclear power

21. The 1986 Chernobyl accident has been extensively reviewed in the UNSCEAR 2008 Report (annex D) [U15]. The total population of the three most affected countries (the Russian Federation, Ukraine and Belarus) was, at the time, 97.9 million of whom 10.1 million (10.3%) were pre-school children, 11.0 million (11.2%) were school children and 5.2 million (5.3%) were defined as adolescents. Of the 114,511 people who were evacuated in 1986, children and adolescents were in similar proportion—11,931 (10.4%) were aged 0–6 years, 13,120 (11.5%) were aged 7–14 years and 5,815 (5.1%) were aged 15–17 years. More than six million residents of the contaminated areas (defined as areas with an activity concentration of ^{137}Cs >37 kBq/m^2) in the Russian Federation, Ukraine and Belarus were not evacuated. The number of children in this group is not known.

22. The number of children exposed as a result of the Fukushima Daiichi nuclear power plant accident is not well defined at the moment. Recent census data from Japan indicate that about 13% of the population is 0–14 years of age.

IV. ANATOMICAL DEVELOPMENT AND PHYSIOLOGY

23. The purpose of this section is to clearly describe the main human anatomical and physiological age-related changes that are relevant for radiation risks from exposure during childhood. General issues are considered first, followed by detailed information on tissue and organ systems.

24. Several factors that vary with age, but predominantly with weight and size, are critical in the assessment of doses and effects. The attenuation of both internal and external radiation by tissue will increase with weight. In particular, the absorbed dose from a given amount of intake of a radionuclide will be greater in a small individual with smaller organ masses than in a large individual.

25. Determining radiation exposure and resulting risks is more complicated for children than for adults owing to the development and associated physiological changes in children. The age-related (and dynamic) factors that contribute to these differences include:

- Size, shape and mass of the individual and organs;
- Growth patterns (developmental dynamics) of the individual including organs and tissues;
- Intake and absorption of material;
- Metabolic requirements;
- Hormonal and endocrine changes and development;
- Dietary intake;
- Physical activity.

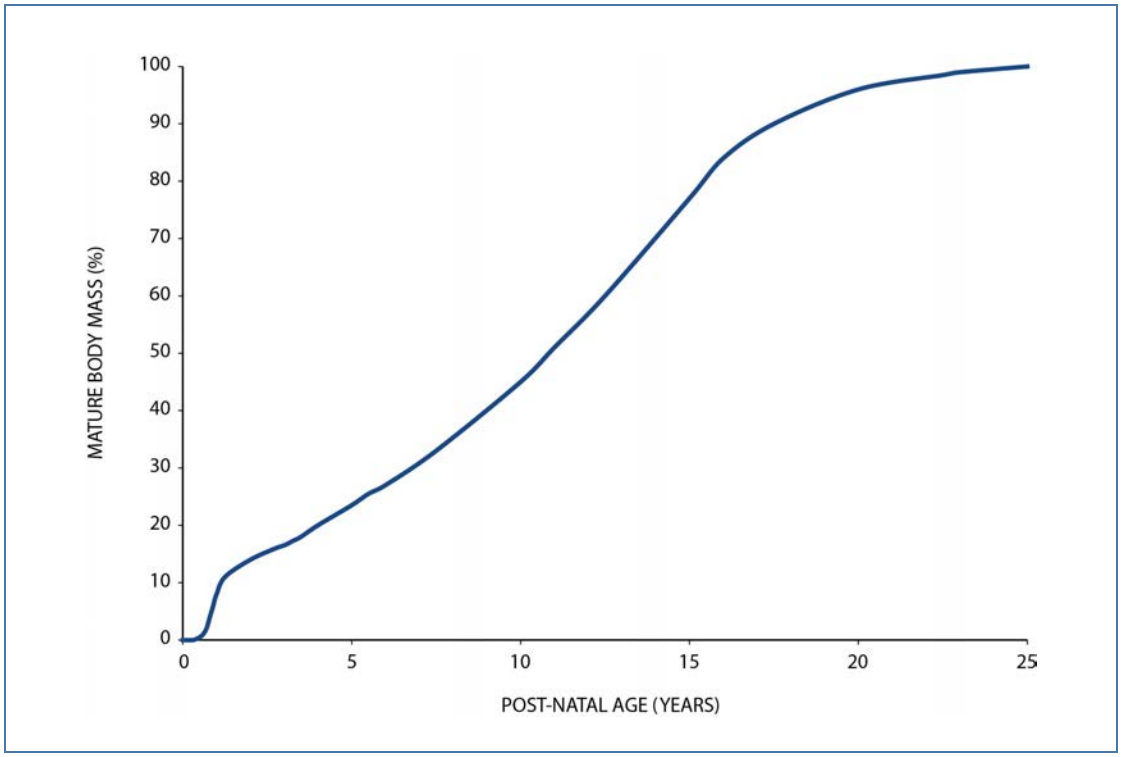
26. The ICRP has considered many of these age-related factors in developing models for dosimetry purposes. The reference data are contained in ICRP Publication 89 [I22]. Specific ICRP models have been developed for the skeleton [I15], the alimentary tract [I24] and the respiratory tract [I14]. The ICRP has derived age-dependent dose coefficients based upon these models for various radionuclides [I16, I17].

27. Reflecting the available data, most of the ICRP models are relevant to a European Caucasian population. However, the parameters involved in particular situations may differ from those assumed in the models. These differences may be on an individual basis (e.g. the size of the child may differ from the average). There may also be significant regional variations (e.g. diet may vary greatly from coastal to rural inland areas of a country). There may also be global variations (e.g. size, customs, habits and diet are often significantly different depending on ethnicity).

28. The growth period of the human body is unusually long among mammalian species, extending for more than a quarter of the normal lifespan. The human growth curve shown in figure I has a distinctive shape that reflects changes in the post-natal growth velocity that are not found in other mammalian species. This long growth period is associated with a delay in most aspects of bodily development, especially skeletal and endocrine maturation. Total body mass continues to increase after maturity, but the rate of increase slows considerably after about age 18 years in males and about age 16 years in females.

Figure I. Increase in body mass during growth as a percentage of mass at age 25 years

Adapted from ICRP Publication 89 [I22] and based on central estimates for Western males



29. There are differences in the growth rate of different parts of the body (see table 3). Studies of the upper and lower limbs indicate that development occurs most rapidly in the distal parts of both regions, and that girls are ahead of boys even in early childhood. In general, growth and development tend to occur faster in the upper part of the body than in the lower part. The trunk represents about one third of the length and nearly half of the volume of the entire body at all stages of development, but the thoracic portion of the trunk develops more rapidly than the pelvic region. Due to this slower development of the pelvic region, the urinary bladder is an abdominal organ in infancy and does not attain its adult position and shape until the age of about six.

Table 3. Subdivision of total surface area of body

Adapted from ICRP Publication 89 [I22]

Age	*Total surface area of body (%)*			
	Head	*Trunk*	*Upper extremities*	*Lower extremities*
Newborn	20.8	31.9	16.8	30.5
1 year	17.2	34.4	17.8	30.6
5 years	13.1	33.0	19.6	34.3
10 years	10.9	33.6	19.4	36.2
15 years	8.8	31.9	21.4	37.9
Adult	7.5	34.6	19.4	38.5

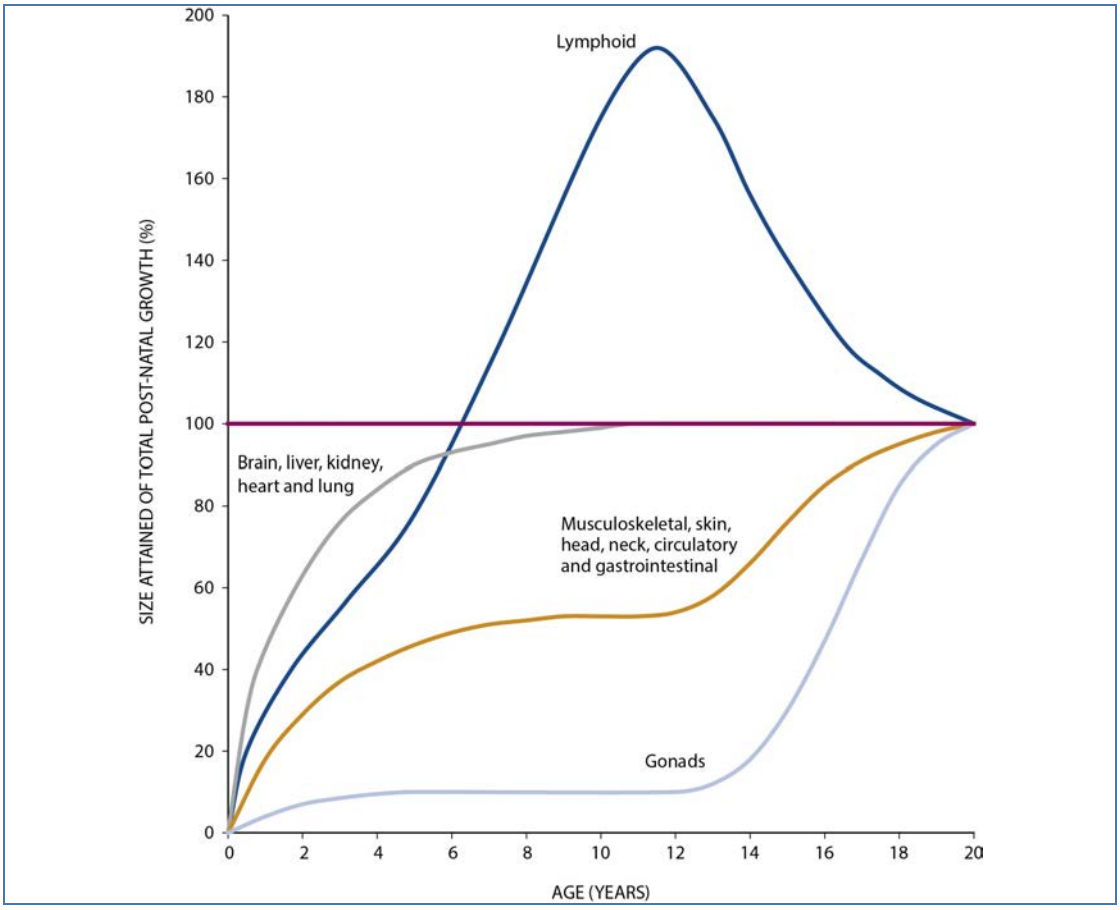
30. There is a marked difference in the growth of the various organ systems from birth to maturity. At birth, the skeleton represents approximately 11% of the body mass. Its post-natal growth parallels that of

the body as a whole, both of which increase in mass by about 20-fold by maturity. The skeletal muscle system forms about 25% of the body at birth and about 40% in the adult male. The central nervous system (CNS) forms about 15% of body mass at birth and 2–2.5% in the adult male. The brain is the largest contributor to the mass of the CNS. The visceral group as a whole forms about 9% of the body mass in the newborn and about 5–7% in the adult male.

31. Organ size and growth vary significantly across tissue types and with age. The percentage of size attained of total post-natal growth for lymphoid tissue, for example, is greatest in late childhood, even greater than in adulthood (figure II). Musculoskeletal tissues grow primarily during childhood and early adolescence, and gonads do not mature until late adolescence. Organs may be divided into four main patterns of post-natal growth: general (most tissues), neural, lymphoid, and reproductive. Some tissues change markedly in their distribution within the body as a person ages, e.g. changes in bone marrow distribution within the bone.

Figure II. Growth curves of different parts and tissues of the body, showing four main patterns of growth

Adapted from ICRP Publications 23 and 89 [I22, I6]



32. Body size and proportion do not grow in a linear or consistent manner. The head and brain are proportionally much larger in younger children. These changes mean that absorbed dose in specific organs from either external or internal irradiation is quite different at different ages and developmental stages. The variation in mass of organs and tissues with age is shown in table 4.

Table 4. Reference values for masses (g) of organs and tissues as function of age

Adapted from ICRP Publication 89 [I22]

Organ/tissue	*Age*							
	Newborn	*1 year*	*5 years*	*10 years*	*15 years*		*Adult*	
					Males	*Females*	*Males*	*Females*
Salivary glands	6	24	34	44	68	65	85	70
Oesophagus (wall)	2	5	10	18	30	30	40	35
Stomach (wall)	7	20	50	85	120	120	150	140
Small intestine (wall)	30	85	220	370	520	520	650	600
Large intestine								
Right colon (wall)	7	20	49	85	122	122	150	145
Left colon (wall)	7	20	49	85	122	122	150	145
Rectosigmoid (wall)	3	10	22	40	56	56	70	70
Liver	130	330	570	830	1 300	1 300	1 800	1 400
Gallbladder (wall)	0.5	1.4	2.6	4.4	7.7	7.3	10	8
Pancreas	6	20	35	60	110	100	140	120
Brain	380	950	1 310 (1180)[a]	1 400 (1220)[a]	1 420	1 300	1 450	1 300
Breasts					15	250	25	500
Circulatory system								
Heart – with blood	46	98	220	370	660	540	840	620
Heart – tissue only	20	50	85	140	230	220	330	250
Blood	290	530	1 500	2 500	4 800	3 500	5 600	4 100
Eyes (2)	6	7	11	12	13	13	15	15
Skin	175	350	570	820	2 000	1 700	3 300	2 300
Muscle, skeletal	800	1 900	5 600	11 000	24 000	17 000	29 000	17 500
Lung – with blood	60	150	300	500	900	750	1 200	950
Lung – tissue only	30	80	125	210	330	290	500	420
Total skeleton	370	1 170	2 430	4 500	7 950	7 180	10 500	7 800
Bone, cortical	135	470	1 010	1 840	3 240	2 960	4 400	3 200
Bone, trabecular	35	120	250	460	810	740	1 100	800
Bone, total	170	590	1 260	2 300	4 050	3 700	5 500	4 000
Marrow, active	50	150	340	630	1 080	1 000	1 170	900
Marrow, inactive	0	20	160	630	1 480	1 380	2 480	1 800
Cartilage	130	360	600	820	1 140	920	1 100	900
Spleen	9.5	29	50	80	130	130	150	130
Thymus	13	30	30	40 (35)[a]	35	30	25	20

Organ/tissue	*Age*							
	Newborn	*1 year*	*5 years*	*10 years*	*15 years*		*Adult*	
					Males	*Females*	*Males*	*Females*
Thyroid	1.3	1.8	3.4	7.9	12	12	20	17
Kidneys (2)	25	70	110	180	250	240	310	275
Urethras (2)	0.77	2.2	4.2	7.0	12	12	16	15
Urinary bladder	4	9	16	25	40	35	50	40
Testes (2)	0.85	1.5	1.7	2	16		35	
Prostate	0.8	1.0	1.2	1.6	4.3		17	
Ovaries (2)	0.3	0.8	2.0	3.5		6		11
Uterus	0.4	1.5	3	4		30		80
Total body (kg)	3.5	10	19	32	56	53	73	60

[a] *Values in brackets are for females.*

33. Variation in height, mass and surface area at various ages is shown in table 5. As mentioned earlier, most reference values refer to Caucasian populations.

Table 5. Reference values for height, mass, and surface area of total body

Adapted from ICRP Publication 89 [I22]

Age	*Height (cm)*		*Mass (kg)*		*Surface area (m^2)*	
	Males	*Females*	*Males*	*Females*	*Males*	*Females*
Newborn	51	51	3.5	3.5	0.24	0.24
1 year	76	76	10	10	0.48	0.48
5 years	109	109	19	19	0.78	0.78
10 years	138	138	32	32	1.12	1.12
15 years	167	161	56	53	1.62	1.55
Adult	176	163	73	60	1.90	1.66

34. The age-related factors that contribute to differences in radiation effects and risks from childhood exposure include size of the individual and organs, growth patterns (rate of development at different ages) of the individual and tissues, intake and absorption of material, metabolic requirements, hormonal and endocrine changes and development, diet and physical activity. Examples of some important differences are presented in table 6.

Table 6. Major anatomical and physiological differences between children and adults

Tissue or factor	*Comments*
Body size	Growth period is unusually long compared to other mammals and occurs for about 25% of lifespan. Rapid growth (about 20-fold) over first 16–18 years; then slows but mass increases
Body proportion	The head and brain are disproportionately large at birth. The trunk represents about one third of the body volume at all stages
Alimentary tract	Transition from liquid to textured diet at age 6 months. Milk is an important component of diet. Increase in transit time of material in the colon with increasing age. Absorption of some radionuclides is greater in infants than in children and adults. Children can ingest variable amounts of dirt
Respiratory system	Significant increase in the number of alveoli up to 2 years of age. After this, there is an increase in alveolar size. 20-fold increase in air-tissue interface between birth and adulthood. Young children are mostly nose breathers. Deposition may be higher in children but volume of inspired air is smaller
Brain	Comprises 10% of infant weight and 2% in an adult. Axon diameter and myelin grow significantly during first 2 years but their growth is not complete until adulthood. Pruning of synapses occurs during childhood. Grey matter peaks at 1 year of age and remains high until 7 and then declines 40% by age 16
Skeletal and cartilage	Bone growth occurs most at the ephipyses at the ends of long bones. The epiphyses fuse during puberty. There is more vascularity and remodelling of bone in infancy and childhood. A much greater percentage of the skeleton is cartilage rather than bone at young age
Bone marrow	With increasing age there is a significant regression of red bone marrow from the peripheral skeleton to the more central portions
Kidneys and bladder	Maximum number of glomeruli are present at birth. Hypertrophy can occur as a result of growth of renal tubules. Bladder moves from abdominal position to the pelvis during childhood. Children void every 2–3 hours and before bladder capacity is reached
Testes	Prior to age 12, the testis is small, increasing in volume by over fivefold during puberty
Ovaries and uterus	Number of primordial follicles peaks shortly after birth. Rate of recruitment to mature follicles increases from birth to age 14 and then declines with age. Rapid growth in size of ovaries with puberty. Uterine volume is <3 ml before age 8 and increases to 15–20 ml by age 13
Thyroid	Rapid rise in thyroid stimulating hormone after birth, declining to normal levels in about 5 days. Uptake of iodine is broadly similar to that of an adult. TSH, triiodothyronine and thyroxine serum values are highest in first year of life and decrease slowly by about 20–40% by late adolescence
Growth hormones	GH level rises throughout puberty, increasing body height
Reproductive hormones	Puberty initiated by the hypothalamus of the brain releasing gonadotropin releasing hormone, luteinizing hormone and follicle stimulating hormone

A. Alimentary tract

35. The alimentary (gastrointestinal or digestive) tract comprises the oral cavity, mouth, pharynx, oesophagus, stomach, small intestine, colon, rectum and anus. Associated organs and tissues are the liver, pancreas and salivary glands. Some parts of the alimentary tract are relatively susceptible to

radiation-induced carcinogenesis (e.g. stomach and colon) while other parts are relatively resistant (e.g. rectum and pancreas). In addition, some parts (e.g. the small intestine) are quite vulnerable to cell killing at doses of the order of a few grays (Gy), owing to the rapid turnover of cells in these parts. As shown in table 4, the masses of the different parts of the alimentary tract increase with age.

36. Starting at age of about six months, infants transition from a liquid diet to increasingly textured foods. Dietary composition varies significantly around the world. Even so, infants and children generally have a higher proportion of milk in their diets than adults. Ingestion of milk is a common route of exposure to the radioisotopes of iodine and strontium. Diet is affected by a variety of factors but metabolic rate and energy expenditure are both important and increase markedly with age. Intake of water, which also increases with age, is a universal requirement [I22].

37. Ingestion of soil by children is a common concern. Soil ingestion can be inadvertent (from hand to mouth transfer) although a few children intentionally ingest soil (pica behaviour). There are only a few studies of the amount of soil eaten by children. Those studies typically use faecal analysis of naturally occurring stable or radioactive isotopes of elements. The estimates of ingestion of soil vary significantly from child to child and average 20–30 mg/day for most children and 80–100 mg/day for children 0.5–4 years of age [U1]. There is also a significant daily variation in intake (up to 20-fold) for any particular child [B4]. In the case of actinide contaminated lands, the critical group is likely to be children because of potentially higher ingestion rates and higher dose coefficients [S80].

38. Transit times of material in the oesophagus, stomach and small intestine do not vary much with age. Transit time for liquids in the oesophagus is relatively fast (seconds) while in the stomach, it is about 30–60 minutes for liquids and 75–100 minutes for solids and is affected by non-age-related factors. Transit time in the small intestine is about 3–4 hours, increasing in the colon with age—about 8–11 hours in a child and 12–16 hours in an adult.

39. Absorption of most radionuclides occurs in the small intestine with the extent of the process depending upon the element and chemical form. Tritiated water has essentially free passage from the alimentary tract to the blood. Caesium ions are absorbed rapidly. Small particles may enter epithelial cells by pinocytosis (engulfment). In adults, this is not an important pathway; however it is important in neonates. There are other routes of absorption in the mouth, stomach and colon. Iodine, for example, can be absorbed both in the mouth and in the stomach.

40. Absorption of many elements (e.g. calcium, radium, lead, cobalt, iron, plutonium, americium) is substantially greater in infants than in adults. In general, absorption values of radionuclides after one year of life are broadly similar to those of adults. Age-related retention of radionuclides in the small intestine has been shown to be important for neonates owing to pinocytosis. Increased levels in the wall of the small intestine have been shown in animal studies for plutonium, thorium, uranium, americium and other elements [F18, F19].

41. A number of elements are secreted into the alimentary tract after having been absorbed. Important examples include iodine secreted by the salivary glands and caesium secreted by the liver into the bile. Age does not appear to play a significant role in these secretory processes [I24].

B. Respiratory system

42. The respiratory system includes the nose, mouth, pharynx, larynx, the airways of the trachea, bronchi and bronchioles, and the alveoli (air sacs). By the age of two, the structure of the lungs is

completely developed. The main changes that occur during childhood are in mass and size of most pulmonary structures, which are closely related to stature. There is a significant increase in the number of alveoli in the first two years of life. The number of alveoli at birth is estimated to be about 20 million and a rapid multiplication of alveolated airways increases the number of alveoli to about 400 million by the age of two. This is followed by an increase in size of the alveoli. These processes allow for a 20-fold increase in the air–tissue interface between birth and adulthood [T25].

43. The variation in mass of the respiratory system with age is shown in table 4. The limited data available indicate that the inner diameter of bronchi is considered to be about 1.0 mm at one year of age, about 1.5–2.0 mm from 2 to 5 years of age, and about 4.0 mm in adults. There is little change in either the cilia length or the epithelial height with age. Before the age of five, there is a disproportion in the peripheral airways (i.e. small children have proportionally more of them than adults do) where the diameters are narrower than those of the central airways, causing increased airway resistance compared to that of adults. There is also a difference between children and adults relative to the larynx. Up to the age of two, the larynx is situated high in the neck to allow for simultaneous breathing and swallowing. As a result, young children are almost entirely nose breathers. Values for the volume of air ventilated daily (m^3) increase dramatically with age as shown in table 7.

Table 7. Daily ventilation volume by age

Adapted from ICRP Publication 71 [I16]

	Daily ventilation							
	3 months	*1 year*	*5 years*	*10 years*	*15 years*		*Adult*	
					Males	*Females*	*Males*	*Females*
Volume (m^3)	2.8	5.1	8.8	15.2	20.1	15.8	22.2	18.2

44. Deposition of material in the respiratory tract is a function of many factors including particle size, shape and density, method of breathing (nose versus mouth), breathing rate, and structure of the airways. Most of the models of deposition of particles in the respiratory tract of children have been derived from the limited empirical data available. Even so, it is known that the deposition rates in children are somewhat higher than those of adults. For example, the fractional deposition of 1 µm particle varies from about 0.39 in a sleeping adult to 0.54 in a sleeping infant. In addition, deposition increases with breathing rate. For example, the fractional deposition of a 1 µm particle increases to 0.53 in an adult at light exercise. Clearance of particles from the respiratory tract is related to mucociliary transport and absorption. The limited data suggest that there is not a major difference in mucociliary transport velocities or clearance rates between children and adults [I14].

45. For purposes of radiation dosimetry, the ICRP divides the respiratory tract into four parts [I14]. This is discussed in detail in appendix A (Dosimetry).

C. Neurological system

46. The mass of the brain at various ages is shown in table 4. The brain is quite large at birth relative to other organs. It is about 10% of the body weight compared to about 2% during adulthood. More than a decade is needed after birth for its development to be completed. Maturation includes development of supporting cells (glia), junctions between nerve cells (synapses), structural properties of the fibres (axons), and the insulation (myelin) around these fibres. Both the brain and spinal cord consist of grey

cell bodies, dendrites and synapses and white matter, which includes bundles of axons coated with a sheath of myelin. Axon diameters and myelin grow significantly in the first two years of life—when synaptic density increases, especially in areas of the brain devoted to vision and hearing—but are not fully mature until adulthood.

47. Many more synapses are produced than are ever needed and a process known as "pruning" refines these connections on the basis of experience. Generally, grey matter of the cortex reaches a peak at about one year of age and remains high until about seven, and then declines by about 40% until about 16 years of age, when the adult level is attained. Some areas (such as the frontal cortex) have peak grey matter at about 12 years of age [G18].

48. Myelin sheaths are extensions of oligodendral cells which are wrapped in a spiral fashion around a portion of an axon. The myelin speeds transmission of signals along the axon. Ionizing radiation can interfere with the formation and renewal of myelin and can also damage myelin [J6]. Repair of myelin can take weeks to months.

D. Skeletal system

49. The skeletal system consists of bone, bone marrow, periosteum, cartilage and blood vessels in those tissues. Bones are rigid organs that support the body, provide protection, produce red and white blood cells and store minerals. The hard outer layer of bones is made of compact (cortical or dense bone) while the interior is an open porous network of trabecular (spongy or cancellous) bone. Compact bone makes up about 80% of total bone mass in an adult while trabecular bone is about 20% of the mass but has ten times the surface area. The relative weights of the various bones differ with age. The skull is 32% of skeletal weight in newborns but only 12% in adults. The proportion of cartilaginous tissue in the skeleton decreases with age. The ICRP reference values for the increases in total bone mass and total skeletal calcium and cartilage with age are shown in table 8 [I15]. Cartilage is of lesser importance as it does not concentrate long-lived radionuclides, nor does it appear to be significantly involved in risk of radiation-induced cancer. It is also quite resistant to high doses of radiation.

Table 8. Reference values for increases in total bone mass and total skeletal calcium and cartilage at different ages

Adapted from ICRP Publication 70 [I15]

Age	*Bone mass (g)*	*Calcium (g)*	*Cartilage (g)*
Newborn	370	28	130
1 year	1 170	100	360
5 years	2 430	240	600
10 years	4 500	460	820
15 years (males)	7 950	830	1 140
15 years (females)	7 180	760	920

50. Ossification of cartilage begins before birth in a primary ossification centre in the central part of each developing bone. By the time of birth, most of the bones have developed their primary and some secondary ossification centres. Tubular bones grow in girth by peripheral migration of osteons forming dense bone and owing to vigorous resorption by osteoclasts to enlarge the marrow cavity and fill it with

trabecular bone. Secondary ossification centres (epiphyses) often appear at the ends of long bones after birth and grow towards the bone finally fusing during puberty. Longitudinal growth proceeds through adolescence ceasing at approximately 18 years of age for females and 20 for males.

51. Bone consists of a cellularly-organized organic matrix with inorganic salts. The osteoid matrix contains proteins (mostly collagen), carbohydrates and lipids. The inorganic material is primarily calcium phosphate and is embedded in not only the osteoid matrix but in the collagen as well. Collagen fibres form 90–95% of the bone matrix and are aligned along lines of stress to provide support. The mineral phase of bone provides a storage function and is composed of mostly calcium and phosphate in the form of salts (hydroxyapatites).

52. The hydroxyapatite crystals have the ability to conjugate with different ions such as lead, sodium, fluoride, potassium, carbon and magnesium. This makes the performance of bone scans in diagnostic nuclear medicine possible but is also the reason for the uptake into bone of long-lived radionuclides including barium, phosphorus, strontium, radium and plutonium.

53. The vascularity and porosity of compact bone change throughout life with more vascularity and remodelling early in infancy and childhood compared to young adulthood. The differences in reference remodelling rates for bone at various ages are shown in table 9.

Table 9. Reference values for bone remodelling rates at different ages (annual percentage)

Adapted from ICRP Publication 70 [I15]

Age	*Cortical bone*	*Trabecular bone*
0–3 months	300	300
1 year	105	105
5 years	56	66
10 years	33	48
15 years	19	35
22 years	9	27
35 years	2	10
60 years	4	20
Average after age 25 years	3	18

54. In the trabecular bone, there is a decrease in the fraction of the spongiosa which is occupied by trabeculae. This decrease is most marked in infancy and slows thereafter.

55. The chemical composition of bone changes somewhat, but not dramatically, with age. The ash content of the skeleton is about 23% by weight at one year of age and 26% at 35. The calcium content of bone is about 17% by weight at one year of age and 21.5% at 35.

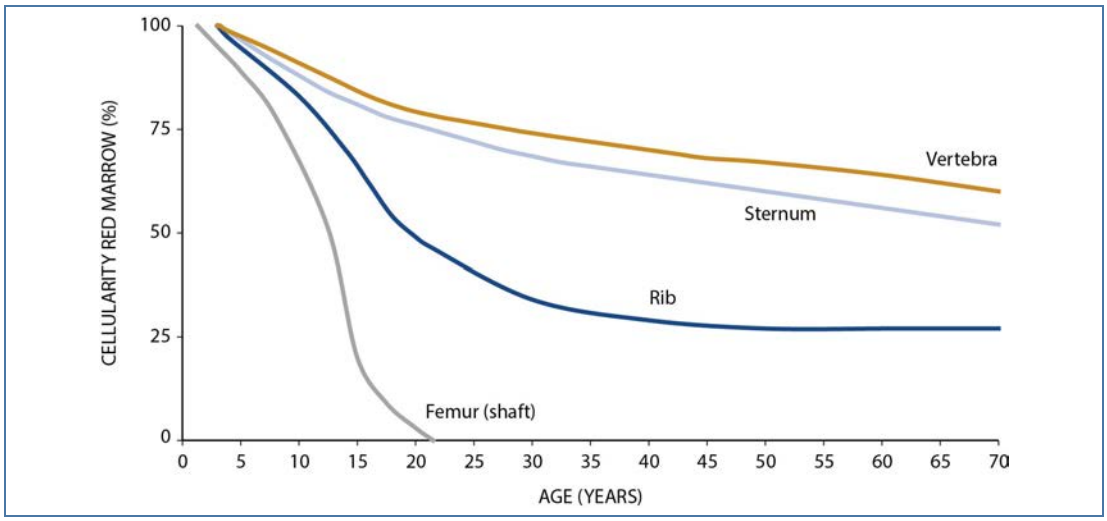
56. Uptake of radionuclides in bone is not uniform. The two principal factors that influence accumulation are extraction efficiency and blood flow. Other factors include capillary permeability, extracellular space hydrostatic pressure, electrical potential and local changes in pH. The differences in skeletal accumulation of radionuclides at various ages are readily seen in diagnostic images from a ^{99m}Tc-metheylene diphosphonate bone scan.

57. Bone marrow is of critical interest owing to the well-documented induction of a range of leukaemia types by radiation and also to the sensitivity of components of the bone marrow to cell

killing at doses of a few grays. The bone marrow is located in the trabecular bone cavities of long tubular bones and the vertebra, ribs, sternum and the flat bones of the skull and pelvis. There are two kinds of marrow—red and yellow. Red marrow contains haematopoietic stem cells and is involved in the production of cellular blood components (red cells, several types of white cells and platelets). Yellow marrow is mostly fat and has little function.

58. The total amount of bone marrow represents about 1.3% of total body weight in a newborn, 1.7% at one year, 2.5% at five years, 3.8% at ten years and about 4.5% in an adult. Although the percentage of total body weight represented by active marrow (about 2–3%) does not change much with age, there is a significant difference in the distribution of bone marrow within the bone as an individual ages. In the infant, all marrow is red but as the individual ages, there is transformation of red to yellow marrow and the red marrow retreats to the more central portions of the skeleton (ribs, pelvis, skull vertebrae) and proximal portions of the femora and humeri (figure III).

Figure III. Graphical representation of change in distribution of active marrow at different ages
Adapted from [M10]



E. Genitourinary system

59. The genitourinary system consists of the kidneys, urethras, bladder, uterus, vagina, ovaries, prostate and penis. The masses of various genitourinary organs at different ages are shown in table 4.

60. At birth, the kidneys are well formed and contain the maximum number of glomeruli. After birth, if there is injury, a kidney can hypertrophy but this is due to hypertrophy of the renal tubules and not an increase in glomeruli. Daily excretion increases with age and body size predominantly as a function of increases in fluid intake (table 10).

61. The dose to the bladder and other tissues from internally-deposited radionuclides excreted in urine is dependent on the size of the bladder and the frequency of voiding and can cause significant differences in age-specific dosimetry. In young children, the bladder is more intra-abdominal and can lead to higher doses to other abdominal organs. In children, there is a non-linear relationship between age and bladder capacity [K3]. In infants, the average bladder capacity is about 100 ml, increasing to about 175 ml at age two, about 250 ml at age five, about 350 ml at age ten. The average adult bladder

capacity is about 400–500 ml. There are, however, substantial individual variations. Children typically void every 2–3 hours. Comparison of excretion rates, bladder capacity and frequency of voiding indicates that most children void before bladder capacity is reached. The ICRP reference bladder parameters for different ages are shown in table 11.

Table 10. ICRP Reference excretion rates per day at various ages

Adapted from ICRP Publication 89 [I22]

Age	*Excretion (ml/day)*	
	Males	*Females*
Newborn	300	300
1 year	400	400
5 years	500	500
10 years	700	700
15 years	1 200	1 200
Adult	1 600	1 200

Table 11. Parameters of urinary bladder model

Adapted from ICRP Publication 67 [I13]

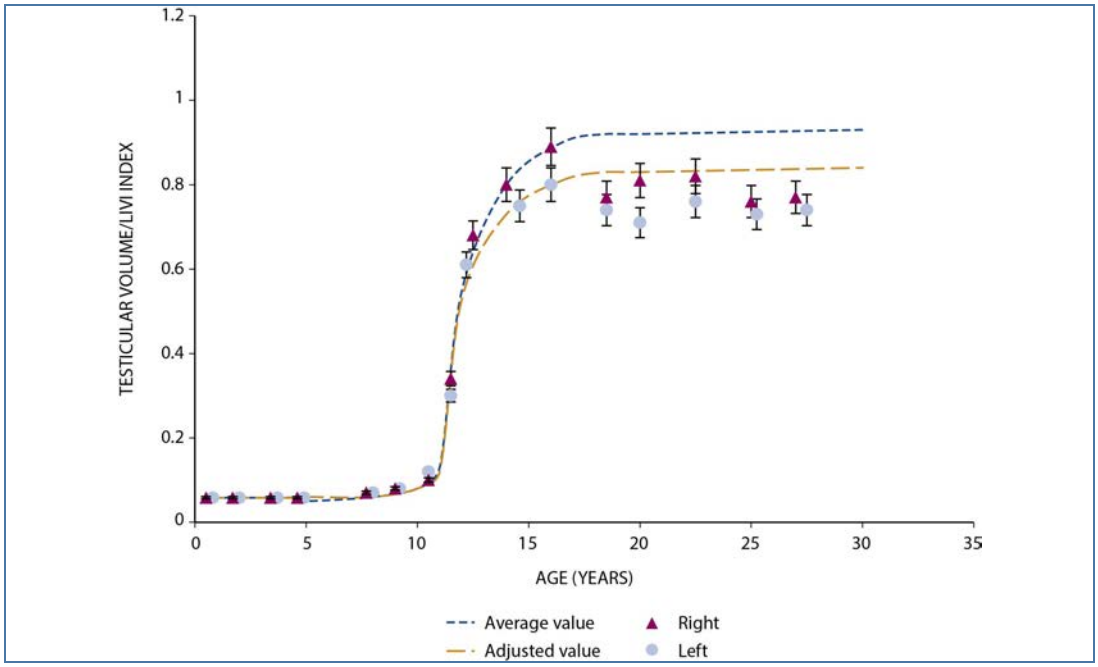
Age	*Number of voids per day*	*Bladder contents (ml)*
3 months	20	15
1 year	16	25
5 years	6	65
10 years	6	75
15 years	6	85
Adult	6	115

62. The testes are characterized by dramatic changes between birth and adulthood. The testes produce both hormones and sperm. Sperm are produced from germ cells lining the seminiferous tubules and supported by epithelium (Sertoli cells). The most conspicuous change in the testes takes place during puberty and the volume of the testes can increase by over 500% compared to their prepubertal size (figure IV). Prior to the age of 12, the testes have a volume of less than 5 ml; by the age 17, the testes have reached the adult size of about 31 ml. This increase in volume is due to a significant increase in the diameter of the seminiferous tubules, proliferation of Sertoli cells and spermatogonia and sperm production [W11]. During puberty, Leydig cells appear in the interstitium and produce testosterone. Leydig cells are much more resistant to radiation than are the germ cells involved in spermatogenesis.

63. Just before and shortly after birth, the ovaries contain the peak number of non-growing (primordial) follicles, probably about 0.3–1 million. The number decreases with age owing to apoptosis. The rate of recruitment to mature follicles increases from birth to about age 14 and then declines with age until menopause. Some primordial follicles develop during the menstrual cycle to become primary oocytes and then secondary oocytes. Ovaries also secrete oestrogen and progesterone. Before puberty, the ovaries are small. At puberty, they enlarge and become more vascular. Ovarian volume is less than 2 ml up to age eight and then there is rapid growth reaching 6 ml by age 15. Uterine volume is less than 3 ml before age eight and then increases to about 15–20 ml by age 13 [H42].

Figure IV. Testicular volume/Livi index curve as the function of age

Adapted from [B14]



F. Endocrine system

64. Maturation of endocrine structures and function relevant to radiation effects predominantly involve the thyroid gland, growth hormones and reproductive hormones.

65. The masses of the thyroid at various ages are shown in table 4. The thyroid gland is stimulated by the thyroid-stimulating hormone (TSH), also known as thyrotropin, from the pituitary gland to produce both thyroid hormones (triiodothyronine and thyroxine). The foetal thyroid begins to accumulate iodine at about 10–12 weeks of gestation. After birth, there is a very rapid rise in TSH reaching a peak in about 24 hours and declining to normal in about five days.

66. The data on the uptake of radioiodine at different ages are limited. However, after the first year of life, it is broadly similar in children, adolescents and adults [C53, S25]. The metabolic rate of radioiodine in children may be somewhat higher than in adults [I33]. TSH, triiodothyronine and thyroxine serum values are all highest in the first year of life and decrease slowly by about 20–40% by the age of 16 to 20 years.

67. Growth hormone is secreted by the anterior pituitary gland. Increase in height during childhood is the most widely known effect of growth hormone. Growth hormone levels rise steadily throughout puberty. It has many other effects including increasing calcium retention, increasing muscle mass and protein synthesis, stimulating the immune system and stimulating growth of all organs except the brain.

68. Puberty is initiated by the hypothalamus of the brain releasing gonadotropin-releasing hormone (GnRH). Cells in the anterior pituitary respond by secreting luteinizing hormone (LH) and follicle-stimulating hormone (FSH) into the circulation. The testes and ovaries respond by growing and beginning to produce the steroid sex hormones, testosterone and oestradiol.

69. A significant portion of testosterone in boys is converted to oestradiol and this mediates bone growth, bone maturation and epiphyseal closure. During teenage years, testosterone levels slowly rise. In girls, during puberty the rising levels of oestradiol produce a growth spurt, bone changes, breast growth, increased fat composition, growth of the uterus and the endometrium.

G. Female breast

70. Whereas in most other mammals breast development is minimal until pregnancy occurs, human females develop full breast tissue before pregnancy. Small divisions of breast tissue (lobes) develop, followed by mammary glands consisting of about 20 lobes. Mammary glands are influenced by hormones during puberty. When the ovaries start to secrete oestrogen, increased fat in the connective tissue causes the breasts to enlarge and the duct system begins to grow. Within six–twelve months, the swelling is beyond the edges of the areola and within about another year, the breasts are approaching mature size and shape. Once ovulation and menstruation begin, secretory glands form at the ends of the milk ducts. The density and amount of glandular tissue change during menstruation with varying oestrogen and progesterone levels [H65].

V. DOSIMETRIC ASPECTS

71. Differences between children and adults in radiation effects and absorbed dose for the same radiation exposure can result from some of the developmental processes mentioned in the section above. Important factors regarding dosimetric differences between children and adults are summarized in table 12 and a more detailed discussion on dosimetric aspects for external and internal exposures is provided in appendix A.

Table 12. Comparison of dosimetry for exposure of children and adults

Kind of exposure	*Dosimetric aspects*	*General differences*[a]	*Comments and exceptions*
EXTERNAL EXPOSURE			
Environment	Dose coefficients	+	Higher dose due to smaller size, organs closer
	Exposure	o	
	Doses	+	
Medicine	Exposure parameters	-	
	Doses	-	Due to lower exposure parameters
INTERNAL EXPOSURE			
Inhalation	Dose coefficients	+	Depends on the radionuclide; for ^{137}Cs, for example, nearly "o"
	Exposure	-	
	Doses	-	Depends on the radionuclide; for ^{131}I, for example, "+"

Kind of exposure	*Dosimetric aspects*	*General differences*[a]	*Comments and exceptions*
Ingestion	Dose coefficients	+	Depends on the radionuclide; for ^{137}Cs, for example nearly "o"
	Exposure	-	Depends on the food; for milk, for example, "+" for young children
	Doses	-	Depends on the radionuclide and food; for ^{131}I and alkaline earths, for example, "+" and also for milk consumption of other radionuclides
NUCLEAR MEDICINE			
	Dose coefficients	+	
	Exposure	-	Less administered activity
	Doses	o	

[a] *(+ = higher values for children; o = values for children and adults approximately the same; - = lower values for children).*

A. External exposure

72. External exposure may be due to radionuclides in the environment (irradiation by radionuclides in the air (submersion) or by irradiation by radionuclides deposited on the ground) or due to medical exposure (in radiological examinations by radiographs, fluoroscopy or CT examinations or by radiotherapy). Children have smaller body diameters, meaning that for a given external exposure the dose to internal organs will be slightly greater than in an adult. They are also shorter than adults, which results in a higher dose from radionuclides on the ground. Age-related correction factors for irradiation from the ground are about 1.4 for infants and 1.1–1.2 for children as compared to adults. These factors are important when considering populations in caesium-fallout areas (such as those around the Chernobyl and Fukushima Daiichi nuclear power plants). In medical exposure, children may receive significantly higher doses than adults for the same examination if the technical parameters would not be specifically adapted. However, in general technical parameters are adapted resulting in lower doses for children.

73. There are some differences between the absorbed doses incurred by children as compared to adults for given exposures. For external exposures, the midline and overall absorbed dose is somewhat higher owing to less soft tissue attenuation. Generally dosimetric differences for external exposure are less than a factor of two- to threefold.

B. Internal exposure

74. In situations involving the intake of radionuclides, absorbed doses per unit activity may be higher in children as a result of the organs being smaller and closer together or because there are differences in metabolism. For selected radionuclides, the dose per unit activity can be tenfold higher for infants compared to adults. Children, however, may have lower intakes of radionuclides than adults. Internal exposure can also differ markedly between children and adults owing to differences in diet and physical activity.

75. Several radionuclides are of particular concern regarding internal exposure of children. Releases of ^{131}I during nuclear power plant accidents have the potential for induction of thyroid cancer as the radioisotope is rapidly concentrated in the thyroid gland resulting in a very high absorbed dose to the thyroid compared to doses received by other organs. The thyroid dose per unit intake in infants may be larger by a factor of 8–9 than it is in adults. Taking account of lower breathing rates for children, estimated inhalation doses are higher by a factor of up to two for children compared to adults exposed to the same air concentration. Because of higher consumption, doses from the ingestion of milk may be 20-fold higher in infants than in adults. For ^{137}Cs—distributed throughout all living tissues within the body—a shorter biological half-life in children has been observed, which compensates for the lower body masses of children such that there is very little difference in organ dose per unit intake as a function of age at intake. Strontium-90 is historically important as a result of fallout from nuclear tests, with ingestion in contaminated milk and concentration of this radionuclide in the skeleton. For ingestion and inhalation, doses per unit intake delivered to the bone surface and red marrow are highest for infants and adolescents owing to a combination of higher intestinal absorption and increased skeletal uptake. For inhalation, the lung dose per unit intake increases with decreasing age because of the lower masses of children but effective doses are lower than in adults when account is taken of breathing rates. Ingested or inhaled ^{228}Ra yields substantially higher doses per unit intake to systemic—principally skeletal—tissues, in infants than in adults. This is due to a combination of higher intestinal absorption, in the case of ingestion, and increased uptake into the skeleton. However, taking account of breathing rates, doses to infants and children are estimated to be lower than for adults exposed to the same air concentrations. Ingestion doses may be substantially higher than in adults, with examples of a 20-fold increase in one-year-old infants consuming vegetables and a sevenfold increase in 15-year-old children consuming milk.

76. Radon is of importance because of the ubiquitous nature of exposure (especially in buildings) and the long-term potential for lung cancer. The lung dose from inhalation is influenced mainly by radiation from daughter radionuclides. For ingestion, the dose is mainly to the stomach wall. The inhalation dose coefficients for lung dose for a child are not more than a factor of five higher than for adults. However, owing to the lower inhalation rates, the doses are nearly the same for all ages.

77. Internal exposure of children also occurs from medical use of radionuclides. A wide variety of radiopharmaceuticals used distribute quite differently in the body. The spectrum of examinations performed on children is different from that performed on adults. In children, studies of the kidney and skeleton predominate. Doses per unit of administered radioactivity are often higher in children; however, in practice, this is offset by the use of lower administered activities.

VI. HEALTH EFFECTS

78. Describing the effects of radiation exposure during childhood or adolescence as compared to those incurred during adulthood is a complex matter. This section summarizes the current knowledge on this topic. A more detailed discussion can be found in appendices B and C.

A. Malignant neoplasms

79. Data on risk of neoplasms at different ages at exposure comes from a variety of sources, but most commonly from studies on the atomic bombing survivors. Another major source of information is therapeutic medical exposure. The UNSCEAR 2006 Report has detailed reviews of the scientific data for each tumour type [U12]. For some tumour types, the data showing an age-at-exposure effect are strong while for other tumour types, the data are intermediate, weak or non-existent. In the absence of strong data, some researchers have combined tumour types and used various statistical models. Assumptions used in those models have important influences on apparent age sensitivity.

80. Often the results are expressed as absolute risk versus relative risk. Relative risk assumes that radiation-related risk is proportional to the baseline risk, which typically may vary by age, sex and other factors, while a measure of absolute risk assumes that the radiation-related risk does not depend on the level of the baseline risk. Compared to the excess absolute risk (EAR, defined as cancer rate in the irradiated group minus the rate in the corresponding unexposed group), the excess relative risk (ERR, defined as the ratio of risk in the exposed group to that in the unexposed group), is often thought to be a better index of the strength of a potential causal association, while the EAR is a better index of the burden of disease (number of excess cases due to the exposure). Both metrics are useful in comparing the impact of exposure of children versus that of adults, so both will be given when available. For a limited period after exposure (e.g. the first 25 years) the EAR is lower for children than for adults since tumours are much rarer at a young age; however, the estimated lifetime EAR for all solid cancers combined is higher after exposure in childhood than it is after exposure in adulthood because children have a longer remaining lifetime in which to incur risk, and at any given age at risk they have a higher excess cancer incidence and mortality. The ERR is most often higher for children (although not for all sites). In evaluating age-at-exposure effects, a number of researchers have used attained age as the other main variable. While this may be useful for modelling background risk, an analysis by time since exposure is useful as a comparison and may sometimes better characterize the time course of radiation risk. There are distinct problems and inconsistencies that arise from using a “one size fits all” model for risk analysis. Confusion, misunderstanding and contradiction easily arise. Some published reports which have estimated the excess number of various tumour types that would occur at different ages of exposure indicate that the risk is 2.5–3-fold higher in infants than in 40-year-old adults for lung, colon, bladder and prostate cancer, which is at variance with actual epidemiological data.

81. For a given radiation dose, children are generally at more risk for tumour induction than are adults. Cancers that may be induced following radiation exposure at young ages may occur within a few years but also decades later. In the 2006 Report to the General Assembly, the Committee stated that lifetime cancer risk estimates for those exposed as children were uncertain and might be a factor of 2–3

times higher than estimates for a population exposed at all ages. This conclusion was based upon a lifetime projection model combining all tumour types.

82. The Scientific Committee has reviewed evolving scientific material and notes that, after radiation exposure, tumour induction in children compared to adults is quite variable and depends on the tumour type, age and sex. The term "radiation sensitivity" with regard to cancer induction refers to the rate of radiogenic tumour induction and does not refer to the degree of malignancy. Broadly, for about 25% of tumour types, children are clearly more radiosensitive regardless of the model. These include leukaemia, and thyroid, skin, breast and brain cancer. For some of these sites, depending upon the circumstances, the risks compared to adults can be quite high. Some of the sites are very important for evaluation of accidental and medical exposures.

83. The Committee has reviewed over 23 tumour sites for age-at-exposure effects. For about 15% of tumour types (e.g. bladder cancer), children appear to have about the same radiosensitivity as adults. For about 10% of tumour types (e.g. lung cancer), children appear less sensitive to external radiation exposure than adults. For about 20% of tumour types (e.g. oesophagus cancer), the data are too weak to draw a conclusion regarding differences in risk with age at exposure. Finally, for about 30% of tumour types (including Hodgkin's lymphoma, prostate, rectum and uterus cancer), there is only a weak or no relationship between radiation exposure and risk at any age of exposure.

84. At present, there are no statistically sufficient projections of lifetime risk for specific tumour sites following exposure at young ages. Currently used estimates do not adequately capture the known variations and additional work is needed.

85. Nevertheless, the examples above indicate that tumour induction after radiation exposure of children as compared to adults is quite variable and that findings depend on the tumour type, specific assumptions and the various models used. Table 13 summarizes the relative sensitivity of children compared to adults for the induction of various tumour types by radiation.

86. *All solid cancers.* In the latest report of the cancer incidence in survivors of atomic bombings, there is a statistically significant variation in excess incidence by age at exposure for the ERR model and even more so for the EAR model [P52]. A recent report on mortality shows a decrease in ERR by 29% per decade of age at exposure [O25]. But estimates for all solid cancers as a group do not necessarily represent age-at-exposure risks for all individual tumour sites. When the data are combined, tumours that may not be induced by radiation (e.g. prostate and rectal cancer) appear to have a risk which is artefactual owing to inclusion of the risk from tumours that are highly inducible by radiation.

87. *Leukaemia*. Most types of leukaemia other than chronic lymphocytic leukaemia can be induced by ionizing radiation with a minimum latency of about two years. Acute forms of leukaemia tend to predominate and occur more rapidly after exposure than chronic granulocytic leukaemia. A linear-quadratic dose response (rather than linear non-threshold) appears to provide the best fit to the data. From several studies covering various types of exposure, exposure in childhood appears to entail a three- to fivefold greater risk than exposure in adulthood [M1, R8].

88. *Multiple myeloma and myelodysplasia.* The UNSCEAR 2006 Report concluded that there was only weak evidence linking myeloma to radiation exposure and that the better quality of information from incidence data would suggest little evidence of an association with low linear energy transfer (LET) radiation. No age-at-exposure effect has been identified [U12]. An excess of myelodysplasia has been identified in atomic bombing survivors with an increased risk at young ages of exposure [I47].

Table 13. Comparison of carcinogenesis risks at age-at-exposure for children versus adults

Cancer site	*More*	*No difference*	*Less*	*No sufficient data*	*Level of evidence*
Oesophagus				X	
Stomach (mortality)	ERR	EAR			Moderate
Small intestine [a]				X	
Colon					
- (incidence)	EAR	ERR			Weak
- (mortality)	EAR & ERR				
Rectum [a]				X	
Pancreas [a]				X	
Liver		X			Weak
Lung			X [b]		Moderate
Skin non-melanoma	X				Moderate
Breast	X				Strong
Uterus				X	
Cervix [a]				X	
Ovary				X	
Prostate [a]				X	
Kidney				X	
Bladder		X			Moderate
Brain	X				Strong
Thyroid	X				Strong
Parathyroid				X	
Hodgkin's lymphoma [a]				X	
Non-Hodgkin's lymphoma				X	
Myeloma				X	
Leukaemia non-CLL	X				Strong
Myelodysplasia	X				Weak

[a] *These tumours are not definitely shown to be increased by radiation exposure.*

[b] *The limited data on radon and lung cancer indicate approximately the same risk after exposure at pre-adult and adult ages.*

89. *Hodgkin's lymphoma.* With the exception of what are thought to be statistical chance associations, radiation has not been found to be associated with the development of Hodgkin's lymphoma, following exposure in either adulthood or childhood [U12].

90. *Non-Hodgkin's lymphoma.* Examination of the atomic bombing survivor incidence data found an increase in estimated EAR but only for males. No age-at-exposure effect was found. Studies of childhood cancer survivors showed an excess of non-Hodgkin's lymphoma, but the data were not examined for radiotherapy versus other treatment and there was no analysis by age at exposure [U12].

91. *Brain and central nervous system tumours.* Ionizing radiation can induce several types of nervous system tumours. There are marked differences with age at exposure. The UNSCEAR 2006 Report pointed out that malignant tumours of the CNS are seen mostly after high doses of radiotherapy and after exposure in childhood [U12]. The risk of glioma is highest at the age of five years or less at irradiation and seems to largely disappear at the age of 20 years or more at irradiation, suggesting that susceptibility decreases as brain development nears completion. The greatest risk of glioma is in the first 20 years after exposure, whereas meningiomas predominate thereafter. The risk from exposure in adulthood is more commonly for benign tumours such as meningioma, neurilemmoma and schwannoma.

92. *Thyroid cancer.* Children are more sensitive to induction of thyroid cancer than are adults. This is true whether one examines ERR or EAR. The data come from a number of sources, but particularly from radiotherapy of the head and neck (primarily for Hodgkin's lymphoma), from the study of atomic bombing survivors and from radioiodine exposure as a result of Chernobyl [J5, N2, P52, S65, U12]. After therapeutic radiation exposure, the risk peaks in mid-dose range (10–30 Gy) and diminishes at higher doses (possibly because of cell killing). The risk of radiation-induced thyroid cancer as a result of adult exposure is too low to be quantified adequately.

93. *Salivary gland tumours.* Benign and malignant tumours of the salivary (particularly the parotid) gland have been reported to follow external exposure in the atomic bombing survivors and in children who have received radiotherapy. Presently, data are insufficient to assess whether there is an age-at-exposure effect or not.

94. *Breast cancer.* Breast cancer is inducible by radiation and the difference in risk from exposure in childhood compared to that in adulthood depends upon the model used. The increased risk in children appears to be about three- to fivefold with most low dose studies showing minimal or no risk from exposure after age 40. However, a pooled analysis that gave preference to attained age (age at risk) showed no additional effect of age at exposure [P48]. Children therapeutically irradiated during the pubertal years may have an increased risk compared to younger children or adults.

95. *Lung cancer.* Both low-LET and radon exposure have been shown to increase the risk of lung cancer. A recent update of the atomic bombing survivor mortality data showed that the age-at-exposure effect was not significant and was −7% (95% CI: −35, 29) per decade. A more detailed analysis that took into account smoking habits even suggested that risk might be greater for those exposed at older ages [F28], which also accords with some other data [R21]. The data on underground miners with radon exposure suggest that lung cancer risk was comparable for those first exposed at ages <15, 15-24 and >24. The findings for both external and internal lung exposures are at variance with the BEIR VII modelling, which estimated that children are about threefold more sensitive than 40-year-old adults to radiation induction of lung cancer [N43].

96. *Stomach cancer.* Increased risk of stomach cancer has been shown in atomic bombing survivors and those who have had radiotherapy for peptic ulcers. The LSS data provide weak evidence that the ERR decrease with increasing age at exposure but the EAR does not [O25]. The very limited evidence from other studies does not support an increased sensitivity among those exposed at young ages.

97. *Colon cancer.* Colon cancer is a good example of a tumour for which evaluating the age-at-exposure risk is problematic. In the atomic bombing survivor data, for those exposed before age 10 the ERR was quite high before age 40, but after age 40 the ERRs for age-at-exposure 10 and age-at-exposure 30 were virtually identical. Both the incidence and mortality data showed no age-at-exposure difference at age 70 for the ERR model, but the EAR did model higher risk for younger ages at exposure [O25, P52].

98. *Rectal cancer.* The rectum has a relatively low sensitivity to radiation-induced cancer but a statistically significant risk is evident after extremely high radiation therapy doses. In the most recent atomic bombing survivor cancer incidence report, the radiation risk for rectal cancer was not statistically significant nor was there significant variation in risk by age at exposure [P52].

99. *Kidney and bladder cancer.* Evidence linking kidney cancer with radiation exposure is weak, and that evidence comes only from studies where the dose is high (i.e. in the radiotherapy range). In those few studies, there does not appear to be any significant age-at-exposure effect. Although there are positive associations between bladder cancer and radiation exposure in radiation therapy and atomic bombing studies, their data do not show any special radiosensitivity among those irradiated in childhood [G26, O25, P52].

100. *Prostate cancer.* There is no convincing epidemiological evidence that prostate cancer is induced as a result of radiation exposure in either adulthood or childhood. The model used by the US National Research Council BEIR VII committee [N43] indicated that there was a 2.7-fold higher risk for children of having prostate cancer induced by radiation than there was for 40-year-old adults. This modelling is at variance with epidemiological data. The UNSCEAR 2006 Report concluded that there was little indication of radiation effect on prostate cancer risk [U12].

101. *Ovarian and uterine cancer*. With the exception of the atomic bombing survivor data, not much epidemiological evidence exists that radiation induction of ovarian cancer occurs in those exposed either as adults or as children. The atomic bombing survivor data do not show a consistent age-at-exposure effect [U12]. The epidemiological literature does not support radiation induction of uterine cancer except, possibly, at very high doses. The absence of an association between cervical cancer and radiation is a consistent finding even after very high doses.

102. *Skin cancer.* A number of epidemiological studies have indicated an association between radiation exposure and non-melanoma skin cancer, but not melanoma. The induced tumours are predominantly basal cell type and, to a lesser extent, squamous cell carcinoma. The relative risk decreases roughly two—fivefold with increasing age at exposure [P52, S70].

103. *Liver cancer.* The LSS of atomic bombing survivors reported an excess of liver cancer but the analysis did not show any statistically significant changes in risk by age at exposure. There was a non-significant age-at-exposure effect in the mortality data [O25]. Both are difficult to interpret owing to a high prevalence of infection with hepatitis C virus in that cohort, which is a major risk factor for liver cancer. A number of other low-LET exposure studies do not show an increase in liver cancer incidence or mortality.

104. *Pancreatic cancer.* Incidence and mortality studies of atomic bombing survivors do not show a statistically significant increase in pancreatic cancer [O25]. Some radiotherapy studies have reported an increase in pancreatic cancer after very high doses but few contain enough patients below the age of 20 to examine an age-at-exposure effect [U12].

105. *Bone and connective-tissue tumours.* Studies reviewed by UNSCEAR in the past indicated that bone sarcomas were unlikely below doses of tens of grays. A recent report on the atomic bombing survivors suggests a dose threshold of about 0.85 Gy with a linear response above that level, but based on small numbers and with no clear age-at-exposure effect. There was a statistically significant increase in soft-tissue sarcomas in relation to dose, but no variation by age at exposure [S13, S12, U12].

B. Deterministic effects

106. Deterministic effects —also called “Harmful tissue reactions”—occur only above a certain dose threshold and their frequency and severity increase with dose. An example of a deterministic effect is a radiation skin burn or ulcer. Few tissues show clinically significant deterministic effects at absorbed doses of less than a few grays.

107. *Pathogenesis.* Cell death, cell malfunction, perturbation of both intracellular and intercellular signalling, and fibrosis are central to all deterministic effects. Increased mitotic activity in developing tissues may relatively increase radiation sensitivity in these tissues during periods of rapid growth. However, cellular damage from radiation can sometimes also occur during intervals when the cellular activity is relatively quiescent but the injury is not expressed until development of that tissue accelerates. The role of stem cells in response to radiation exposure at various ages is unclear. Stem cells can be depleted by radiation, with injury expressed as the patient ages. However, a greater abundance of stem cells in some tissues at younger ages may decrease radiation sensitivity because of compensatory mechanisms. Conversely, limitations in cellular repair capacities at older ages can sometimes actually increase the sensitivity of some normal tissues in developed or senescing tissues. Deterministic effects depend on the absorbed dose received, volume and type of tissue irradiated, quality or type of radiation, time over which the dose was received and age of the individual. The magnitude and type of effects observed depend upon the time of observation after the exposure.

108. *Acute versus late effects.* Acute deterministic effects are caused by injury to rapidly proliferative stem or progenitor cells, which results in temporary or permanent lack of mature cells. Delayed lesions are due to complex processes, including progressive fibrosis, blood vessel narrowing, disturbances in cellular signalling, and immune and genetic factors. The spectrum of late responses varies with age. Radiation-induced impairment of growth and maturation is unique to children whereas organ damage and problems with tissue repair are common to both adults and children [P19].

109. One of the most valuable and comprehensive data sources regarding deterministic effects from childhood exposure is the Childhood Cancer Survivor Study (CCSS). This study followed 14,370 children diagnosed with various malignancies between 1970 and 1986 who survived for at least five years, and compared their outcome data with that of siblings. The CCSS is somewhat complicated in that many of the children received multimodal therapy. In spite of this, there are many conclusions that can be drawn regarding ionizing radiation. There are also useful epidemiological data regarding a number of effects from the atomic bombing survivor studies.

110. Differences in deterministic effects from exposure in childhood versus that in adulthood are complex and often involve interaction of different tissues and pathways. In each organ (for example the thyroid), there are multiple potential effects—each with different mechanisms and different times of expression. Similar to carcinogenesis, there are some instances in which childhood exposure poses more risk than adult at same radiation doses (e.g. brain, cataracts, thyroid nodules). There are other instances where the risk appears to be about the same (e.g. neuroendocrine, kidney) and there are a few instances where children’s tissues are more resistant (lung, marrow and ovaries). The main differences between children and adults for deterministic effects are evident at doses only in excess of 0.5 Gy and usually at doses substantially higher associated with radiotherapy. A comparison of risks—following internal and external (radiotherapy) exposure of children versus that of adults—of developing physiological abnormalities of some organ systems is given in table 14.

Table 14. Comparison in children and adults of risks of developing physiological abnormalities following internal and external exposure

Most of the age-at-exposure effects are not seen at doses of less than 0.5 Gy

Organs	*More*	*Same*	*Less*	*No sufficient data*	*Levels of evidence*	*Comments*
Deterministic risks following radiotherapy in children versus adults						
Brain	X				Strong	Neurocognitive reduction
Neuroendocrine		X			Strong	Consequences greater owing to growth hormone suppression
Cataracts	X				Weak	
Cerebrovascular accident	X				Moderate	Stroke
Heart	X				Strong	Prevents growth and remodelling, valvular abnormalities
Breast hypoplasia	X				Strong	Most severe during puberty
Lung			X		Weak	Depends on end point: maximum capacity decreased if chest wall growth is inhibited
Thyroid hypofunction		X			Weak	
Thyroid nodules	X				Strong	
Thyroid autoimmune				X		
Kidney		X			Weak	
Bladder	X				Strong	Bladder capacity reduced
Testes	X				Strong	Most severe during puberty. Reduction in sperm and hormones
Ovaries			X		Moderate	Less sensitive at younger age
Uterus	X				Moderate	Uterine vasculature impaired
Musculoskeletal	X				Strong	Hypoplasia, deformity, osteochondroma
Immune				X		
Marrow whole body			X		Strong	Less available marrow when older
Deterministic risks following internal exposures in children versus adults						
Thyroid hypofunction				X		
Thyroid nodules	X				Strong	
Thyroid autoimmune		X			Moderate	Insufficient evidence

111. *Neurological effects*. As mentioned earlier, the brain develops over at least two decades. Radiotherapy experience has shown that the brain is particularly radiosensitive and adverse effects are greater at a younger age at exposure [P2, R31]. The potential for these effects is increased when certain chemotherapeutic agents (e.g. methotrexate, cytosine arabinoside) are also administered. The brain is most radiosensitive when rapidly developing in the first two years of life but effects also occur at a later age at exposure. Higher doses of radiation (>20–30 Gy, depending on patient age) interfere with the process of myelinization of nerve axons and synaptogenesis. Also, there can be loss of brain volume [R14]. These changes can result in lethargy, poor school performance, ataxia, spasticity, progressive dementia and even death [P4].

112. *Neurocognitive effects.* After fractionated doses of over 54 Gy, children over the age of 12 who have had localized volumes of cranial radiotherapy have little reduction in intelligence quotient (IQ) while those exposed under the age of five at treatment to similar volumes have a significant decline of 15–35% [M29]. Other neurologic sequelae can include late onset of coordination problems, seizures, headaches, impairment in task efficiency and difficulty in emotional regulation.

113. *Neuroendocrine effects.* These occur as a result of hypothalamic irradiation. The most common effect is a reduction in growth hormone secretion that, if untreated, results in short stature. Other problems include gonadotropin deficiency, precocious puberty, hyperprolactinemia, adrenocortical hormone deficiency and central hypothyroidism. Manifestations of damage to the hypothalamic-pituitary axis depend on the hormonal axis that is affected, but can include loss or gain of weight, altered development of secondary sexual characteristics, dry skin, slow pulse, genital atrophy and temperature disregulation [C47, M56, S85].

114. *Cataracts, cortical opacities.* Changes in the lens of the eye following irradiation have been recorded for many decades [D23, N6, S68] and children appear to be more sensitive than adults to induction of early lens opacities and clinically significant cataracts requiring surgery. While children who receive low radiotherapy doses to the orbit (5–15 Gy with risk depending on their age) may suffer from cataracts, higher doses of >20–30 Gy are necessary to cause dry eyes, retinitis and keratoconjunctivitis.

115. *Hearing and the ear*. The ear is relatively radioresistant; however, cranial radiotherapy (>30 Gy) in children can produce late effects, including vestibular abnormalities and hearing loss. These changes can be exacerbated when the child is also treated with select chemotherapeutic agents. Susceptibility can be greater at a young age [M29].

116. *Oral cavity and pharynx.* The lining of the mouth and pharynx are more radiosensitive to acute effects than is the skin because of the higher renewal rate of the epithelial cells. The reactivity of children is greater than that of adults but a more rapid recovery compensates for this and the end effect seems to be less Most patients receiving fractionated radiotherapy schemes totalling 60-70 Gy have impairment in taste for several years [K45]. High radiation doses administered at young ages can cause delayed pharyngeal hypoplasia.

117. *Teeth.* In children, effects on teeth may occur even after >10–20 Gy therapeutic irradiation (depending on age at exposure), and also from chemotherapy. Effects are greatest in children under the age of five who had received such therapy before developing deciduous dentition [S98]. These include increased caries, root stunting, reduced calcification, abnormal enamel, dry mouth and, occasionally, even lack of development of the jaw bone. Tooth abnormalities are also reported in teenagers who were injected with high activities of ^{224}Ra.

118. *Salivary glands.* Radiotherapy (>25 Gy) can reduce secretions of the parotid, submaxillary and sublingual glands with resultant dry mouth, but this is generally not pronounced below doses of 40 Gy [D31, F20]. There is little data concerning the sensitivity of these glands in children versus adults.

119. *Thyroid.* Effects of interest are primarily hypothyroidism, autoimmune thyroiditis and thyroid nodule formation. After radiotherapy to the head and neck, thyroid function can be reduced; however, the effect of age at exposure is controversial [S83, U8]. Very limited data indicate that an increased risk of hypothyroidism is observed as age at exposure decreases; however, most radiotherapy studies have failed to confirm this. No epidemiological study has demonstrated hypothyroidism from external doses of <1 Gy.

120. The available data indicate that autoimmune thyroiditis is unlikely to be induced by exposure to radiation in childhood. The most recent follow-up of thyroid abnormalities among survivors of the atomic bombings did not find a dose-response relationship for the presence of antithyroid antibodies or antithyroid antibody positive hypothyroidism [I34]. Most studies of populations exposed to fallout from nuclear weapons and discharges from nuclear facilities do not show an increase in autoimmune hypothyroidism. Multiple early studies of populations exposed to fallout from Chernobyl produced conflicting results but the majority of recent studies do not show a relationship between thyroid dose and autoimmune thyroiditis in adults or children [T38].

121. There is a vast literature of epidemiological studies of thyroid nodules after radiation exposure. These include studies of atomic bombing survivors, medical radiation exposure, nuclear fallout, nuclear facility discharges and accidents. Although there is no question that the incidence of thyroid nodules increases as a result of radiation exposure. Both the Israeli and New York tinea capitis studies found increased risk at thyroid doses of 100 mGy (0.1 Gy) or less. These studies have been complicated by use of varying criteria and the high spontaneous rate of benign thyroid nodules in unexposed populations. Most studies have demonstrated an increased risk of radiation-induced thyroid nodules with decreasing age at exposure [N18, S71].

122. *Parathyroid glands.* The parathyroid glands are quite radioresistant. Although some reports suggest, post-radiotherapy parathyroid hyperfunction or calcitonin deficiency, there is no clear evidence of increased susceptibility of children.

123. *Female breast.* Adult breast tissue is quite radioresistant to deterministic effects; however, breast development is readily inhibited by radiotherapy in infancy and severe hypoplasia has been reported in women who have had a history of breast irradiation in childhood. Doses reported to cause these effects were >2 Gy.

124. *Cardiovascular.* There are only a few studies that allow evaluation of age-at-exposure differences for the risk of development of cardiovascular disease. The data from survivors of the atomic bombings do not show a clear increased risk of cardiovascular disease at doses lower than 0.5 Gy and there is no evidence of difference in risk with age at exposure [S57]. In the paediatric radiotherapy literature, there is an increased cardiovascular risk for various cardiac injuries at doses in excess of 15 Gy, and the risk increases slightly as the age at exposure decreases. A recent meta-analysis of low dose studies suggests that there is a reduction in risk with increasing age at exposure [M58]. Cardiovascular complications from chemotherapy, particularly anthracyclines, are well described, and augment effects from radiation therapy.

125. *Pulmonary.* Radiation-related respiratory effects in children can impede the formation of new alveoli or result in skeletal deformity and smaller lungs owing to impaired chest development. Overall, however, respiratory damage in children is somewhat less than in adults at the same doses. The reasons

for this are that children have less pre-existing disease and better repair capability. In spite of this, there can be adverse pulmonary effects in children at fractionated doses totalling 10–20 Gy [V16].

126. *Gastrointestinal.* There are reports of a wide spectrum of acute complications and late effects after childhood or adolescent radiotherapy involving the gastrointestinal track. The risk of such complications is increased for children who have been treated with certain chemotherapeutic agents in addition to radiotherapy or who have had abdominal surgery However, interestingly, children who were younger than three at cancer diagnosis had a 20–50% lower risk of upper and lower gastrointestinal complications than did older children. The reason for this is unclear [G19].

127. *Liver.* A number of liver abnormalities may occur after high-dose hepatic irradiation. A number of historical studies indicated that decreasing age was a risk factor for liver complications following radiotherapy of children at doses >12 Gy. However, a recent analysis in the CCSS suggests that children over the age of three at cancer diagnosis had a higher risk than those children who were under three years of age [C7].

128. *Pancreas.* Children and young adults treated with whole body or abdominal radiotherapy with doses in excess of 10 Gy are known to be at increased risk of insulin resistance and diabetes mellitus. Children under two are more sensitive by about 50% than older patients [D29].

129. *Testes.* Radiation effects on the testes are both age and dose dependent. Germ cells are the most sensitive. Complete sterilization can occur after fractionated doses of 2–4 Gy. Doses of 10 Gy have been shown to produce primary gonadal failure of various degrees in the majority of boys regardless of pubertal status. Doses higher than 20 Gy will also affect the more resistant Leydig cells of the testes [K26].

130. *Ovaries and uterus.* The ovaries and subsequent fertility is an example of children being more resistant than adults to radiation effects. Since the ovaries contain the most primordial follicles at or near birth and there is quite a dramatic decline in number with increasing age, there is much less reserve to allow fertility as age increases. With ovarian radiotherapy doses of 2.5–5 Gy, patients under 14 did not develop sterility compared to 30–40% for those treated at 15–40 years of age and 90% in those who were over 40 at treatment. High doses to the uterus of girls can result in a small fibrotic uterus, which increases the risk of spontaneous abortion or premature delivery [M36].

131. *Fertility and reproduction.* Fertility and reproduction can be reduced by a number of factors, including those outlined above for the testes, ovaries and uterus. Other factors would include patency of fallopian tubes and pituitary/hypothalamic axis endocrine problems. While there are no data indicating that radiation susceptibility of the neuroendocrine axis is greater at younger age, uterine development is clearly compromised by pelvic irradiation and, thus, is age dependent. Conversely, the ovaries, and perhaps the testes, may be more resistant to radiation at a younger age [K26, M36].

132. *Skin.* Children appear to be less sensitive than adults for the acute effect of moist desquamation, perhaps because of faster repair by the skin cells. Otherwise, there appears to be little or no difference between children and adults in skin sensitivity with regard to tissue reaction.

133. *Musculoskeletal system.* The musculoskeletal system is quite radioresistant after growth is complete, but radiosensitive during development. Children can experience unique late effects that do not occur as a result of adult irradiation. Few, if any, changes are seen below fractionated doses of 10 Gy and most changes occur at doses >20 Gy. Radiation therapy can affect the musculoskeletal system of a growing child or adolescent with inhibition of normal bone and muscle development. Late effects can include short stature, premature closure or slippage of epiphyses, scoliosis/kyphosis, limb length discrepancy, and radiation-induced fractures. Exposure at less than six years of age and during

puberty is associated with the greatest relative impairment. Other post-radiotherapy effects can include induction of benign bone growths (osteochondromas), increased body fat composition and metabolic syndrome.

134. *Urinary system.* Radiotherapy doses above 12 Gy to the kidneys of children have been shown to cause nephritis, reduced creatinine clearance, renal insufficiency and hypertension. The urethras and bladder are more resistant to late radiation effects than are the kidneys. There are no data to suggest that a child's urinary system is more radiosensitive than that of an adult.

135. *Immune system.* Studies of radiation effects on the immune system are difficult because of its immense complexity. The results relative to age at exposure are mixed and most studies are related to laboratory rather than clinical findings. Studies of T-cell immunity of survivors of the atomic bombings suggest that there is increased perturbation of the immune system in those exposed at older ages. Other studies related to genetic regulation of the immune system suggest more sensitivity among persons exposed at less than 20 years of age. Since the data are sparse and often contradictory, there do not seem to be clinically identifiable differences in risk between children and adults.

C. Heritable effects

136. Extensive reviews of the heritable effects of radiation exposure are available in ICRP Publication 83 [I21] and in the UNSCEAR 2001 Report [U11]. The UNSCEAR 2001 Report contained a section reviewing two studies on genetic disease in the offspring of long-term survivors of childhood and adolescent cancer and in the offspring of those treated for haemangioma in infancy. As with adults, there is no evidence that radiation exposure in childhood confers any measurable risk of heritable effects in offspring.

137. Over the past decade, there have been additional studies that have focused on survivors of childhood and adolescent cancer. Gonadal doses from radiotherapy often range from tenths of a gray up to twenty grays. There has been little evidence in the offspring of irradiated parents of chromosomal instability, minisatellite mutations, transgenerational genomic instability, change in sex ratio of offspring, or congenital anomalies. A number of papers have been published using data from the CCSS and the atomic bombing survivor LSS, and there is no apparent increase in cancer in the offspring.

138. Many studies in the last decade have been directed at searching for possible heritable effects after childhood exposure, the vast majority of which involve the offspring of persons who received radiotherapy as children or adolescents. The results of such studies are important as the survivors of childhood cancer reach the age of fertility. Winther et al. [W33] studied female cancer survivors and found only a minimally higher incidence of induced abortion. There is also an increased risk of low birth weight and pre-term delivery of babies for those females who received pelvic radiotherapy. This is presumably the direct effect of radiation on the uterus and ovaries.

139. Curwen et al. [C57, C58, C56] investigated the possible association between G2 chromosomal radiosensitivity in Danish survivors of childhood and adolescent cancer and their offspring. There was strong evidence of heritability of the radiosensitive phenotype but not a statistically significant relationship between the chromosomal radiosensitivity and cancer predisposition.

140. Tawn et al. [T8] examined chromosomal instability among 25 adult survivors of childhood cancer, their 26 partners and 43 offspring. Frequencies of all aberration categories were significantly lower in the offspring group. Genomic instability was not associated with radiotherapy nor was it found

to be a transgenerational radiation effect. Tawn et al. [T9] also studied germ line minisatellite mutations in survivors of childhood and young adulthood cancer who had been treated with radiation. No significant difference was observed in the paternal mutation rate of 5.6% in exposed fathers with a mean preconceptional dose to the testes of 1.23 Gy and that of 5.8% in unexposed fathers. The maternal mutation rate of 1.6% in cancer survivors with a mean preconceptional dose to the ovaries of 0.58 Gy was lower than that of unexposed mothers (2.1%).

141. Winther et al. [W30] studied chromosomal abnormalities among 2,630 live-born offspring of the survivors of childhood cancer compared with 5,504 offspring of their siblings. The proportion with abnormal karyotypes was identical at 0.21%. Thirty-seven per cent of the group had received radiotherapy.

142. Winther et al. [W35] also performed a case–cohort study of 472 survivors of childhood and adolescent cancer and their 1,037 pregnancies. Adverse outcomes included 159 congenital malformations, six chromosomal abnormalities, seven stillbirths and nine neonatal deaths. The risk of genetic disease was similar among the children of irradiated survivors when compared with non-irradiated survivors (relative risk (RR) = 1.02; 95% CI: 0.59, 1.44; $p = 0.94$)). However, a statistically significant association between abdomino-pelvic irradiation and malformations, stillbirths and neonatal deaths was not seen in the children of female survivors overall ($p = 0.07$) or in the children of mothers receiving high uterine doses (mean 13.5 Gy, max 100 Gy) (RR = 2.3; 95% CI: 0.95, 5.56). An earlier population-based cohort study by the same authors [W32] found a slightly higher, non-significant increase in congenital malformations which was unrelated to gonadal dose.

143. A recent retrospective cohort analysis was performed by Signorello et al. [S77] of 4,699 children of 1,128 male and 1,627 female childhood cancer survivors within the CCSS. Neither the dose to the ovaries (mean dose 1.19 Gy; odds ratio (OR) = 0.59; 95% CI: 0.20, 1.75), nor the dose to the testes (mean dose 0.48 Gy; OR = 1.01; 95% CI: 0.36, 2.83) was related to congenital anomalies.

144. Additional studies have been conducted on reproductive outcomes, cancer incidence and hospitalization of offspring. Green et al. [G31] studied patients in the CCSS, including 1,227 male survivors who sired 2,323 pregnancies and 1,915 female survivors who had 4,029 pregnancies. Offspring of women who had received doses to the uterus of more than 5 Gy were more likely to be small for gestational age. There was no difference in proportion of offspring with simple malformations, cytogenetic syndromes or single-gene defects. In another study of the same data base, Signorello et al. [S75] also reported low birth weight and pre-term delivery in those who had received high doses to the uterus from pelvic irradiation. Another study by Signorello et al. [S76] examined the occurrence of stillbirth and neonatal death. There was no increase in these in the offspring of men exposed to gonadal irradiation. However, uterine and ovarian irradiation had serious adverse effects probably related to uterine damage (and not heritable causes).

145. The possibility of sex ratio alterations after childhood radiotherapy has been studied by Winther et al. [W29] in a Danish study of 1,100 survivors of childhood cancer who became the parents of 2,130 children. The sex ratio for male (0.99) and female (1.00) offspring did not differ significantly from that for the Danish population as a whole (1.06) and there was no evidence of a radiation dose effect. The authors point out that sex ratio may not be a good or even valid indicator of genetic effects in humans. A study of hospitalization of offspring of survivors of childhood cancer has been conducted by Winther et al. [W34]. This was done on the basis that hospitalization might be an indicator of multifactorial genetic disease. Once heritable cancer syndromes had been eliminated, there were no significant associations.

146. The risk of cancer in offspring of the survivors of the atomic bombings has been studied by Izumi et al. [I48, I49]. They did not find an increase in the mortality or cancer rates of offspring from exposed parents. They indicated that most parents were between 10 and 30 years of age at the time of the bombings with the mean age for males being 24.4 years and that for females 19.8 years. Owing to the negative findings and small numbers of deaths in offspring, their reports do not allow a distinction between risks at the younger and older ages of the parents at the time of the bombings.

147. There are several recent studies of potential heritable effects in populations living in areas of high natural background radiation, particularly in Kerala, India. These studies have been negative for multiple end points, so they are not able to elucidate differences between radiosensitivity of children compared to adults [D12, D13, J9, R6].

148. A recent review by Little et al. [L31] of transgenerational effects in the offspring of irradiated parents included both radiotherapy patients, atomic bombing survivors, and occupationally and environmentally exposed groups. The authors concluded that human health was not significantly affected by transgenerational effects of radiation, perhaps because these effects might be restricted to relatively short times post-exposure and because conception shortly after exposure was rare.

VII. FUTURE RESEARCH

149. The Committee recognizes that continued research is needed to identify the full scope and expression of effects, mechanisms, differences in radiosensitivity and risk of exposure in children as compared to adults. This is necessary because for a number of studies (such as those on the atomic bombing survivors, on children exposed after the Chernobyl accident to radioiodine and on patients who have had CT scans), the lifetime results remain incomplete. Future long-term studies following childhood exposure will face significant difficulties owing to unlinked health records, administrative and political barriers, as well as ethical and privacy considerations.

150. There also is a need for development of statistically sufficient projections of lifetime risk for specific cancer types following exposure at young ages. Current ERR and EAR estimates do not adequately capture the subtleties of both attained age and time since exposure.

151. Important areas of future research include evaluation of potential radiation effects on children *(a)* in areas of high radon and other natural background exposure; *(b)* after CT scans and high dose medical interventional fluoroscopy; and *(c)* after cancer radiotherapy (including potential interaction with other therapies). Moreover, the Committee identified other areas of research that may prove useful, including development of radiation dose databases for children who can be tracked in the long term, and evaluation of juvenile organ-specific and partial organ-volume effects. Studies at the molecular, cellular, tissue and juvenile animal level are likely to be informative and should include consideration of developmental effects on the cellular organization of tissues, the response of tissues and cells to radiation damage, and identification of cells at risk. Application of the range of available proteomic, genomic and metabolomic technologies may be beneficial.

VIII. SUMMARY AND CONCLUSIONS

152. The effects of radiation exposure during childhood or adolescence as compared to those during adulthood is a complex matter. The commonly held notion that children might be two–three times more sensitive to radiation than adults is true for some health effects but certainly not for all. Published models assuming that after radiation exposure, the same increased relative risk of carcinogenesis in children as in adults applies to nearly all tumour types are overly broad generalizations without clear scientific support. In fact, for a few effects (e.g. lung cancer), children are more resistant than adults.

153. While there are clear instances of increased risk of some tumours (e.g. leukaemia, breast and brain cancer) in children compared to adults, there are other tumour types (e.g. bladder cancer) for which there appears to be little or no difference in risk by age at exposure, and some in which the published models are not supported by the data. Similar conclusions regarding age dependency for adverse health risks can be drawn from the data on deterministic effects. For many of these effects, there are significant variations in magnitude during the span from infant, through childhood and into adolescence. Thus, in a discussion of effects of childhood radiation exposure, generalizations are best avoided and attention should be directed to the specifics of the exposure, age at exposure, absorbed dose to certain tissues, attained age at the time of assessment, and the particular effects of interest.

(a) The reason for these differences is easy to explain for some effects (e.g. the developmental and physiological status of the brain) while in many other instances, the reason for different effects in children versus adults is not known. An accurate assessment of risks to children would involve identifying the specifics of the exposure, the situation in which the exposure occurred, and variables relating to the host. More knowledge will be obtained with longer follow-up of the survivors of the atomic bombings and childhood cancer. It also is recognized that, currently, a number of epidemiological studies are under way—which may yield information in the next decade—regarding exposure from CT scans in childhood and possible induction of neoplasms. For a given radiation dose, children are generally at more risk for tumour induction than are adults. Cancers that may be induced following radiation exposure at young ages could occur within a few years but also decades later. In the 2006 Report to the General Assembly, the Committee stated that lifetime cancer risk estimates for those exposed as children were uncertain and might be a factor of two–three times higher than estimates for a population exposed at all ages. This conclusion was based upon a lifetime project model combining all tumour types.

(b) The Scientific Committee has reviewed evolving scientific material and notes that, after radiation exposure, tumour induction in children compared to adults is quite variable and depends on the tumour type, age and sex. The term “radiation sensitivity” with regard to cancer induction refers to the rate of radiogenic tumour induction and does not refer to the degree of malignancy. Broadly, for about 25% of tumour types, children are clearly more radiosensitive regardless of the model. These include leukaemia, and thyroid, skin, breast and brain cancer. For some of these sites, depending upon the circumstances, the risks for children compared to adults can be quite high. Risks may also vary significantly at different ages during childhood. Some of the tissue sites are very important for evaluation of exposures from accidental and medical situations.

(c) For about 15% of tumour types (such as bladder cancer) children appear to have about the same radiosensitivity for tumour induction as adults. For about 10% of tumour types (e.g. lung cancer), children appear less sensitive to external radiation exposure than adults. For about 20% of tumour types (including oesophagus cancer), the data are too weak to draw a conclusion regarding differences in risk with age at exposure. Finally, for about 30% of tumour types (including

Hodgkin's lymphoma, prostate, rectum and uterus cancer), there is only a weak or no relationship between radiation exposure and risk at any age of exposure.

(d) At present, there are no statistically sufficient projections of lifetime risk for specific tumour sites following exposure at young ages. Currently used estimates do not adequately capture the known variations and additional work is needed.

154. For direct effects (deterministic) that occur after high acute or high fractionated doses, the differences between exposure in childhood and in adulthood are complex and can be explained by the interaction of different tissues and pathways. These effects may be seen after radiation therapy or following accidental exposure. "Radiation sensitivity" of children versus adults for deterministic effects in a specific organ is often different from that for tumour induction. There are some instances in which childhood exposure poses more risk than adulthood exposure (e.g. for cognitive defects, cataracts and thyroid nodules). There are other instances where the risk appears to be about the same (e.g. neuroendocrine and kidney) and there are a few instances where children's tissues are more resistant (e.g. lung function, marrow and ovarian failure).

155. Because of the above considerations, the Committee recommends that in a discussion of effects of childhood radiation exposure, generalizations are best avoided and attention should be directed to the specifics of the exposure, age at exposure, absorbed dose to certain tissues, attained age at assessment, and the particular end points of interest.

156. There have been many human studies of possible heritable effects following radiation exposure; these studies were reviewed by the Committee in 2001. It has been generally concluded that no heritable effects in humans due to radiation exposure have been identified (specifically in studies of offspring of atomic bombing survivors). Over the past decade, there have been additional studies that have focused on survivors of childhood and adolescent cancer, and gonadal doses from radiotherapy are often very high. There is essentially no evidence of an increase in chromosomal instability, minisatellite mutations, transgenerational genomic instability, change in sex ratio of offspring, congenital anomalies or increased cancer risk in the offspring of parents exposed to radiation.

157. Heath effects and risks depend upon a number of physical factors. Regarding external radiation exposure, because children have smaller body diameters and there is less shielding by overlying tissues, for a given external exposure the dose to children's internal organs will be higher than for an adult. Also, because they are shorter than adults, children may receive a higher dose from radioactivity distributed on the ground. These factors are important when considering doses to populations in some areas (such as those around the Chernobyl and Fukushima-Daiichi nuclear power plants, areas of high natural background) with elevated levels of radionuclides on the ground. In medical exposure, children may receive significantly higher doses than adults for the same examination if the technical parameters are not specifically adapted.

158. Regarding exposure from sources of radiation inside the body (internal exposure), because of the smaller size of infants and children—and, therefore, because their organs are closer together—there is more opportunity for radionuclides concentrated in one organ to irradiate other organs. There are also many other age-related factors with regard to metabolism and physiology that make a substantial difference in dose with age. Several radionuclides are of particular concern regarding internal exposure of children. In a nuclear power plant accident, radioiodines are significant sources of exposure, which have potential to induce thyroid cancer. The dose to the thyroid for infants is larger by a factor of eight or nine than it is for adults. For a dose from ^{137}Cs, there is very little difference between children and adults. Internal exposure of children also occurs in the medical use of radionuclides. The spectrum of examinations normally performed on children is different from that performed on adults. Potentially

higher doses in children, in practice, are offset by the use of a lower amount of administered radioactivity.

159. Developmental processes and mechanisms give rise to differences between children and adults both for the absorbed dose from a given exposure to a source of ionizing radiation and for the resulting effects on health. The Scientific Committee recognizes that continued research is needed to identify the full scope and expression of effects and risk from exposure in childhood as compared to adulthood. This is necessary because for a number of studies (such as those on the atomic bombing survivors, on children exposed after the Chernobyl accident to exposure from radioiodine and on patients who have had CT scans), the lifetime results remain incomplete. Future long-term studies following childhood exposure will face significant difficulties because of unlinked health records, administrative and political barriers and ethical and privacy considerations.

160. Important areas of future research and work include evaluation of potential radiation effects on children in areas of high radon and other natural background exposure, effects of high dose medical interventional fluoroscopy procedures, and effects of cancer radiotherapy (including potential interactions with other therapies), development of radiation dose databases that can be combined and tracked long term, and evaluation of juvenile organ-specific and partial volume effects. Studies at the molecular, cellular, tissue and whole organism level are likely to be informative and should include consideration of developmental effects on the cellular organization of tissues, the response of tissues and cells to radiation damage, and identification of cells at risk. Application of the range of available 'omics technologies may be beneficial.

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APPENDIX A. DOSIMETRY

I. INTRODUCTION

A1. This appendix gives a short overview on dosimetric quantities and describes differences between children and adult doses for external and internal exposure from environmental and medical sources. The differences in radiation effects and absorbed dose for the same radiation exposure can result from some of the developmental processes and anatomical differences. This appendix deals with factors regarding dosimetric differences between children and adults, and discusses the dosimetric aspects for external and internal exposures.

A. Dose quantities and units

A2. The absorbed dose, D, is defined as the quotient of d$\bar{\varepsilon}$ by dm, where d$\bar{\varepsilon}$ is the mean energy imparted to matter of mass dm by ionizing radiation, that is

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

The SI unit is joules per kilogram (J kg^{-1}) and its special name is gray (Gy).

A3. In calculations for radiation protection purposes, the absorbed dose is generally averaged over a target region r_T, either a target organ (e.g. liver or kidneys) or a target tissue (e.g. muscle), $D(r_T)$. In some cases, averaged doses to radiosensitive regions of an organ or tissue instead of doses to the whole organ or tissue are considered. Examples for this are the walls of the human respiratory tract [I14] and the human alimentary tract [I24], the skeleton (consideration of a 10 µm thin layer at the surface of the bone), and the skin (a thin layer at a depth of 70 µm from the skin surface) [I7].

A4. Some types of radiation are biologically more effective than others in causing cancer or cancer-related end points [I25]. For radiation protection purposes, ICRP makes simple adjustments to reflect these differences using radiation weighting factors, w_R, and by the introduction of the term *equivalent dose*. The equivalent dose to a target organ or target region r_T, $H(r_T)$, is defined by

$$H\left(r_T\right) = \sum_R w_R \cdot D_R\left(r_T\right)$$

where $D_R(r_T)$ is the mean dose to the target organ or tissue r_T due to radiation type R and w_R the radiation weighting factor. Because w_R is dimensionless, the SI unit of the equivalent dose is also joules per kilogram (J kg^{-1}), but its special name is sievert (Sv).

A5. The radiation weighting factors used by the ICRP are 1 for photons and electrons, and 20 for alpha particles [I11, I25]. It should be noted that these simple adjustments made in the calculation of

equivalent dose for protection purposes do not fully reflect the extent of scientific knowledge, with evidence, for example, for differences in low-LET radiation (photons and electrons) according to their energies [I25]. For alpha particle irradiation, there is evidence for different relative biological effectiveness (compared with low-LET radiation) for different biological end points, including different cancer types.

A6. In internal dosimetry, the *committed equivalent dose*, i.e. the equivalent dose delivered over a defined period, T_D, is considered:

$$H\left(r_T, T_D\right) = \int_0^{T_D} \dot{H}\left(r_T, t\right) dt$$

where $\dot{H}\left(r_T, t\right)$ is the equivalent dose rate in the target organ or tissue r_T at time t. In general, T_D is taken to be 50 years for adults and the time until the age of 70 years for infants, children and adolescents. Because of the rather short half-lives of the radionuclides used in nuclear medicine, T_D is taken to be infinite in those applications.

A7. The effective dose provides a measure for the radiation-induced detriment like cancer and hereditary effects. It is a weighted mean value of the tissue doses with tissue weighting factors w_T that reflect contributions to total cancer detriment. The sum over all tissue weighting factors is 1 with, for example, values of 0.12 for lung and colon. The tissue weighting factors of ICRP Publication 60 have still been used in this report [I11].

A8. In the methodology of ICRP Publications 26 and 60 [I7, I11] the effective dose E is:

$$E = \sum_T w_T \cdot H\left(r_T\right)$$

A9. The tissue weighting factors are mean values for the whole population of both sexes and all ages. Therefore, the same tissue weighting factors are applied to children and adults. Furthermore, tissue weighting factors are simplified rounded values in which organs/tissues are grouped and assigned one of a few weighting factors. For these reasons, the effective dose cannot be used to quantify the radiation risk to individuals and specific groups such as children. For the assessment of the radiation risk for individuals or groups of children, organ-absorbed doses have to be used in combination with data on the biological effectiveness of the respective ionizing radiation and tissue-specific risk coefficients.

B. Dose coefficients

A10. Dose coefficients give the (organ or effective) dose per unit intake for internal exposure and, for example, per unit activity concentration in air or per unit activity on a unit area on the ground for external environmental exposure.

A11. For internal exposure, age-dependent effective dose coefficients for members of the public are given in ICRP Publication 119 [I30] for ingestion and inhalation. For the application of radiopharmaceuticals, organ and effective dose coefficients are given in ICRP Publications 53, 80 and 106 [I9, I20, I27]. All these dose coefficients give the committed absorbed organ dose (for patients), the

committed equivalent organ dose (for members of the public) or the committed effective dose per unit intake. For a known intake, the doses can be calculated by multiplication of the intake and the dose coefficient. The dose coefficients for internal exposure also take into account the contribution from any daughter radionuclides that are formed within the body.

A12. For external exposure, dose rate coefficients are given for adults in ICRP Publication 74 [I19] and for environmental sources in air, water, and soil in Eckerman and Ryman [E6]. For the calculation of dose, these dose coefficients must be multiplied by the amount of exposure (e.g. the activity per unit area on the ground) and the exposure time.

II. EXTERNAL EXPOSURE

A13. External exposure may be due to radionuclides in the environment (irradiation by radionuclides in the air, i.e. submersion, or by radionuclides deposited on the ground) or to medical exposure (in radiological examinations by radiography, fluoroscopy or CT, or by radiotherapy).

A. Environmental exposure

A14. Doses to children from submersion or by irradiation from the ground are larger because of the smaller distances between organs and body surface and, in the case of irradiation from the ground, additionally by the shorter distances between the organs and the radiation source (table A1).

Table A1. Age-related correction factors for submersion and irradiation from ground dependent on gamma energy

Adapted from [B19]

	Age-related correction factors					
	≤1 year	*1–2 years*	*2–7 years*	*7–12 years*	*12–17 years*	*>17 years*
Submersion >200 keV	1.4	1.4	1.3	1.2	1.1	1.0
Submersion ≤200 keV	1.8	1.7	1.5	1.3	1.1	1.0
Irradiation from the ground; >200 keV	1.6	1.5	1.3	1.2	1.1	1.0
Irradiation from the ground; ≤200 keV	1.7	1.6	1.4	1.3	1.1	1.0

A15. Drexler et al. [D47] and Petoussi et al. [P28] noted that the dose to organs from external radiation increases with decreasing body size. This effect is more pronounced at low photon energy, and for organs located near the middle of the body, which are shielded by overlying tissues. Petoussi et al. [P28] also noted that doses to the organ of an infant may be about 40% higher for energies larger than 100 keV. Below 100 keV the difference may approach a factor of three for deeper organs such as the ovaries and colon.

A16. Yamaguchi [Y3] calculated dose rate coefficients for six age groups (newborn, 1-, 5-, 10-, 15-year-old and adult) under five irradiation geometries. For isotropic radiation fields, effective dose coefficients for newborns and one-year-old infants normalized to kerma in free air were about 20–30% higher than those for adults at energies above 115 keV.

A17. Recently, calculations of external dose rate coefficients have been performed for various individuals whose CT images were segmented to voxel models. For the daughter nuclide ^{137m}Ba of ^{137}Cs, a correction factor of 1.3 for an eight-week-old infant was derived for submersion and irradiation from the ground [P27].

B. Medical radiation uses

A18. External doses received during medical examinations depend on the examination type, the equipment used, the dose settings applied, and the patient's size and the illness. In order to monitor the amount of radiation imparted during an examination, most modern equipment is equipped with dosimetric devices. This enables the assessment of patient dose, and the comparison with diagnostic reference levels (DRLs) that have been introduced by ICRP Publication 73 [I18]—as an indication whether, in routine conditions, the patient dose from a specified procedure is unusually high or low for that procedure.

A19. However, the dose quantities used for this purpose are given in terms of air kerma or absorbed dose to standard phantoms only. In order to assess patient-related dose quantities—such as organ dose and effective dose—appropriate conversion factors have to be applied, which have to take into account differences in patient size and organ position between adult and paediatric patients. The assessment of organ doses is quite cumbersome and can best be achieved using appropriate dose calculation software.

A20. For conventional X-rays imaging techniques, i.e. radiography and fluoroscopy, the dose quantities used are the same, but the dose levels in fluoroscopy are significantly higher. Cross-sectional imaging techniques, such as CT, require different dose quantities for monitoring radiation exposure. Contrary to radiation protection aspects in diagnostic radiology, application of the prescribed dose to the target volume is intended in radiotherapy, necessitating dedicated therapy planning.

A21. All computational methods and software solutions presented in this appendix refer to standard patients of the specified age and size. Depending on the actual anatomy, individual doses—in particular doses to organs that are not or not fully covered by the X-rays beam—may deviate from the calculated values.

1. Radiography

A22. In radiography, the most common dose descriptor used for dose monitoring is the air kerma-area product (KAP). The KAP is an integral dose quantity that combines both the incident air kerma (IAK), i.e. "intensity", and the extension of the irradiation. As long as backscatter from the patient to the KAP meter can be neglected, the KAP is independent from the distance between the radiation source and the patient and it can conveniently be measured using flat ionization chambers attached to or integrated into the beam-limiting device. Alternatively, the KAP can also be calculated from the exposure and collimator settings. KAP values are displayed at or close to the operator's console and are documented in the dose report or in the structured report that is provided on modern equipment.

A23. The measurement of local dose—i.e. IAK or entrance surface dose (ESD), including backscattered radiation—requires dose meters attached to the patient's surface. Either thermoluminescent dosimeters (TLDs) or small semiconductor probes can be used for this purpose. Owing to the inconvenience associated with this procedure (time and cost), the assessment of local dose is not routinely applied, but rather restricted to dedicated studies.

A24. To illustrate typical dose levels in paediatric radiography, recommendations for the most frequent types of examination from a number of European countries are listed in table A2. DRLs for paediatric radiographs were established in the United Kingdom [N44] as ESD values, in Germany [B21] as KAP values and in Austria [H64] as both ESD and KAP values.

Table A2. Comparison of European recommendations for DRLs in paediatric radiography

Examination	*Age (years)*	*Europe [E4]*	*UK [N44]*	*Austria [H64]*		*Germany [B21]*
		ESD (mGy)			*KAP (Gy cm²)*	
Abdomen	0			0.10		
	1	0.70	0.40	0.172	0.035	0.20
	5	1.00	0.50	0.511	0.110	0.25
	10		0.80	0.966	0.360	0.35
	15		1.20			
Thorax AP/PA	0	0.08	0.05	0.055	0.017	0.005
	1	0.135	0.05	0.069	0.023	0.015
	5	0.10	0.07	0.082	0.026	0.025
	10		0.12	0.108	0.037	0.035
	15			0.112	0.073	
Skull AP/PA	0			0.379		
	1	1.69	0.80	0.69	0.10	
	5	1.54	1.10	0.880	0.19	0.20
	10		1.10	0.998	0.31	0.30
	15		1.10	1.123	0.37	
Skull lat	0			0.294	0.08	
	1		0.50	0.70	0.23	0.20
	5	1.078	0.80	0.506	0.20	0.25
	10		0.80	0.557	0.25	
	15		0.80	0.676	0.33	

A25. A rough estimate of the effective dose (E) can be made by multiplying the KAP with an appropriate conversion factor (normalized value of effective dose per unit KAP) k:

$$E = KAP \times k$$

The conversion factor must at least account for differences in radiation sensitivity between different body regions (head, neck, chest abdomen, pelvis and extremities) and also for size- or age-related effects (adults, children of different age). An example of conversion factors for three common examinations (chest, abdomen and pelvis/hips) and different age groups (adults and five paediatric age groups from newborn to 15 years old) is shown in table A3. Depending on the patient's size, the conversion factors vary by one order of magnitude, with the highest values for newborn.

Table A3. Normalized values of effective dose per kerma-area product ("k factors") for estimation of effective dose to children and adults for three frequent types of radiographic examinations

Adapted from [W8] using ICRP Publication 60 [I11] for the estimation of effective dose; total beam filtration used is 3 mm Al

Examination	*k factors*					
	Newborn	*1 year*	*5 years*	*10 years*	*15 years*	*Adults*
CHEST PA						
Voltage (kV)	70[a]	73	75	80	80	86
K (mSv/Gy cm^2)	2.2[a]	0.58	0.41	0.28	0.16	0.15
ABDOMEN AP						
Voltage (kV)	60	60	80	80	85	75
K (mSv/Gy cm^2)	2.0	0.91	0.64	0.40	0.28	0.20
PELVIS/HIPS AP						
Voltage (kV)	60	60	70	75	80	71
K (mSv/Gy cm^2)	2.2	1.1	0.60	0.28	0.21	0.22

[a] *AP: Anterior-posterior.*

A26. For the purposes of estimating effective dose in radiography, this quick method has two major drawbacks: *(a)* because the KAP is based on IAK, the conversion factors are strongly dependent on beam quality, i.e. on differences in tube voltage settings and total beam filtration [G23, S116]; *(b)* although with units of μGy m^2, meanwhile, a standardized unit for the KAP exists, other combinations of dose and area units (Gy cm^2, dGy cm^2, cGy cm^2, mGy cm^2) are also used on dose displays, in dose reports and conversion factor tables, which can easily lead to errors of one order of magnitude or even more.

A27. Assessment of organ doses requires tables with conversion factors for various types of examinations, different combinations of tube voltage and total beam filtration, and different age groups. The most commonly used source that serves for both adult and paediatric patients has been published in report NRPB-R279 [H26]. In order to calculate organ dose H_T, either ESD or the IAK, depending on the input requirements of the conversion factor table, has to be multiplied with the appropriate conversion factors k_T:

$$H_T = ESD \cdot k_T \quad \text{or} \quad H_T = IAK \cdot k_T$$

Some of the required input dose quantities are interrelated, namely:

$$ESD = IAK \cdot BSF \quad \text{or} \quad IAK = KAP/A \cdot \left(FID/FSD\right)^2$$

with BSF = backscatter factor, FSD = focal spot-to-skin distance, FID = focal spot-to-image receptor distance, and *A* = irradiated field size at the image receptor. Backscatter factors for various conditions of irradiation (field size, object thickness, beam quality) are tabulated in [D40].

A28. Organ and effective dose assessment is greatly facilitated when making use of dedicated software. Comprehensive software solutions have been released such as CalDose_X online, which is a web-based Monte Carlo application [K48] and PCXMC, a versatile Monte Carlo program [T5]. The latter program calculates organ and effective doses according to both ICRP 60 and ICRP 103 tissue weighting factors. The anatomical data are based on mathematical hermaphrodite phantom models [C51], representing patients in six different age groups: newborn, 1-, 5-, 10-, 15-year-old and adult patients. These phantoms were modified to some extent in order to make them more realistic for external irradiation conditions. PCXMC allows a free adjustment of the X-rays beam projection and other examination conditions of projection radiography and fluoroscopy. A considerable advantage of this program is that the phantom sizes are adjustable at will to a patient's weight and height.

2. Fluoroscopy

A29. As in radiography, the most common dose descriptor used for dose monitoring in fluoroscopy is the KAP, representing the integral dose. To illustrate typical dose levels in paediatric fluoroscopy, KAP values for three common paediatric fluoroscopic examinations are given in table A4. However, owing to new technical developments during recent years, the KAP values given in table A4 may now be much lower. For micturating cysto-urethrography in the first year of life, for example, KAP values lower by more than a factor of 10 have been reported recently by Schumacher and Allmendinger [S42] when pulsed digital fluoroscopic equipment was used.

A30. As the dose levels in fluoroscopy are significantly higher than those in simple radiographic examinations, particularly during interventional procedures, local dose is of interest, too, to prevent deterministic skin injuries. For this purpose, a patient entrance reference point is defined by the manufacturer in relation to the mechanical construction of the system. According to the relevant IEC standard [I31], the interventional reference point (IRP) is located from the isocentre towards the X-rays tube for any source-to-image receptor distance. The IRP is intended to represent the location where the X-rays beam enters the patient's skin surface, but seldom coincides with the patient's actual skin position. Dose rate and cumulative dose at the IRP are displayed where the operator can see them during the performance of the procedure and are documented in the examination report after the procedure has been finished.

A31. Methods for the assessment of effective and organ doses are identical to those used in radiography. However, as fluoroscopy is a dynamic imaging procedure, the varying irradiation conditions during the procedure (beam quality, field size, X-rays beam projection, dose rate) make dose calculations more complex. Under these circumstances, even the use of dedicated software programs will result in only rough estimates, particularly for the doses to organs that are not fully covered by the X-rays beam.

Table A4. Different KAP values for three common paediatric fluoroscopic examinations
Adapted from [H27]

Examination	*Age (years)*	*KAP per examination (Gy × cm²)*
Micturating cystourethrography	0	0.43
	1	0.81
	5	0.94
	10	1.64
	15	3.41
Barium meal	0	0.76
	1	1.61
	5	1.62
	10	3.19
	15	5.67
Barium swallow	0	0.56
	1	1.15
	5	1.01
	10	2.40
	15	3.17

3. Computed tomography

A32. In CT, volume computed tomography dose index ($CTDI_{vol}$) and dose-length product (DLP) are routinely used as descriptors for dose monitoring. Contrary to the situation with the KAP, the units used (mGy and mGy cm, respectively) are unequivocal. While $CTDI_{vol}$ represents the local dose, DLP serves an integral dose quantity that combines both the "intensity" ($CTDI_{vol}$) and the scan length (L), i.e. the extension of the irradiation (analogue to the KAP in conventional X-rays imaging). Both quantities are calculated from the exposure settings ("scan protocol") and are displayed on the operator's console and documented in the examination report.

A33. Contrary to IAK and KAP, which are measured free-in-air, $CTDI_{vol}$ and DLP refer to absorbed dose in standard PMMA phantoms: a "head phantom" with 16 cm diameter representing the patient in head examinations of adults ($CTDI_{vol}$–16), and a "body phantom" with 32 cm diameter for examinations in the trunk region of adults ($CTDI_{vol}$–32). For the same exposure settings, $CTDI_{vol}$–16 amounts to approximately twice the corresponding $CTDI_{vol}$–32.

A34. While $CTDI_{vol}$–16 is better suited to represent the smaller size of paediatric patients up to 10 years, the $CTDI_{vol}$ displayed on the console and in the examination report up to now depends on the applied scan mode only. As a consequence, $CTDI_{vol}$-32 and DLP-32 are used regardless of the patient's size for scans in the trunk region (abdomen, chest) performed in body scanning mode.

A35. In order to avoid misinterpretation, newer scanners (or those updated with a newer scanner software) explicitly state the underlying standard phantom diameter. In cases where no statement of the underlying phantom diameter is given, $CTDI_{vol}$ and DLP for examinations in the trunk region usually refer to the 32 cm standard phantom. However, this may not be valid for scanners that apply a different beam shaping filter that better fits to smaller patient diameters.

A36. To illustrate typical dose levels in paediatric CT examinations, the German DRLs [B21], based on a nationwide survey on paediatric CT practice in 2005/2006 [G2], are given in table A5. For patients up to 10 years, $CTDI_{vol}$ and DLP values are stated for both standard phantom sizes. These values, which are orientated to the relatively high corresponding German DRLs for adults, can be significantly lowered if scan protocol optimization is applied as the current Swiss DRLs showed [B1].

Table A5. German dose reference levels for paediatric CT examinations

$CTDI_{vol}$ and DLP are based on both 16 cm and 32 cm standard phantom measurements; adapted from [B21]

Examination	*Age or weight group*	*$CTDI_{vol}$-16 (mGy)*	*$CTDI_{vol}$-32 (mGy)*	*DLP-16 (mGy cm)*	*DLP-32 (mGy cm)*
Cranium	Newborn	27	n.a.	300	n.a.
	≤1 year	33	n.a.	400	n.a.
	2–years	40	n.a.	500	n.a.
	6–10 years	50	n.a.	650	n.a.
	11–15 years	60	n.a.	850	n.a.
	>15 years	60	n.a.	950	n.a.
Mid-face	Newborn	9	n.a.	70	n.a.
	≤1 year	11	n.a.	95	n.a.
	2–5 years	13	n.a.	125	n.a.
	6–10 years	17	n.a.	180	n.a.
	11–15 years	20	n.a.	230	n.a.
	>15 years	20	n.a.	250	n.a.
Chest	Newborn (≤5 kg)	3	1.5	40	20
	≤1 year (6–10 kg)	4	2	60	30
	2–5 years (11–20 kg)	7	3.5	130	65
	6–10 years (21–30 kg)	10	5	230	115
	11–15 years (31–50 kg)	n.a.	8	n.a.	230
	>15 years (51–80 kg)	n.a.	12	n.a.	400
Abdomen w. pelvis	Newborn (≤5 kg)	5	2.5	90	45
	≤1 year (6–10 kg)	7	3.5	170	85
	2–5 years (11–20 kg)	12	6	330	165
	6–10 years (21–30 kg)	16	8	500	250
	11–15 years (31–50 kg)	n.a.	13	n.a.	500
	>15 years (51–80 kg)	n.a.	20	n.a.	900

A37. Like in conventional X-rays imaging, a rough estimate of the effective dose *E* can be made by multiplying the integral dose quantity (i.e. DLP) with an appropriate conversion factor *k*:

$$E = DLP \cdot k$$

As the DLP refers to absorbed dose in phantoms (unlike the KAP, which refers to IAK), differences in beam quality are almost negligible in CT. The most widely used set of conversion factors for paediatric CT examinations has been published by Shrimpton et al. [S73] and has subsequently been adopted by AAPM report 96 [A1]. The corresponding values are listed in table A6. Special attention is required when applying these conversion factors for paediatric examinations of the neck and trunk region of patients up to 10 years, as the factors assume DLP–16. If the scanner's dose display and examination report are given in terms of DLP-32 in these cases, the dose values have to be multiplied by two—thus converting DLP–32 into DLP-16 values—before applying the conversion factors.

Table A6. Normalized values of effective dose per DLP ("k factors") over various body regions and standard patient ages

Adapted from [A1]. Conversion factors for adult head and neck and paediatric patients assume use of the head CT dose phantom (16 cm). All other conversion factors assume use of the 32-cm diameter CT body phantom

Body region	*k factors (mSv mGy^{-1} cm^{-1})*				
	Newborn	*1 year old*	*5 year old*	*10 year old*	*Adult*
Head and neck	0.013	0.0085	0.0057	0.0042	0.0031
Head	0.011	0.0067	0.0040	0.0032	0.0021
Neck	0.017	0.012	0.011	0.0079	0.0059
Chest	0.039	0.026	0.018	0.013	0.014
Abdomen and pelvis	0.049	0.030	0.020	0.015	0.015
Trunk	0.044	0.028	0.019	0.014	0.015

A38. The conversion factors given in table A6 refer to the organ-weighting scheme of ICRP 60. As the subdivision into body regions is fairly rough, the differences between that scheme and the new organ-weighting scheme of ICRP 103 are normally small (up to ±10%) except for pelvis where ICRP 103-based k factors are lower by about 25% [D30]. For more restricted scan regions with a few highly-weighted organs (e.g. the mamma in cardiac CT examinations), the difference between ICRP 60- and ICRP 103-based assessment of effective dose is significantly larger.

A39. Assessment of organ doses requires tables with conversion factors for different age groups and different types of scanners. Zankl et al. [Z2] provide a full set of conversion coefficients for paediatric patients which are based on Monte Carlo simulations using voxel phantom data, but for an eight-week-old infant ("BABY") and a seven-year-old child ("CHILD") and for one specific type of scanner only. Although newer Monte Carlo based data for mathematical phantoms representing more refined age groups (newborn, 1, 5, 10, 15 years, and adults) have been calculated later for a total of three types of scanners [K29], the full set of these data has not been made available up to now.

A40. The conversion factors *k* (organ z) in the tables of Zankl et al. [Z2] are listed in increments of 1 cm along the patients longitudinal axis ("z axis") for various organs. In order to calculate organ dose H_T, the contributions from all slices along the scan range (from position z− to z+) have to be summed up, multiplied with the $CTDI_{free\text{-}in\text{-}air}$ and corrected for pitch-related effects if the pitch factor p differs from 1:

$$H_T = {}^{1}\!/_{p} \cdot CTDI_{free-in-air} \cdot \sum_{z-}^{z+} k\left(organ, z\right)$$

As $CTDI_{free\text{-}in\text{-}air}$ is neither displayed on the scanner's console nor documented in the examination report, it has to be deduced from $CTDI_{vol}$ using the equations:

$$P_H = \frac{CTDI_{w,H}}{CTDI_{free-in-air}}\ ,\ P_B = \frac{CTDI_{w,B}}{CTDI_{free-in-air}} \text{ and } CTDI_w = p \cdot CTDI_{vol}$$

where P_H and P_B are the phantom factors for either the standard head (H) or body (B) phantom, and $CTDI_w$ is the weighted CTDI. And as the conversion factors apply to one particular type of scanner only, appropriate corrections for different beam qualities and beam shaping filters have to be applied by using scanner-specific correction factors k_{CT}. These factors and also phantom factors have been published for a large number of scanners by Nagel et al. [N3].

A41. The calculation of organ doses is significantly facilitated by using dedicated CT dose calculation software. For paediatric CT, the CT-Expo software serves these purposes [S109]. This Excel-based program provides sex-specific organ and effective dose calculation for a large number of existing scanners. However, as the software is based on the tabulated conversion coefficients from Zankl et al. [Z2], dose assessment is possible only for eight-week-old infants and seven-year-old children. The software requires selection of age group and sex, input of the upper and lower scan range limits, selection of the type of scanner and input of the exposure settings. The calculation yields all relevant dose quantities ($CTDI_w$, $CTDI_{vol}$ and DLP), all referring to the 16 cm standard phantom and also effective dose (according to both ICRP 60 and ICRP 103 [I11, I25]) and organ doses.

A42. For CT examinations such as those for other external medical exposure, the dose distribution within the body is quite inhomogeneous. Table A7 gives some age-dependent examples for organ and effective doses for chest CT examinations on the basis of exposure parameters specified as German reference levels (see table A5). It can be seen that all doses decrease with decreasing age. However, the decrease for the dose to the lungs is much more pronounced than for the dose to adjacent organs like spleen and thyroid because these are located closer to the direct beam for younger ages.

Table A7. Different organ and effective doses resulting from a chest CT examination

Calculated with CT-Expo [S109] on the basis of German diagnostic reference levels

	Infant (six week)	*Child (seven years)*	*Male adult*
Organ dose (mSv)			
Lungs	3.6	11	19
Endosteal surfaces	3.7	7.7	13
Spleen	3.4	7.2	7.4
Thyroid	1.7	12	8.0
Effective dose (mSv)	1.5	4.2	5.7

A43. As a consequence of the increased awareness of radiation exposure arising from CT examinations, it can be anticipated that other software solutions for a comprehensive paediatric dose assessment in CT, including organ doses, will become available in the next years. These might come either as stand-alone PC software, as applications for mobile devices or as web-based applications. For dose assessment of adults, these solutions are already available. Owing to the increased computational

power of today's hardware, Monte Carlo programs like PCXMC for conventional X-rays imaging should also be feasible, provided that the characteristics of the beam shaping filters, which differ from scanner to scanner, will be made available by the manufacturers.

A44. In epidemiological studies, in order to assess the risk of cancer as a function of radiation doses received from CT examinations in childhood and adolescence, individual doses to specific relevant organs need to be estimated from birth to 20 years of age. It is therefore necessary to generate a CT organ dose database with phantoms with smaller age gaps (from newborn to adults) with a realistic anatomy. In addition to the application to a wide range of patient ages for both sexes, an ongoing large European epidemiological study to quantify risks for paediatric computerized tomography and to optimize doses (EPI-CT) will include improvements in CT dosimetry [T17].

4. Radiotherapy

A45. The goal of radiotherapy is to deliver a prescribed dose to the target tissue and to keep the dose to the surrounding healthy tissues as low as possible. This goal can be achieved only by using dedicated therapy planning software systems that also calculate organ doses. The dose to be delivered to the target tissues is considered to be independent of age. The treatment parameters are assessed by computerized algorithms taking into account tumour location and size, patient size, and tissue density and shape, and are not specifically age dependent.

A46. Children treated with radiation therapy for malignancies are at risk for a spectrum of normal tissue injuries, and these toxicities are dependent on the specific region, volume, and dose delivered to the tissues, and also the developmental status of those tissues. Modern techniques attempt to reduce the high dose volumes and the most sensitive subsections of the exposed tissues in order to minimize potential damage. Techniques such as intensity modulated radiation therapy using modern treatment algorithms accomplish this but at the expense of delivering lower radiation doses to larger tissue volumes, which may pose an increased risk for induction of cancer. This requires research into *(a)* the dose-volume dosimetry in order to quantify this exposure and *(b)* long term tracking of patients in order to determine outcome.

A47. In addition, incidental radiation is delivered to the various normal tissues through *(a)* internal radiation scatter, *(b)* radiation leakage from the accelerator "head", *(c)* verification methodologies including beam films and image-guidance techniques that often involve CT and *(d)* the radiation dose from CT that are used in the simulation (treatment planning) procedures.

III. INTERNAL EXPOSURE

A48. In this section, the behaviour of incorporated radionuclides within the body and their age dependence will be described. For the quantification of the effects of this age dependence of models on doses, biokinetic and dosimetric models used by the ICRP to calculate dose coefficients [I30] will be used for illustration purposes. Some relevant examples of age-dependent dose coefficients and doses from environmental sources will be presented.

A. Models in internal dosimetry

A49. Internal doses cannot be measured; they can only be assessed using biokinetic and dosimetric models. Biokinetic models describe the deposition of radionuclides within the body, their transfer to other internal body regions and their excretion from the body. They are used to calculate the number of nuclear transformations in the various regions within the body ("source regions"). Dosimetric models are used to calculate the doses to relevant organs and tissues ("target tissues") caused by these nuclear transformations.

A50. For radiation protection purposes, the ICRP specifies the committed equivalent dose to a target tissue r_T, calculated by:

$$H\left(r_T, T_D\right) = \sum_{r_S} \int_0^{T_D} A\left(r_S, t\right) \cdot S_w\left(r_T \leftarrow r_S, t\right) dt$$

where $A(r_S,t)$ is the activity in the source region r_S at time t and the weighted S coefficient $S_w(r_T \leftarrow r_S,t)$ is the equivalent dose rate in r_T per unit activity in r_S. For adults, the weighted S coefficient is considered to be independent of time (age). However, age dependence applies for infants, children and adolescents because of growth and changing organ masses and distances.

A51. The weighted S coefficients are calculated by:

$$S_w\left(r_T \leftarrow r_S, t\right) = \sum_R w_R \sum_i E_{R,i} \cdot Y_{R,i} \cdot \frac{\phi(r_T \leftarrow r_S, E_{R,i}, t)}{M\left(r_T, t\right)}$$

where $E_{R,i}$ is the (mean) energy of the i^{th} nuclear transition of radiation type R, $Y_{R,i}$ is the number of the i^{th} nuclear transitions per nuclear transformation of radiation type R and ϕ $(r_T \leftarrow r_S, E_{R,i}, t)$ is the absorbed fraction—the fraction of energy $E_{R,i}$ emitted in the source region r_S at time t which is absorbed in the target organ or tissue r_T—and $M(r_T,t)$ is the mass of the target organ or tissue r_T at time t.

A52. The quotient from the absorbed fraction and the target mass is called the specific absorbed fraction:

$$\Phi(r_T \leftarrow r_S, E_i, t) = \frac{\phi(r_T \leftarrow r_S, E_i, t)}{M\left(r_T, t\right)}$$

The methods to calculate absorbed fractions are described in [C51]. While the methodology described here applies to the calculation of equivalent dose, the same principles apply to the calculation of absorbed doses to organs/tissues, the primary scientific dosimetric quantity.

B. Biokinetic models and their age dependence

A53. In general, biokinetic models are first-order compartment models. This means that the movement of a radionuclide within the body is described by compartments that represent (parts of) the source regions where the radionuclide accumulates. The retention of the radionuclide within such a compartment is described by first-order differential equations; this means that the retention (without consideration of the physical decay) can be characterized by a biological half-time (i.e. a time at which

half of the radionuclide present in such a compartment is moved to other compartments). There are biokinetic models for the alimentary tract, the respiratory tract, systemic circulation and excretion developed by the ICRP. These models and their age dependence for infants, children and adolescents are described here. It is not within the scope of this report to comment on the reliability of the models used by the ICRP. Rather, their biological basis is briefly addressed and they are used to illustrate differences in doses as a function of age at intake.

1. Models for the alimentary tract

A54. Biokinetic models for the alimentary tract describe the transfer from the input compartment (the oral cavity for ingestion of a radionuclide, the oesophagus for a radionuclide mechanically transferred to the alimentary tract from the respiratory tract or, for example, the small intestine for a radionuclide secreted from systemic circulation) to faecal excretion, and also the absorption from the alimentary tract to systemic circulation.

A55. For transit through the upper part of the alimentary tract, the transit times are largely independent of age. However, for infants, shorter transit times have been observed because of their consumption of a more liquid diet. For colonic transit, an increase in transit time with age has been observed, particularly for the first year of life [A22, C50].

A56. Absorption from the alimentary tract to blood is greatest for infants [O6] and, for some elements, higher fractional absorption values have also been observed for children and adolescents than for adults, e.g. for alkaline earth elements as shown by animal experiments [T12] with limited support from human studies [M60].

A57. The biokinetic model for the alimentary tract described in ICRP Publication 100 [I24] supersedes the gastrointestinal tract model of ICRP Publication 30 [I8], which was based on a model by Eve [E15].

A58. The gastrointestinal tract model of ICRP Publication 30 [I8] is a four-compartment model (stomach, small intestine, upper large intestine and lower large intestine). Absorption from the gastrointestinal tract to blood is considered to occur only from the small intestine and the fraction of ingested material that is absorbed to blood is called f_1. Transit between the stomach and small and large intestine compartments was considered to be independent of age and sex.

A59. The more recent ICRP model [I24] has more compartments within the tract (oral mucosa, oesophagus, three instead of two colon compartments). Transport rates through the tract are age- and sex- dependent. Table A8 shows the mean transit times according to the ICRP. Faster transit times for infants and young children are partly due to different food composition.

A60. Table A9 shows examples of age-dependent f_1 values [I13, I17], which quantify the fraction of ingested material absorbed from the small intestine to blood. This fraction can be very small (10^{-5} for insoluble plutonium compounds) but can also be very large. For example, iodine and caesium are assumed to be essentially completely absorbed. In table A9, it can be seen that there are higher fractional absorption values at younger ages for some elements.

A61. On the basis of recommendations of an OECD/NEA expert group [O6], the ICRP [I10] assumed as a default that the f_1 value for an infant in the first year of life is higher than that for adults by a factor of 2–10 if no specific information is available. As a default, the assumption made was:

– f_1 (infant) = 1 if f_1 (adult) > 0.5

– f_1 (infant) = 2 · f_1 (adult) if 0.01 ≤ f_1 (adult) ≤ 0.5

– f_1 (infant) = 0.02 if 0.001 < f_1 (adult) < 0.01

– f_1 (infant) = 10 · f_1 (adult) if f_1 (adult) ≤ 0.001.

However, it must be considered that the use of the default rule involves inherent uncertainties.

Table A8. Age-dependent mean transit times through alimentary tract

Adapted from ICRP Publication 100 [I24]

Region	*Mean transit times*				
	3 months	*1 year*	*5–15 years*	*Male adult*	*Female adult*
Oral cavity	2 s	12 s	12 s	12 s	12 s
Oesophagus[a]	4 / 30 s	7 / 40 s	7 / 40 s	7 / 40 s	7 / 40 s
Stomach	75 min	70 min	70 min	70 min	95 min
Small intestine	4 h	4 h	4 h	4 h	4 h
Right colon	8 h	10 h	11 h	12 h	16 h
Left colon	8 h	10 h	11 h	12 h	16 h
Rectosigmoid	12 h	12 h	12 h	12 h	16 h

[a] *Fast/slow compartment.*

Table A9. ICRP age-dependent f_1 values for different elements

Adapted from ICRP Publications 67 and 69 [I13, I17]

Element	*f_1 values*					
	3 months	*1 year*	*5 years*	*10 years*	*15 years*	*Adults*
Iron	0.6	0.2	0.2	0.2	0.2	0.1
Cobalt	0.6	0.3	0.3	0.3	0.3	0.1
Strontium	0.6	0.4	0.4	0.4	0.4	0.3
Barium	0.6	0.3	0.3	0.3	0.3	0.2
Lead	0.6	0.4	0.4	0.4	0.4	0.2
Radium	0.6	0.3	0.3	0.3	0.3	0.2

2. Model for the respiratory tract

A62. Inhaled aerosols containing radionuclides are partly deposited within the respiratory tract while the rest is exhaled. The fraction of the inhaled aerosol deposited in the lung depends on the physical properties of the inhaled aerosol—mainly the particle size—and on age, sex and breathing behaviour, which itself is also age-dependent.

A63. The ICRP [I14] has developed a biokinetic and dosimetric model for the human respiratory tract. While the deposition of aerosols in the various regions of the respiratory tract is age dependent,

the mechanical transfer rates (to the environment by extrinsic means, to lymph nodes and to the upper airways by mucociliar clearance) and absorption to blood are considered to be independent of age and sex. For absorption to blood, the ICRP has proposed standard absorption rates dependent on the solubility of the inhaled aerosol: there are default absorption Types F, M, and S for material that is absorbed at rates classified as fast, moderate, or slow.

A64. The fraction of an inhaled aerosol deposited in the respiratory tract depends on its physical properties and on the anatomy and physiology of the person who inhales the aerosol. It therefore also depends on the breathing pattern, which depends on the physical activity of the person, whether sleeping, sitting, or undertaking light or heavy exercise. ICRP defined the daily mix of physical activities for the age-dependent reference persons (see table A10) [I14].

Table A10. Daily distribution of time

Adapted from ICRP Publication 66 [I14]

Activity	*Daily distribution of time (h/d)*					
	3 months	*1 year*	*5 years*	*10 years*	*15 years*	*Adults*
Sleeping	17	14	12	10	10	8
Sitting	—	3.33	4	4.67	5.5	6
Light exercise	7	6.67	8	9.33	7.5	9.75
Heavy exercise	—	—	—	—	1	0.25

A65. Assuming an aerosol size with the default activity median aerodynamic diameter (AMAD) of 1 μm for the members of the public, the ICRP [I16] derived age-dependent deposition values for the extrathoracic region, in the bronchiolar, the bronchioles and in the alveolar interstitial region. These are listed in table A11. It can be seen that the total amount deposited in the respiratory tract is larger for younger age groups. The deposition in the extrathoracic region is higher for these age groups while the deposition in the alveolar region is highest for adults.

Table A11. Age-dependent deposition values in different regions of respiratory tract

Adapted from ICRP Publication 66 [I14]. The calculated values are for an activity median aerodynamic diameter of 1 μm and may be more precise than the underlying data would support

Region of respiratory tract	*Deposition values*					
	3 months	*1 year*	*5 years*	*10 years*	*15 years*	*Adults*
Extrathoracic	0.482	0.484	0.397	0.406	0.320	0.339
Bronchiolar and bronchioles	0.031	0.027	0.029	0.029	0.037	0.023
Alveolar interstial	0.086	0.096	0.099	0.095	0.107	0.115
Total	0.599	0.607	0.525	0.530	0.464	0.477

3. Systemic activity

A66. Systemic biokinetic models describe the behaviour of radionuclides injected or absorbed into blood. For several elements, a shorter retention in children is known: e.g. for iodine a shorter retention time for younger ages in the thyroid, where iodine mainly accumulates, has been observed [D50, S110]

by up to a factor of about six; for caesium there is a shorter retention time in the whole body by up to almost a factor of ten [L18] which may be related to different body masses and/or potassium content. For elements with a long accumulation in the skeleton such as the alkaline earth elements, strontium and radium, a higher skeletal uptake at younger ages was observed in beagle studies [B68] which is assumed to be proportional to the calcium addition rate to bone [L19], with peaks for infants and adolescents. However, the retention time in the skeleton is lower for younger ages in relation to the bone resorption rates [L19]. There are many elements for which no age-dependent information is available.

A67. ICRP has developed age-dependent systemic models for tritium, carbon, strontium, iodine, caesium, barium, lead, radium, thorium, uranium, neptunium, plutonium, americium, and curium [I13, I17, I16].

4. Excretion

A68. The main excretion routes are via kidneys and urinary bladder to urine and via liver, gall bladder and the intestinal tract to faeces. For faecal excretion, in the generic ICRP models it is assumed that the radionuclide is transferred to the upper large intestine or to the right colon and is then transported to faecal excretion [I8, I13, I24]. It would be physiologically more correct to consider secretion into the small intestine but this would imply consideration of possible re-absorption from the small intestine, which would complicate the modelling.

A69. For urinary excretion, for infants and young children, a higher frequency of bladder voiding compared to adults has been observed [G17]. For the calculation of the activity in the contents of the urinary bladder of a member of the public, the ICRP made the simplifying assumption of first-order kinetics with a transfer rate of 12 d^{-1} for adults, which corresponds to a bladder voiding interval of four hours or to six voids per day. For young children, a more frequent bladder voiding was assumed: a bladder voiding interval of 1.5 hours for a one-year-old child and of 1.2 hours for a three-month-old infant [I13].

A70. In radiopharmaceutical dosimetry, however, because of the shorter half-lives of the radioisotopes used, a more realistic biokinetic model is used by the ICRP [I27] for urinary excretion, which takes the kinetics of filling and voiding of the urinary bladder into account. An age-dependent bladder-voiding interval is considered, which is 3.5 hours for adults and 10- and 15-year-old children, 3 hours for five-year-old children and 2 hours for one-year-old children and three-month-old infants.

C. Dosimetric models and their age dependence

A71. Dosimetric models are used to calculate energy deposition in target organs, tissues and regions within tissues as a result of radioactive disintegration occurring in source organs, tissues or regions. The weighted S coefficients $S_w(r_T \leftarrow r_S, t)$ are calculated for source regions r_S and target tissues r_T at age t. These coefficients include physical decay data of the radionuclide considered as listed—for example, by the ICRP in Publication 107 [I26]—and the specific absorbed fraction, which takes anatomical characteristics into account. The ICRP calculates SAFs for reference persons, for which the age-dependent masses of target tissues are given by ICRP Publication 89 [I22]. Then, for the calculation of weighted S coefficients, it is necessary to derive the absorbed fractions $\phi(r_T \leftarrow r_S, E_{R,i}, t)$ for a given energy $E_{R,i}$ of radiation type R and the age t.

A72. In general, for non-penetrating radiation (alpha and, to a lesser extent, beta radiation), it is assumed that the absorbed fractions are 1 for $r_T = r_S$ and 0 for $r_T \neq r_S$; that is, all energy from radioactive disintegration is deposited in the region in which the disintegration occurred. This is an adequate approximation for larger regions r_T and r_S and in these cases, the age dependence of the weighted S coefficients is related only to the age dependence of the target tissue masses. This assumption is not adequate, however, for small target regions as in the skeleton and in content/wall pairs of walled organs like the respiratory tract, the alimentary tract and the urinary and gall bladders, for which more explicit calculations have been performed to account for irradiation between regions.

A73. For penetrating radiation (mainly gamma radiation), the absorbed fractions can be derived using Monte Carlo calculations, which describe the photon transport within an anatomical phantom. For these calculations, the activity is assumed to be homogeneously distributed within the source regions, and the average doses to the target tissues are calculated.

A74. For these calculations, a family of mathematical phantoms that describe the human body—including its organs—by geometrical figures has been used. These mathematical phantoms are being replaced by more realistic voxel phantoms, which have been developed on the basis of images of real persons. The ICRP has adapted such phantoms to the anatomical characteristics of its reference persons [I22]. New ICRP reference voxel phantoms for male and female adults have been published [I28] and reference paediatric phantoms are being developed.

D. Age dependence of dose coefficients and doses to public

A75. This section provides some examples of age-dependent dose coefficients as published by the ICRP and resulting doses from environmental sources that take age-dependent intake rates into account. Table A12 shows the air inhaled per day by the reference persons of different age, according to the ICRP [I14] and the annual intake of different kinds of foodstuff by different age groups presented by the IAEA [I4]. These data are used below to compare doses for different age groups.

Table A12. Age-dependent intake rates for members of public

Inhalation values are adapted from ICRP Publication 66 [I14] and ingestion values from [I4]

	Intake rates					
	3 months	*1 year*	*5 years*	*10 years*	*15 years*	*Adults*
Inhalation rate (m^3/d)	2.86	5.16	8.72	15.3	20.1 [a]	22.2 [a]
Consumption of leafy vegetables (g/d)		58	74	79	86	94
Consumption of milk (g/d)		560	140	180	210	230

[a] *For males.*

1. Iodine-131

A76. Extensive human data are available on which to base biokinetic model structures and parameter values [I10]. The current ICRP biokinetic model for iodine [I10] is similar to that given earlier [I8]. In this model, 30% of the iodine in blood is transferred to the thyroid; the rest is excreted in

urine. Iodine is assumed to be retained in the thyroid of adults with a biological half-time of 80 days. From the thyroid, it is transported to all other tissues as organic iodine where it is retained with a biological half-time of 12 days. Twenty per cent of this organic iodine is excreted into faeces via the upper and lower large intestine while the remaining 80% is recycled to blood. The iodine is once again available to be taken up as inorganic iodine in the thyroid or excreted in urine [I13]. For children, the available human data show that iodine is retained in the thyroid and other tissues with shorter retention times (see table A13) [I10].

Table A13. Age-dependent biological half-times of iodine in thyroid and other tissues

Adapted from ICRP Publication 67 [I13]

	Biological half-times (d)					
	3 months	*1 year*	*5 years*	*10 years*	*15 years*	*Adults*
Thyroid	11.2	15	23	58	67	80
Rest of body	1.12	1.5	2.3	5.8	6.7	12

A77. Table A14 shows dose coefficients for the intake of ^{131}I for different age groups. For inhalation, absorption Type F has been used as a default [I16]. Because even the shorter biological half-times of iodine in the thyroid are longer than the physical half-life of ^{131}I (8 d), they do not have a great impact on dose. The ingestion and inhalation dose coefficients for children are higher than those for adults because of the higher specific absorbed fraction values for children, which is a consequence of their smaller organ masses. In the case of ^{131}I, the effective dose coefficient is almost exclusively determined by the dose to the thyroid. Both the dose coefficient for the thyroid and the effective dose coefficient are larger by a factor of 8–10 for infants than those for adults.

Table A14. Dose coefficients and age-dependent doses in relation to adult doses for ^{131}I

Adapted from ICRP Publications 67 and 71 [I13, I16]

	Age					
	3 months	*1 year*	*5 years*	*10 years*	*15 years*	*Adults*
Dose coefficients (Sv/Bq)						
Thyroid dose coefficient from ingestion	3.7×10^{-6}	3.6×10^{-6}	2.1×10^{-6}	1.0×10^{-6}	6.8×10^{-7}	4.3×10^{-7}
Effective dose coefficient from ingestion	1.8×10^{-7}	1.8×10^{-7}	1.0×10^{-7}	5.2×10^{-8}	3.4×10^{-8}	2.2×10^{-8}
Thyroid dose coefficient from inhalation	1.4×10^{-6}	1.4×10^{-6}	7.3×10^{-7}	3.7×10^{-7}	2.2×10^{-7}	1.5×10^{-7}
Effective dose coefficient from inhalation	7.2×10^{-8}	7.2×10^{-8}	3.7×10^{-8}	1.9×10^{-8}	1.1×10^{-8}	7.4×10^{-9}
Effective dose relative to the adult effective dose						
Inhalation	1.1	1.9	1.8	1.6	1.4	1
Ingestion of leafy vegetables		5.2	3.8	2.0	1.4	1
Ingestion of milk		20	3.0	1.8	1.4	1

A78. Because of the lower inhalation rates for children, inhalation doses from contaminated air are higher only by up to a factor of two for children. Doses from the ingestion of milk may be 20-fold higher for young children than for adults because of their higher milk consumption rate.

2. Caesium-137

A79. Caesium behaves similarly to potassium in body tissues, being taken up actively by living cells. Differences in concentration between tissues are small and systemic caesium is therefore assumed to be distributed homogeneously in the whole body in the current ICRP biokinetic model [I10]. On the basis of human data, it is assumed to be retained in the body of adults with biological half-times of 2 d (10%) and 110 d (90%). Eighty per cent of the systemic caesium is taken to be excreted in urine, and the other 20% in faeces. There is good evidence that the rates of loss of caesium from the body are greater in children than in adults and these data are reflected in ICRP model assumptions (table A15).

Table A15. Biokinetic model for caesium

Adapted from ICRP Publication 67 [I13]

	Age					
	3 months	*1 year*	*5 years*	*10 years*	*15 years*	*Adults*
Long biological half-time (d)	16	13	30	50	93	110
Short biological half-time (d)	—	—	9.1	5.8	2.2	2
Fraction of whole body activity which is cleared with the long biological half-time	1	1	0.55	0.7	0.87	0.9

A80. For ingestion and for inhalation of soluble compounds of caesium, the organ dose coefficients are quite similar because of the homogeneous distribution of caesium within the body. Table A16 shows effective dose coefficients for different age groups for ingestion and inhalation. For inhalation, absorption Type F has been used as a default [I16]. The dose coefficients are quite similar for children and adults, although greater for infants, because in general the shorter retention times in younger ages are compensated by the higher SAF values.

Table A16. Dose coefficients and age-dependent doses in relation to adult doses for ^{137}Cs

Adapted from ICRP Publications 67 and 71 [I13, I16]

	Age					
	3 months	*1 year*	*5 years*	*10 years*	*15 years*	*Adults*
Dose coefficients (Sv/Bq)						
Effective dose coefficient from ingestion	2.1×10^{-8}	1.2×10^{-8}	9.6×10^{-9}	1.0×10^{-8}	1.3×10^{-8}	1.3×10^{-8}
Effective dose coefficient from inhalation	8.8×10^{-9}	5.4×10^{-9}	3.6×10^{-9}	3.7×10^{-9}	4.4×10^{-9}	4.6×10^{-9}
Effective dose relative to the adult effective dose						
Inhalation	0.25	0.27	0.31	0.55	0.87	1
Ingestion of milk		0.57	0.58	0.65	0.91	1
Ingestion of vegetables		2.2	0.45	0.60	0.91	1

A81. As a consequence, the actual doses from the inhalation or ingestion of environmental caesium are lower for children than for adults because of lower intake rates, except for the ingestion of milk by young (one-year-old) children.

3. Strontium-90

A82. Strontium is an alkaline earth element and, for this group of elements, the ICRP has developed a generic biokinetic model [I13] with skeleton (cortical and trabecular bone surfaces and volume), liver, kidneys and other soft tissues as specified source regions. A simplified model is used for strontium without red blood cells as a separate source compartment and without liver and kidney compartments, because strontium is retained principally in the mineralised bone of the skeleton. The parameters of the model are age dependent—the main differences being in the kinetics of uptake and retention in the skeleton—and are based on knowledge of bone metabolism and a large quantity of data on the age-specific behaviour of strontium in humans [I10]. There is a larger skeletal uptake for infants and adolescents of age 15 years and a lower retention in the non-exchangeable bone volume compartments for younger ages. Moreover, the absorption from the gastrointestinal tract is higher for younger ages (see table A8).

A83. Table A17 shows dose coefficients for ingestion and inhalation (with absorption Type M) of ^{90}Sr for different age groups. The doses to bone surfaces and red marrow from ingestion are highest for three-month-old infants and for 15-year-old adolescents; the same is true for the effective dose. For inhalation, the dose to the lung (and the effective dose) increases with decreasing age mainly because of the lower masses of children.

A84. The ingestion and inhalation doses for ^{90}Sr from environmental sources are highest for 15-year-old adolescents, except for the ingestion of milk when the dose to one-year-old children is highest.

Table A17. Dose coefficients and age-dependent doses in relation to adult doses for ^{90}Sr

Adapted from ICRP Publications 67 and 71 [I13, I16]

	Age					
	3 months	*1 year*	*5 years*	*10 years*	*15 years*	*Adults*
Dose coefficients (Sv/Bq)						
Red bone marrow dose coefficient from ingestion	1.5×10^{-6}	4.2×10^{-7}	2.7×10^{-7}	3.7×10^{-7}	4.9×10^{-7}	1.8×10^{-7}
Bone surfaces dose coefficient from ingestion	2.3×10^{-6}	7.3×10^{-7}	6.3×10^{-7}	1.0×10^{-6}	1.8×10^{-6}	4.1×10^{-7}
Effective dose coefficient from ingestion	2.3×10^{-7}	7.3×10^{-8}	4.7×10^{-8}	6.0×10^{-8}	8.0×10^{-8}	2.8×10^{-8}
Red bone marrow dose coefficient from inhalation	3.1×10^{-7}	1.2×10^{-7}	7.7×10^{-8}	1.0×10^{-7}	1.3×10^{-7}	7.0×10^{-8}
Bone surfaces dose coefficient from inhalation	4.8×10^{-7}	2.1×10^{-7}	1.8×10^{-7}	2.9×10^{-7}	5.0×10^{-7}	1.6×10^{-7}
Lung dose coefficient from inhalation	8.2×10^{-7}	7.0×10^{-7}	4.3×10^{-7}	2.9×10^{-7}	2.3×10^{-7}	2.1×10^{-7}

	Age					
	3 months	*1 year*	*5 years*	*10 years*	*15 years*	*Adults*
Dose coefficients (Sv/Bq)						
Effective dose coefficient from inhalation	1.5×10^{-7}	1.1×10^{-7}	6.5×10^{-8}	5.1×10^{-8}	5.0×10^{-8}	3.6×10^{-8}
Effective dose relative to the adult effective dose						
Inhalation	0.54	0.71	0.71	0.98	1.3	1
Ingestion of milk		1.6	1.3	1.8	2.6	1
Ingestion of vegetables		6.3	1.0	1.7	2.6	1

4. Radium-228

A85. Radium is also an alkaline earth element and the ICRP alkaline earth model [I13] applies. The ICRP model is based on consideration of similarities between the alkaline earth elements and also on an extensive literature on the behaviour of strontium in adult humans, together with more limited human data for children, supplemented by animal data [I13]. In contrast to the approach used for strontium, it considers liver explicitly as a source organ.

A86. Radium-228 is used here as an illustrative example because, for this radioisotope, the infant dose coefficients are very high compared to those for adults. The age distribution of dose coefficients is similar to that for ^{90}Sr, except that there is a larger peak dose for infants, which is caused partly by a higher f_1 value. The dose coefficients are highest for infants by up to a factor of almost 60 (ingestion dose coefficient for the red bone marrow) compared to those for adults. The ingestion effective dose coefficient for infants is a factor of about 40 higher than for adults. Because of the smaller variation in lung dose, for inhalation the corresponding factors are about 9 for red marrow and 6 for effective dose.

A87. Inhalation doses from environmental sources are highest for 15-year-old adolescents; ingestion doses for children of all ages are higher than for adults, up to a factor of seven for ingestion for leafy vegetables and up to a factor of 20 for milk (table A18).

Table A18. Dose coefficients and age-dependent doses in relation to adult doses for ^{228}Ra

Adapted from ICRP Publications 67 and 71 [I13, I16]

	Age					
	3 months	*1 year*	*5 years*	*10 years*	*15 years*	*Adults*
Dose coefficients (Sv/Bq)						
Red bone marrow dose coefficient from ingestion	1.3×10^{-4}	2.1×10^{-5}	1.2×10^{-5}	1.3×10^{-5}	1.8×10^{-5}	2.3×10^{-6}
Bone surfaces dose coefficient from ingestion	8.5×10^{-4}	1.6×10^{-4}	1.1×10^{-4}	1.4×10^{-4}	2.3×10^{-4}	2.2×10^{-5}
Liver dose coefficient from ingestion	4.3×10^{-5}	9.6×10^{-6}	5.3×10^{-6}	4.7×10^{-6}	5.4×10^{-6}	1.0×10^{-6}
Effective dose coefficient from ingestion	3.0×10^{-5}	5.7×10^{-6}	3.4×10^{-6}	3.9×10^{-6}	5.3×10^{-6}	6.9×10^{-7}

	Age					
	3 months	*1 year*	*5 years*	*10 years*	*15 years*	*Adults*
Dose coefficients (Sv/Bq)						
Red bone marrow dose coefficient from inhalation	4.2×10^{-5}	2.4×10^{-5}	1.4×10^{-5}	1.0×10^{-5}	1.0×10^{-5}	4.7×10^{-6}
Bone surfaces dose coefficient from inhalation	2.7×10^{-4}	1.6×10^{-4}	1.2×10^{-4}	1.1×10^{-4}	1.3×10^{-4}	5.6×10^{-5}
Liver dose coefficient from inhalation	1.5×10^{-5}	9.2×10^{-6}	5.3×10^{-6}	3.6×10^{-6}	3.4×10^{-6}	2.4×10^{-6}
Lung dose coefficient from inhalation	4.2×10^{-5}	3.6×10^{-5}	2.2×10^{-5}	1.4×10^{-5}	1.2×10^{-5}	9.7×10^{-6}
Effective dose coefficient from inhalation	1.5×10^{-5}	1.0×10^{-5}	6.3×10^{-6}	4.6×10^{-6}	4.4×10^{-6}	2.6×10^{-6}
Effective dose relative to the adult effective dose						
Inhalation	0.74	0.89	0.95	1.2	1.5	1
Ingestion of milk		5.1	3.9	4.8	7.0	1
Ingestion of vegetables		20	3.0	4.4	7.0	1

5. Radon-222

A88. For ^{222}Rn inhalation, by far the highest dose is the lung dose—caused mainly by the radon progeny—while for ingestion the dose to the stomach wall—caused mainly by the radon gas itself—is highest. Harley [H25] calculated inhalation ^{222}Rn absorbed dose coefficients for lung regions for the one- and ten-year-old children and for adults. The dose coefficients for one- and ten-year-olds were about a factor of two higher than those for adults. Age-dependent dose coefficients for ^{222}Rn were published in NRC reports for one-, five,- ten-, and fifteen-year-olds and adults. The dose coefficients for children were higher by a factor of two to three compared to those for adults for ingestion [N40] while the dose coefficients were similar for all age groups for inhalation [N39].

A89. Age-dependent dose coefficients for ^{222}Rn and its short-lived decay products have been derived by Kendall and Smith [K23] for children aged one and ten years, and for adults. The inhalation dose coefficient for young children was higher by a factor of four to five compared to that for adults, and higher by a factor of about seven for ingestion. However, because of the lower breathing rates and water consumption rates that apply to children, the effective dose from inhalation is similar for all ages for exposure to the same air concentrations of radon and progeny.

E. Age dependence of dose coefficients and doses for patients in nuclear medicine

A90. In almost all cases, no age-dependent biokinetic parameters are known for radiopharmaceuticals [E2]. Therefore, the adult biokinetic parameters are usually applied to all ages. For radiopharmaceuticals, the ICRP published age-dependent dose coefficients in its Publications 53, 80, and 106 [I9, I20, I27]. In these publications, the ICRP uses adult biokinetic parameters for all ages with the exception of the urinary bladder for which a generic assumption for the bladder-voiding interval was applied. This is 3.5 hours for adults and ten- and 15-year-old children, three hours for five-year-old children and two hours for one-year-old children and three-month-old infants [I27].

A91. Most nuclear medicine examinations of children are kidney scintigraphies followed by scintigraphies of the skeleton and the total body. Table A19 shows the effective doses for the radiopharmaceuticals that are most frequently used for kidney scintigraphies. While for ^{99m}Tc-MAG_3 and ^{99m}Tc-DTPA, the effective dose to a one-year-old child is higher by a factor of about three compared to that for adults, it is higher by a factor of about four for ^{99m}Tc-DMSA. This is because for MAG_3 and DTPA, the urinary bladder receives the highest dose and the retention in the urinary bladder is shorter for young children while for DMSA, the kidneys receive the highest dose and the contribution of the urinary bladder to the effective dose is less.

Table A19. Effective dose coefficients for radiopharmaceuticals used for kidney scintigraphies
Adapted from ICRP Publication 106 [I27]

	Effective dose coefficients (mSv/MBq)				
	1 year	*5 years*	*10 years*	*15 years*	*Adults*
^{99m}Tc-MAG_3	0.022	0.012	0.012	0.009	0.007
^{99m}Tc-DTPA	0.016	0.009	0.0082	0.0062	0.0049
^{99m}Tc-DMSA	0.037	0.021	0.015	0.011	0.0088

A92. However, the higher doses to children are partly compensated by the lower activities administered to children. There are European recommendations [L10, L9, P32] for the fractions of the radionuclide activities used for adults that should be administered to children depending on their body weight. The latter recommendations are based on a publication by Jacobs et al. in which fractions of adult administered activities were recommended for children, which were intended to result in approximately the same effective dose for children as for adults [J7]. Recommendations for administered activities in paediatric nuclear medicine have also been issued in the United States of America [G6]. Age-dependent administered activities and the resulting effective doses are shown in table A20. It can be seen that, in most cases, the higher dose coefficients for the younger ages are compensated by lower administered radionuclide activities, resulting in quite similar doses for all ages.

Table A20. Age-dependent administered activities for radiopharmaceuticals used for kidney scintigraphies and resulting effective doses

The determined age-dependent effective doses were obtained using the German DRLs for adults [B20, B22] as a basis (100 MBq for MAG_3, 150 MBq for DTPA and 70 MBq for DMSA) and the total body weights of the ICRP reference persons [I22] and the age-dependent ICRP dose coefficients [I20]

Radiopharmaceutical	*Reference*	*Administered activities (MBq)*[a]					
		Newborn	*1 year*	*5 years*	*10 years*	*15 years*	*Adults*
^{99m}Tc-MAG_3	[P32]	15	27 (0.59)	45 (0.54)	65 (0.78)	92 (0.83)	100 (0.70)
	[L9]	15	23 (0.51)	33 (0.40)	45 (0.54)	62 (0.56)	
	[G6]	37	37 (0.81)	70 (0.84)	118 (1.40)	148 (1.30)	148 (1.00)
^{99m}Tc-DTPA	[P32]	20	41 (0.66)	68 (0.61)	98 (0.80)	138 (0.86)	150 (0.74)
	[L9]	20	38 (0.61)	65 (0.59)	102 (0.84)	150 (0.93)	
	[G6]	-	-	-	-	-	-
^{99m}Tc-DMSA	[P32]	15	19 (0.70)	32 (0.67)	46 (0.69)	64 (0.70)	70 (0.62)
	[L9]	18	33 (1.20)	48 (1.00)	64 (0.96)	70 (0.77)	
	[G6]	18.5	18.5 (0.68)	35 (0.74)	59 (0.89)	104 (1.10)	135 (1.20)

[a] *The values in parentheses are effective doses (mSv).*

F. Nuclear medicine therapy

A93. Especially in children, therapeutic applications of open radioactive sources are usually based on individual calculations of tumour, organ and tissue doses before and during therapy. This requires the delineation of tissue masses out of imaging procedures and the evaluation of individually measured biokinetic data. In some clinical units, the internal dosimetry models described above are individually adjusted to the patient. Software programs are being developed to provide dosimetric data from tomographic imaging procedures [S46].

APPENDIX B. MALIGNANT NEOPLASMS

I. INTRODUCTION

B1. It has commonly been thought that radiation exposures in childhood cause two–three times as much excess cancer as exposures in adulthood. While this may be true on average, it is an overgeneralization: for some cancers the risk is higher for exposure in childhood than in adulthood, for others it is equal and for some others it is even lower. Greater lifetime risk from exposure during childhood than from that during adulthood has two aspects. In part, it reflects greater risk per unit dose at comparable ages at risk or times since exposure for childhood exposures, but it also reflects the longer period of risk for those irradiated at younger ages since excess risk continues throughout the remaining lifetime. Radiation-induced cancers at early ages also have a long-term impact on quality of life and may induce anxiety about recurrences or other health detriments.

B2. Risks associated with age at radiation exposure may be correlated with other cancer risk factors or genetic susceptibility factors, especially in studies of risk after initial childhood cancer radiotherapy, although little is known about this possibility. A limited but growing body of data suggests that genetic variation has a role in susceptibility to genotoxic exposures, or that genetic susceptibility syndromes confer an increased risk of cancer, such as the Li-Fraumeni syndrome. Table B1 below summarizes the spectrum of neoplasms, affected genes, and Mendelian mode of inheritance of selected syndromes of inherited cancer predisposition.

Table B1. Selected syndromes of inherited cancer predisposition

Syndrome	*Major tumour types*	*Affected gene*	*Mode of inheritance*
Adenomatous polyposis of the colon	Colon, hepatoblastoma, intestinal cancers, stomach, thyroid cancer	APC	Dominant
Ataxia telangiectasia	Leukaemia, lymphoma	ATM	Recessive
Beckwith-Wiedemann syndrome	Adrenal carcinoma, hepatoblastoma, rhabdomyosarcoma, Wilms' tumour	CDKN1C/NSD1	Dominant
Bloom's syndrome	Leukaemia, lymphoma, skin cancer	BLM	Recessive
Fanconi anaemia	Gynaecological tumours, leukaemia, squamous cell carcinoma	FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG	Recessive
Juvenile polyposis syndrome	Gastrointestinal tumours	SMAD4/DPC4	Dominant
Li-Fraumeni syndrome	Adrenocortical carcinoma, brain tumour, breast carcinoma, leukaemia, osteosarcoma, soft tissue sarcoma	TP53	Dominant

Syndrome	*Major tumour types*	*Affected gene*	*Mode of inheritance*
Multiple endocrine neoplasia 1	Pancreatic islet cell tumour, parathyroid adenoma, pituitary adenoma	MEN1	Dominant
Multiple endocrine neoplasia 2	Medullary thyroid carcinoma, pheochromocytoma	RET	Dominant
Neurofibromatosis type 1	Neurofibroma, optic pathway glioma, peripheral nerve sheath tumour	NF1	Dominant
Neurofibromatosis type 2	Vestibular schwannoma	NF2	Dominant
Nevoid basal cell carcinoma syndrome	Basal cell carcinoma, medulloblastoma	PTCH	Dominant
Peutz-Jeghers syndrome	Intestinal cancers, ovarian carcinoma, pancreatic carcinoma	STK11	Dominant
Retinoblastoma	Osteosarcoma, retinoblastoma	RB1	Dominant
Tuberous sclerosis	Hamartoma, renal angiomyolipoma, renal cell carcinoma	TSC1/TSC2	Dominant
von Hippel-Lindau syndrome	Hemangioblastoma, pheochromocytoma, renal cell carcinoma, retinal and central nervous tumours	VHL	Dominant
WAGR syndrome	Gonadoblastoma, Wilms' tumour	WT1	Dominant
Wilms' tumour syndrome	Wilms' tumour	WT1	Dominant
Xeroderma pigmentosum	Leukaemia, melanoma	XPA, XPB, XPC, XPD, XPE, XPF, XPG, POLH	Recessive

II. ALL SOLID TUMOURS

B3. Although the biology of cancers differs by organ site and even by subtype within site, for purposes of radiation protection it is common to examine the cumulative radiation risk for all types of solid cancers as an overall index of radiation risk, so it will be considered here. When examining differentials by age, sex or other modifying factors, however, caution needs to be taken not to overgeneralize, as for example in applying overall age-at-exposure effects to individual tumour sites.

A. Atomic bombing Life Span Study (LSS) modelling of risk

B4. In the latest LSS report of cancer incidence, for total solid cancers there is statistically significant variation in excess incidence by age at exposure for the ERR model and even more so for the EAR model (figure B-I) [P52]. The ERR was estimated to decrease by 17% (90% CI: 25, 7) per decade of age at exposure, and the EAR by 24% (90% CI: 32, 16) per decade of age at exposure. Table B2 shows estimated ratios of the risks for those young at exposure compared to ones older at

exposure for representative ages. Similarly, the recent summary of cancer mortality reports a decrease in ERR by 29% (95% CI: 41, 17) per decade of age at exposure [O25].

Table B2. Ratios of excess risk by age at exposure (AAE) for total solid cancer in LSS of atomic bombing survivors

Ratio by AAE	*ERR ratio, cancer incidence*[a]	*EAR ratio, cancer incidence*[a]	*ERR ratio, cancer mortality*[b]
AAE 5 / AAE 30	1.6	2.0	2.4
AAE 5 / AAE 40	1.9	2.6	3.3
AAE 10 / AAE 40	1.7	2.3	2.8

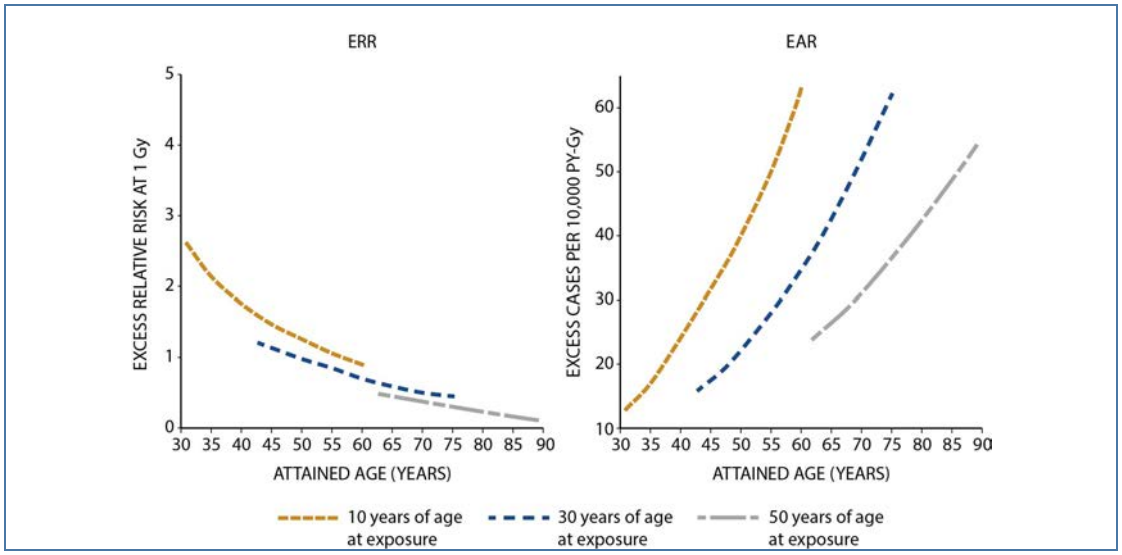
[a] *Cancer incidence estimates based on [P52].*

[b] *Cancer mortality estimates based on [O25].*

B5. Though a large fraction of tumour sites are thought to be compatible with a common dose-response slope, subject to variation because of statistical imprecision [P21], the degree of consistency across those sites in variation in risk due to age at exposure is unclear. Recent analyses of the atomic bombing data have tended to feature primarily ERR estimates that emphasize attained age (age at risk), based on modelled risk at age 70 after exposure at age 30 (figure B-I). Those comparisons intermix time and attained age effects (e.g. for those exposed at age 50 the risk represents risk 20 years after exposure, whereas for those exposed at age five it would be 65 years after exposure. Temporal variation in risk by time since exposure appears to be important biologically. Given that, a comparison based on some specific attained age irrespective of time since exposure would tend to confound time-since-exposure and age-at-exposure effects and, therefore, may not represent latter well. The EAR may vary less by time since exposure than the ERR does, though that has not been rigorously addressed. If so, then EAR comparisons of age-at-exposure effects at age 70 may be preferable to ERR comparisons (figure B-I). It would be especially desirable for research to report presented analyses by time since exposure and age at exposure, as well as by attained age and age at exposure, which would tend to give a different picture of age-at-exposure effects.

Figure B-I. Excess risks for all solid cancers at various attained ages, after exposure at ages 10, 30 or 50 years

Adapted from [P52]. The curves represent sex-averaged risks after exposure to 1 Gy



B6. From a public health perspective lifetime risk probably represents a better index by which to compare risks by age at exposure. However, because of the complexities of computing lifetime risks and the fact that lifetime risk calculations based on most studies would involve uncertain projections of future risk, research reports have tended not to calculate lifetime risks at all, or at least not in sufficient detail to show age-at-exposure variations for particular tumour sites. The recent UNSCEAR report [U12] did present lifetime risks for total solid cancers for selected ages at exposure (see table B3), but not for specific tumour sites. The table shows, for a representative population, that the lifetime risk after exposure at ages 0–9 is about 2.6 times as great as that at ages 40–49 for the ERR model and 2.1 times as great for the EAR model comparison. Part of the difference is due to variations in risk estimates and part by the fact that those younger at exposure have a longer remaining lifetime to express risk, albeit the absolute number of excess cases would be relatively small at young ages. A further consideration from a public health viewpoint is that the average years of life lost per cancer case is greater for those exposed at young ages (table B3, last column) which, of course, is attributable to the fraction of excess deaths at early ages for those who were young at exposure.

Table B3. Lifetime risk estimates for solid cancer mortality by age-at-exposure group, projected to the current United Kingdom population (using LSS mortality risk estimates [P51])

Extracted from UNSCEAR 2006 Report (annex A, table 61) [U12]

Age at exposure	*ERR: Per cent excess cancer deaths at 1 Sv*[a]	*EAR: Per cent excess cancer deaths at 1 Sv*[b]	*ERR: Years of life lost per radiation-induced cancer death*
0–9	12.77	10.35	16.2
10–19	10.64	9.17	14.9
20–29	8.65	7.89	13.9
30–39	6.73	6.52	12.8
40–49	4.87	5.07	11.4
50–59	3.18	3.62	9.6
60–69	1.78	2.28	7.7
≥70	0.56	0.90	5.5

[a] *ERR model includes dose (linear), sex, attained age, years since exposure.*

[b] *EAR model includes dose (linear), attained age, years since exposure.*

B7. Keeping in mind the caveats for ERR and EAR analyses based on limited attained ages and that any lifetime projections from those models are based on expectations and not actual observed data for those who were young at exposure, the estimated variation and confidence intervals by age at exposure are shown in table B4 for both the ERR and EAR models from the latest report of cancer incidence among atomic bombing survivors. The ERR and EAR models show a fair degree of concordance with regard to age-at-exposure effects. Both show greater risk for younger age at exposure for total solid cancers, non-melanoma skin cancer and, more recently, thyroid cancer [F29]; and both models show no significant difference by age at exposure for stomach, liver, lung, bladder and miscellaneous other solid cancers. However, the EAR shows greater risk for younger age at exposure for colon cancer and female breast cancer, but the ERR model indicates no significant difference in risk by age at exposure.

B8. It would be of interest to see whether age-at-exposure differences are seen for various tumour sites using other models (e.g. models including age at exposure and time since exposure) and for lifetime risk estimates, but such analyses are generally not available. However, for breast cancer an alternative analysis [L5] was conducted that included age at exposure and attained age, but had certain

variations from the Preston et al. [P52] modelling approach, for instance, not limiting the risk projection to an attained age of 70. They found a higher ERR for age at exposure of subjects under age 20 compared older subjects with their parametric model approach and also with a non-parametric model. These results differ from the breast cancer results in table B4 and highlight the importance that different assumptions or constraints chosen in the course of modelling can have for the estimation of age-at-exposure effects.

B9. In summary, the finding that people exposed to radiation when young are more susceptible to total solid cancer than those exposed at older ages does not imply that all solid cancers show age-at-exposure effects. To broadly summarize the results in table B4, of the nine tumour sites listed (including the grouping of “other cancers”), for the ERR model only five had negative coefficients (central estimates) of change by age at exposure, implying greater risk after exposure in childhood than after exposure in adulthood. For the EAR model, eight of the nine had negative coefficients. For various other cancer sites not listed in that table, the direction and degree of change by age at exposure were not reported in the original paper [P52], but may possibly help account for the overall negative age-at-exposure effect for total solid cancers.

Table B4. Changes in cancer-incidence risk estimates by age at radiation exposure in LSS of atomic bombing survivors

Age-specific estimates are taken from [P52] (table 11)

Tumour site	*ERR*[a]				*EAR*[a]			
	Age 10 (%)	*Age 30 (%)*	*Age 50 (%)*	*Age-at-exposure coefficient*[b] *(%)*	*Age 10 (%)*[c]	*Age 30 (%)*	*Age 50 (%)*	*Age-at-exposure coefficient*[b] *(%)*
All solid	67 (52, 85)	47 (40, 54)	32 (24, 42)	–17 (–25, –7)	90 (68, 113)	52 (43, 60)	30 (22, 39)	–24 (–32, –16)
Stomach	44 (20, 83)	34 (22, 47)	25 (12, 44)	–13 (–35, 15)	9.9 (4.5, 18)	9.5 (6.1, 14)	9.2 (4.2, 16)	–2 (–26, 29)
Colon	52 (21, 120)	54 (30, 81)	55 (15, 120)	1 (-36, 45)	41 (17, 91)	8.0 (4.4, 12)	1.6 (0.3, 3.9)	–56 (–74, –34)
Liver	28 (6, 78)	30 (11, 55)	32 (7, 85)	3 (–37, 68)	6.8 (0.0, 22)	4.3 (0.0, 7.2)	2.6 (0.5, 6.4)	–21 (–57, 378)
Lung	56 (26, 110)	81 (56, 110)	115 (69, 180)	20 (–7, 54)	7.3 (3.4, 14)	7.5 (5.1, 10)	7.8 (4.6, 12)	2 (–20, 28)
Non-melanoma skin	228 (4, 780)	17 (0.3, 55)	1 (0, 8)	–73 (–85, –55)	2.3 (0.2, 7)	0.35 (0.03, 1.1)	0.05 (0.0, 0.29)	–61 (–75, –42)
Breast (females)	86 (47, 150)	87 (55, 130)	87 (44, 150)	0 (–19, 24)	23 (15, 34)	9.2 (6.8, 12)	3.7 (2.1, 5.9)	–37 (–48, –24)
Bladder	132 (28, 410)	123 (59, 210)	115 (34, 250)	–3 (–42, 56)	4.8 (0.7, 16)	3.2 (1.1, 5.4)	2.1 (0.5, 4.5)	–19 (–54, 41)
Thyroid	121 (43, 290)	57 (24, 110)	27 (5, 77)	–31 (–59, 4)	4.0 (1.7, 7.8)	1.2 (0.5, 2.2)	0.4 (0.0, 1.3)	–46 (–68, –12)
Other solid[d]	165 (69, 350)	91 (50, 140)	51 (14, 110)	–26 (–51, 4)	7.7 (3.3, 16)	5.0 (2.7, 7.7)	3.3 (1.1, 6.5)	–19 (–44, 9)

[a] *90% CI in parentheses.*

[b] *Per cent change in ERR or EAR coefficients by decade of year of age at exposure.*

[c] *Estimated sex-averaged excess absolute rate at 1 Gy for attained age 70 after exposure at the indicated ages with units of excess cases per 10,000 PY Gy.*

[d] *Includes cancers of small intestine, certain other parts of the digestive and respiratory tracts, nasal cavity, larynx, thymus, bone and connective tissues, melanomas, male breast cancers, female and male genital organs, parts of urothelial and endocrine systems, and ill-defined sites.*

III. LEUKAEMIA

B10. An increased incidence of leukaemia was first suspected of being caused by exposure to radiation as early as 1911. The most substantial human data on radiation-induced leukaemia come from studies of three major population groups: the survivors of the atomic bombings in Japan, persons exposed to high doses of pelvic radiation therapy, and those treated with X-rays for ankylosing spondylitis or other diseases. Several of these populations included children.

B11. Age at exposure is a significant modifying factor of the risk estimates. The incidence and mortality data for the survivors of the atomic bombings in Japan suggest that ERRs were highest for the youngest survivors.

A. External exposure

1. Background radiation

B12. A recent study analysed childhood leukaemia risk in relation to natural residential background external radiation levels and radon levels in the United Kingdom [K24]. The study included over 27,000 leukaemia cases in the National Registry of Childhood Tumours during 1980−2006 along with 36,000 matched (on sex and date of birth) controls drawn from the same birth register as the cases. Radiation doses were based on estimated mean exposure levels for the county district in which the mother resided at the child's birth, and information on socioeconomic status was based on the mother's census ward or the father's reported occupation. The main measure of radiation was cumulative exposure to the red bone marrow (RBM) which was basically the imputed external exposure rate plus radon dose rate, based on the geographic location of the mother's domicile, times the age at diagnosis. The mean RBM cumulative dose at diagnosis was about 4.0 mSv (range 0 to 31 mSv), with about 10% of the RBM dose contributed by radon on average. The analysis using that metric produced a highly significant trend, with an estimated risk of ERR mSv^{-1} of 12% (95% CI: 3, 22) (i.e. ERR of 120 Sv^{-1}). The study should be interpreted with caution because of the large uncertainties associated with using an ecological measure of dose. The major studies of high-background radiation areas have not examined childhood leukaemia risk [N4, T4].

2. Atomic bombing survivors

B13. Between 1950 and 1987, a total of 237 leukaemia cases were reported to have occurred among the survivors with estimated doses [P47]. The effect of age at exposure was unclear with an EAR model, but the tabled data suggested that radiation exposure accounted for greater fractions of the leukaemia cases occurring among those who were young at the time of exposure, namely, 60%, 43% and 46% for those who were <20, 20–39 and ≥40 years of age, respectively, with similar dose distributions. A clear age-at-exposure effect was seen for acute lymphocytic leukaemia.

B14. Mabuchi et al. [M1] reported on leukaemia risk on a scale of ERR per gray based on essentially the same data, and found an age-at-exposure effect such that those young at exposure had the highest risk (figure B-II). Richardson et al. [R20] reported on leukaemia mortality among the survivors of the atomic bombings for the period 1950–2000. Their modelling clearly showed a greater risk among those who were young at the time of exposure (figure B-III).

B15. The data on leukaemia incidence were recently updated through 2001 and included 312 pathologically reviewed cases with estimated doses after excluding chronic lymphocytic leukaemia and adult T-cell leukaemia [H70]. It was found that a concave upward linear-quadratic dose-response curve fitted the data better than pure linear or pure quadratic curves. They reported that models incorporating attained age and age at exposure or attained age and time since exposure fit the data about equally well. Basing their estimates on risk at the attained age of 70 years, they reported only a small age-at-exposure effect: the ERRs at 1 Gy were 6.5 (95% CI: 4.0, 10.3), 3.9 (2.3, 6.1) and 4.0 (2.1, 6.9) for exposures at ages 0–19, 20–39 and ≥40, respectively (figure B-IV). However, the highest ERRs were seen shortly after exposure among those exposed early in life, as the earlier reports also had shown (figure B-III), so a comparison at age 70 may be misleading. Furthermore, a substantial excess of childhood leukaemia cases has been observed in the atomic bombing survivor study: 10 observed against about 1.6 expected [W6]. Examination of the age- and temporal patterns for the broad subtypes of acute myeloid leukaemia, acute lymphoblastic leukaemia (ALL) and chronic myeloid leukaemia showed complex variations from which it was difficult to draw conclusions regarding variation in risk by age at exposure. A recent paper found an association of atomic bombing exposure and the incidence of myelodysplastic syndromes, with an indication that the risk was greater for those who were young at exposure [I47].

Figure B-II: Excess relative risk at 1 Gy for all types of leukaemia, incidence, 1950–1987

Adapted from [M1]

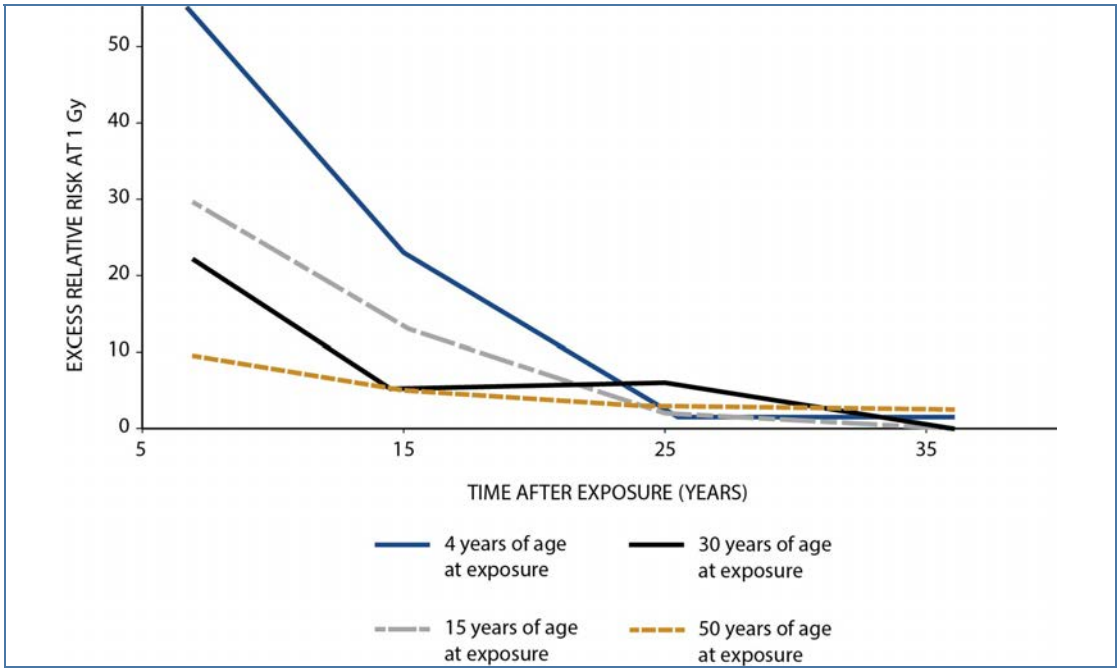


Figure B-III. Predicted city-averaged ERR at 1 Gy for leukaemia mortality (all types as a function of age at exposure and time since exposure)

Adapted from [R20]

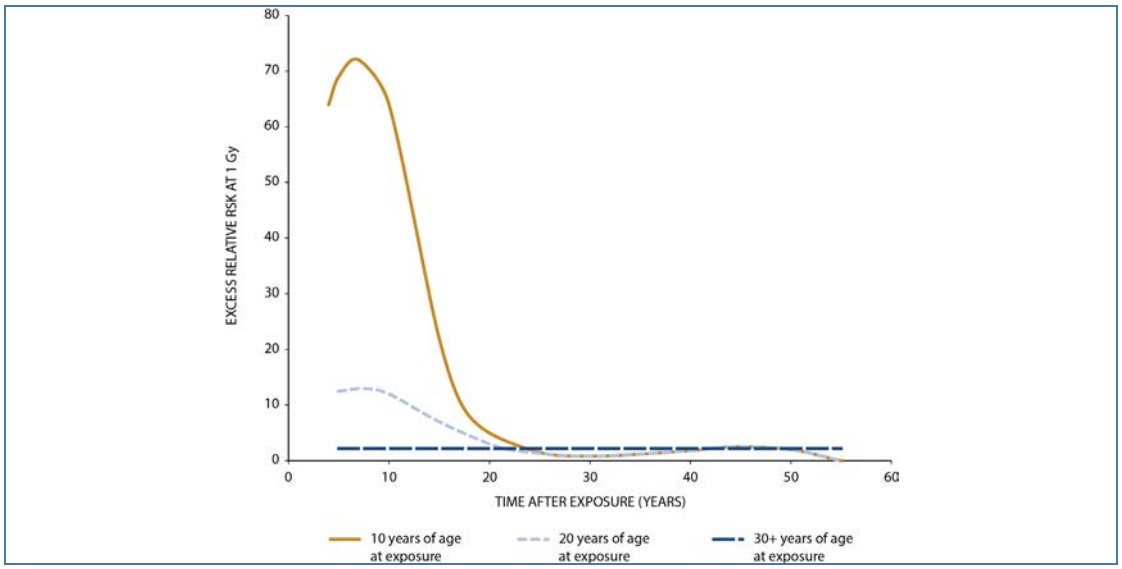
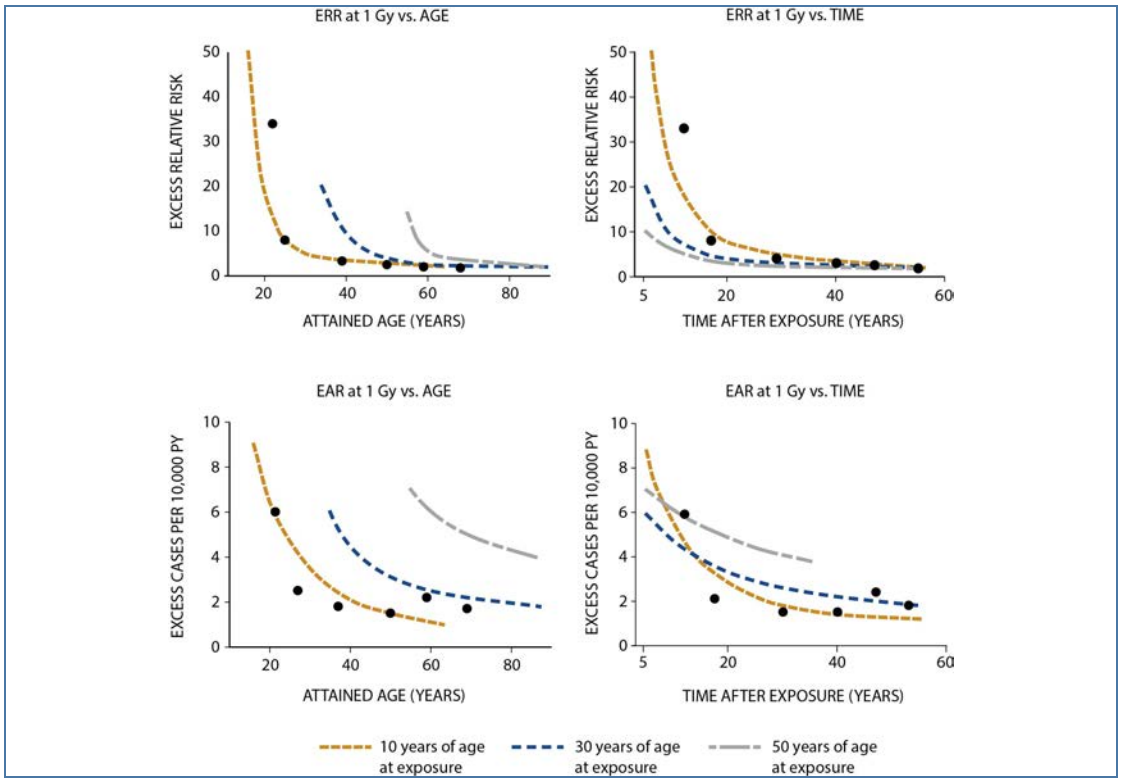


Figure B-IV. Leukaemia risk at 1 Gy in LSS according to age at exposure and temporal pattern: ERR and EAR estimates, 1950–2001

Adapted from [H70]



3. Persons exposed to fallout

B16. Fallout from nuclear weapon testing in the Marshall Islands caused a substantial bone marrow dose to some of the islanders. However, acute myelogenous leukaemia subsequently developed in only one inhabitant [C41]. This single case may be due to chance, although the possibility of it being induced by radiation cannot be excluded.

B17. A study in French Polynesia [V14] indicated higher rates of childhood leukaemia in the period 1985–1989 compared to the period 1990–1995 but these rates were similar to those in Hawaii. Furthermore, given the time lag between atmospheric weapon testing and these higher rates, a connection is not likely. A case-control study of leukaemia in Utah following testing of nuclear weapons showed a small increase of acute leukaemia in the decade following the major fallout events among those who were under age 20 at exposure [S114]. The estimated median red bone marrow dose was 3.2 mGy, with a maximum dose of 26 mGy.

B18. To date, studies on the populations exposed to fallout from the Chernobyl accident have shown no increase in incidence of leukaemia [U10, U15]. Studies of adults living in the Bryansk area of the Russian Federation have been published by Osechinsky et al. [O17] and [G4], with negative results. Studies in the most contaminated areas of the Kaluga oblast by Ivanov [I45, I43] also yielded negative results. Both Bebeshko [B10] and Prisyazhniuk [P56] found no increased incidence of leukaemia in the contaminated areas of Ukraine and Belarus. However, Noshchenko et al. [N33] reported an increased incidence of leukaemia but only among children born in 1986. Steiner et al. [S113] and Parkin et al. [P10, P11] have also observed an increase in the incidence of infant leukaemia in western Europe but it was not related to the radioactive contamination of the ground, which was used as a surrogate for radiation exposure. Furthermore, no increased incidence of infant or childhood leukaemia has been found in Belarus, the Russian Federation or Ukraine related to the Chernobyl accident according to UNSCEAR [U10, U15]. While Noshchenko et al. [N35, N33, N34] indicated an increase in leukaemia among children exposed at ages 0–5 to more than 10 mSv, there are questions about possible biases in control selection, and these results have not been confirmed in several other studies summarized in the report of the Chernobyl Forum [W21]. A subsequent paper examining leukaemia risk in Ukraine, Belarus and the Russian Federation concluded that an apparently elevated risk in Ukraine may have been at least partially due to sampling bias and was not generally supported by the results from the other two countries. However, the combined data from the three countries did show a significant dose–response trend [D19].

B19. Studies of the incidence of leukaemia at greater distances from Chernobyl are unlikely to yield additional useful information because of the lower doses received by the populations. Studies in Hungary have shown no increased incidence of leukaemia [T31]. A suggested increase in the incidence of infant leukaemia in Scotland and Wales [B71] was not confirmed in a larger study of the United Kingdom [C9]. Two further studies, conducted in Finland [A28] and Sweden [H51], did not find a statistically significant excess risk of childhood leukaemia in relation to fallout exposure levels. Cardis et al. [C4] have estimated the potential impact of Chernobyl fallout in Europe. They estimated that the accident might result in 2,400 excess leukaemia cases and 1,650 excess leukaemia deaths or an attributable fraction of 0.04%. However, the epidemiological data to date do not indicate a measurable increase in risk and the small hypothetical percentage increase would probably not be possible to detect. The UNSCEAR 2000 and 2008 Reports [U10, U15], the 2005 Chernobyl Forum report [W21] and also the 2006 BEIR VII report [N43] have summarized the studies of leukaemia incidence in children and adults living in areas contaminated by the Chernobyl accident. On balance, these studies indicate that the existing evidence does not support the conclusion that incidence of either childhood or adulthood leukaemia has increased as a result of radiation exposure, at least not to a degree that is detectable.

B20. The incidence of leukaemia in the population downwind of the Semipalatinsk nuclear testing site—who were estimated to have received an effective dose of 2 Sv or more—was nominally, but not statistically significantly, elevated (OR = 1.9; 95% CI: 0.4, 9.7) [A3]. No information was presented on the incidence of leukaemia according to age at exposure. A study of residents near the Three Mile Island nuclear power plant did not find an increase in leukaemia incidence after the nuclear accident, either for childhood leukaemia [H28] or leukaemia at all ages [H29].

4. Persons living near nuclear facilities

B21. Studies of the risk of leukaemia in populations living around nuclear power plants in the United States have been discussed in detail by Jablon et al. [J2]. To date, no consistently significant increase in leukaemia incidence attributable to radiation has been found in the United States of America, Canada [M20] or Israel [S96]. There are several articles concerning the possibility of increased incidences of leukaemia around a number of specific nuclear installations in Europe, including Sellafield, Dounreay and La Hague. Apart from Sellafield and Dounreay, no other sites in the United Kingdom have shown an excess incidence of leukaemia among the local populations [C39]. Reviews of these findings have been presented by Laurier et al. [L12, L14, L13, W20] and UNSCEAR [U12, U13]. They have all concluded that there is no relationship between the increased incidences of leukaemia and radiation exposure; however, an infectious aetiology could not be excluded. A review of leukaemia incidence around Japanese nuclear power plants by Yoshimoto et al. [Y9] also does not support an association. Boice et al. [B41] examined childhood leukaemia rates in a county with a nuclear power station, but found no excess compared to control counties. A study of leukaemia among children below five years of age in the vicinity of French nuclear power plants also showed no effect [L15].

B22. However, the recent KiKK study, prompted by an apparent excess of childhood leukaemia near the German Krümmel nuclear power plant, examined the incidence of leukaemia diagnosed at ages 0–5 years among residents in the vicinity of the 16 German nuclear power plants [K1]. They reported an odds ratio of 2.2 (90% CI: 1.5, ~3.2) for children within 5 km of a plant compared to those living further away. For those within 10 km compared to those living further away, the odds ratio was 1.3 (90% CI: 1.1, ~1.7). Both German [S108] and British [C40] reviewers have examined this study in detail and pointed out certain methodological limitations, though not fatal flaws. The KiKK study prompted a nationwide cohort study in Switzerland of cases of cancer among children aged 0–15 years [S106]. For children born within 5 km of a nuclear power plant compared to those born 15 or more kilometres away, they found an odds ratio of 1.2 (95% CI: 0.6, 2.4) for leukaemia diagnosed at ages 0-4 years, and 1.05 (95% CI: 0.6, 1.9) for those diagnosed at ages 0–15 years.

B23. There are several papers concerning potential uranium contamination and incidence of leukaemia among members of the public. The papers by Boice et al. [B39, B40] indicated a non-significant elevation of leukaemia incidence with a relative risk (RR) of 1.15 (95% CI: 0.9, 1.6) around a uranium mining and milling facility in Texas and a non-significant decrease near a uranium facility in Pennsylvania. A study in a uranium mining and milling area in New Mexico found no association with leukaemia incidence: a standardized incidence ratio (SIR) of 1.3 (95% CI: 0.95, 1.7) for all non-CLL cases, and an SIR of 1.6 (95% CI: 0.91, 2.7) for childhood leukaemia (ages 0–19 years) [B43]. Also, the mortality data did not indicate an association with the incidence of childhood leukaemia; the standardized mortality ratio (SMR) was 1.06 (95% CI: 0.7, 1.6). No difference in the incidence of leukaemia was found by Boice et al. [B42] in a study of persons residing near the Hanford site, United States of America. A paper by Bithell et al. [B27] examined contamination by ^{235}U and found no evidence of an association with childhood leukaemia. Leukaemia incidence has also been studied by

Grosche et al. [G36] around two nuclear facilities that discharge tritium. The results did not support an association. For the facility with the higher discharges, there was a non-significantly decreased rate of childhood leukaemia while for the other facility with discharges several orders of magnitude smaller, there was a significant increase in the incidence of childhood leukaemia.

5. Diagnostic radiology

B24. Several case–control studies have been performed of the incidence of leukaemia and diagnostic radiation exposure. A New Zealand study of 590 leukaemia cases diagnosed during 1958–1961, along with age–sex matched hospital controls, reported an association between leukaemia incidence and therapeutic radiation exposure, but not with diagnostic irradiation. No breakdown by age at exposure or diagnosis was given [G38].

B25. In a case–control study of the incidence of childhood leukaemia (>300 cases and >800 controls), Graham et al. [G25] reported a relative risk of 1.14 (p >0.5) for post-natal diagnostic irradiation received at least one year prior to diagnosis.

B26. Bartley et al. [B6] studied 711 cases of childhood ALL and 116 childhood cases of acute myeloid leukaemia (AML) in relation to reported post-natal diagnostic X-rays administered one or more years prior to diagnosis. For ALL they found a statistically significant association (OR = 1.85; 95% CI: 1.12, 2.79) for three or more diagnostic X-rays, but not for AML (OR = 1.05; 95% CI: 0.90, 1.22).

B27. Infante-Rivard [I36] similarly studied reported post-natal diagnostic X-rays among childhood cases of ALL and found an increasing risk with number of X-rays—odds ratio = 1.48 (95% CI: 1.11, 1.97) for two or more X-rays. On the other hand, at least three studies have reported no significant statistical association between diagnostic X-ray exposure and childhood leukaemia risk [M25, R3, S74].

B28. A recent cohort study examined leukaemia incidence following CT scans given to over 178,000 juveniles at ages 0–21 [P22]. For a dose-response analysis they estimated average red bone marrow doses for various CT procedures during two time periods and summed estimated doses across CT scans for each individual. From 74 observed cases of leukaemia, they found an ERR Gy^{-1} of 36 (95% CI: 5, 120). However, they included myelodysplastic syndrome (MDS) with the leukaemia cases, and the MDS cases had an extremely high relative risk. Without the MDS cases, the estimated risk was still high, but no longer statistically significant (ERR Gy^{-1} of 19 (95% CI: −12, 79)).

B29. Mathews et al. [M9] reported a very large paediatric CT study in Australia, based on about 680,000 children who received CT scans during the period 1985-2005 and 10,000,000 with no record of such exposures. It included about 147,000 who received CT scans before age 10, and 533,000 whose first CT scan was in the age range 10–19. On the basis of type of examination, age at examination, and time period (1985–2000 or 2001-2005), they estimated effective doses (mean of 4.5 mSv per scan), red bone marrow doses and brain doses and conducted a record-linkage follow-up through 2007. It was concluded that overall cancer incidence was 24% (95% CI: 20, 29) greater in the CT group, with a statistically significant trend by recorded number of CT scans. They reported excesses in the CT group for digestive organs, melanoma, soft tissue, female genital, urinary tract, brain, thyroid, leukaemia, myelodysplasia, Hodgkin's lymphoma and ill-defined/unspecified sites. The risk estimate for "all cancers, excluding brain cancer after brain CT" risk was statistically incompatible with the data at comparable ages from the Japanese LSS study on atomic bombing survivors [M9] (ERR Sv^{-1} of 27 (95% CI: 17, 37); LSS, 3 (95% CI: 2, 6)). On the basis of a total of 211 leukaemia cases in the exposed

group, they reported a relative risk of 1.19 (95% CI: 1.03, 1.37; excess of 34 leukaemias) compared to the unexposed group. For leukaemias plus myelodysplasias, the excess was 48 out of 246 total cases and a RR of 1.23 (95% CI: 1.08, 1.41). On the basis of the estimated doses and a dose lag of one year, the ERR Gy^{-1} for leukaemias plus myelodysplasias was 39 (95% CI: 14, 70).

B30. Concerns about possible biases and the interpretation of the study arise for several reasons. Reverse causation (cancers were caused by the medical conditions prompting the CT scans rather than by the CT dose) as a potential bias could not be examined in the study since no documentation was available on the indications for the CT scans. The choice of focusing on cancers that occurred at least one (rather than five or ten) year after the initial CT scan amplified the potential for reverse causation and is biologically implausible. The finding of generally stronger associations if they included years one–four after the CT scan than if they included only later years reinforces this concern. Missing subsets of CT exposures included those due to unrecorded repeat CT scans (e.g. because of patient movement) and those occurring outside the age or time ranges of the study. Missing doses would tend to inflate the estimates of risk per unit dose. Implausible CT and tumour associations included radiation excesses seen for melanoma and Hodgkin's lymphoma, neither of which is known to be associated with radiation, but not for breast cancer, a radiosensitive site. No clear excess of leukaemia was seen for those exposed before age ten but it appeared for those exposed at later ages, unlike other studies of radiogenic childhood leukaemia, which tend to show the greatest leukaemia risk for exposure at early ages.

B31. Lundell and Holm [L42] studied 14,624 infants who were given radiotherapy in infancy to treat skin haemangiomas. There were no significant associations between incidence of childhood leukaemia and radiation dose, but the mean marrow dose was estimated to be only about 0.13 Gy. A small excess incidence of leukaemia was reported in children who had been treated with radiotherapy for tinea capitis. In a report on ~10,800 tinea capitis patients, Ron et al. [R37] assumed a dose of 0.3 Gy averaged across all the bone marrow. For 14 leukaemia cases in the exposed group and 9 among unexposed controls, the ERR was marginally elevated at 4.3 (95% CI: 0, 15) Sv^{-1} with an EAR of 9 (95% CI: 0, 33) $(10^4 \text{ PY Sv})^{-1}$. They reported that the relative risks for leukaemia were 3.3, for 0–5-year-old group, 2.6 for the 6–8-year-old group, and lower for the 9–15-year-old group (the ages being the ages at exposure), but the comparison was based on a very small number of cases [R35].

B32. In a group of ~2,200 children given X-rays therapy for tinea capitis, eight leukaemia patients were observed (SIR = 3.2; 95% CI: 1.5, 6.1) associated with a dose of about 4 Gy to the cranial bone marrow [S41, S71]. If one assumes that the mean bone marrow dose was 0.3 Gy, as in the Ron et al. report, then the ERR would have been 7.3 (95% CI: 1.7, 17) Sv^{-1}. Damber et al. [D3] reported a cohort follow-up study of ~20,000 patients treated for benign lesions of the locomotor system. The ERR for leukaemia was non-significant, but only 115 patients were treated before the age of 20.

6. Radiotherapy

B33. There have been reports of an increased incidence of acute leukaemia in patients after treatment of Hodgkin's lymphoma, multiple myeloma, breast cancer, and other neoplasms [G37, R55, Z3]. The aetiology of the increased risk is unclear, and it is likely multifactorial, including radiation, chemotherapy, the primary disease, or even an underlying immunodeficiency.

B34. A number of studies have examined the risk of second tumours after treatment for childhood cancers [T46, T47]. There was a strong dose–response relationship between leukaemia risk and the dose of alkylating agents. The relative risk of leukaemia reached 23 in the highest chemotherapy dose

group. A lower risk was seen for doxorubicin. The radiation dose had no influence on leukaemia risk. In another study, Rosenberg and Kaplan [R54] found an increased leukaemia risk after MOPP chemotherapy, but this was largely independent of radiation dose. A report by Hawkins et al. [H33]—in which over 16,000 survivors of childhood cancer were studied—indicated that radiation, and also specific chemotherapy involving alkylating agents or epipodophyllotoxins, can induce secondary leukaemia. A follow-up of survivors of Hodgkin's disease and leukaemia by Kaldor et al. [K5] found a marginally significant increase in ERR of 0.24 (95% CI: 0.04, 0.43) Sv^{-1}. A recent report on the follow-up of 14,359 patients in the CCSS by Friedman et al. [F17] found an observed over expected ratio of 41/7 and an SIR of 6.1 (4.5, 8.2) for leukaemia.

B. Internal exposure

B35. A number of studies have examined the relationship between radon exposure and leukaemia incidence. Most of the studies have been negative or non-significant. Kaletsch et al. [K7] concluded that there was no association between indoor residential radon exposure and incidence of childhood leukaemia. Lubin et al. [L36] conducted a case–control study of indoor radon exposure and incidence of ALL. There was no evidence for an association. A similar conclusion was reached by Law et al. [L16] in the United Kingdom regarding adult acute leukaemia. Steinbuch et al. [S112] studied the risk of childhood acute myeloid leukaemia and radon exposure and concluded there was no association. However, Raaschou-Nielsen et al. [R2] examined domestic radon levels and childhood leukaemia incidence in Denmark and reported a statistically significant dose response with a 56% increase in the rate of ALL per 10^3 Bq/m^3-years. Kendall et al. [K24], in a large case-control study of childhood cancer and background radiation in the United Kingdom, examined the influence of radon upon childhood leukaemia risk and did not find an association.

B36. Residents along the Techa River were exposed to effluent releases from the Mayak nuclear production facility. The main source of exposure to the red bone marrow was from ^{90}Sr, a bone seeking radionuclide. Red bone marrow doses ranged up to over 1 Gy. For non-chronic lymphocytic leukaemia, Krestinina et al. [K52] observed an approximately linear dose response with an ERR of 4.9 (95% CI: 1.6, 143; n=53) Gy^{-1} but the age-at-exposure effect was not statistically significant.

C. Summary

B37. There is little doubt that non-CLL is induced by radiation, with a minimum latency of approximately two years. The tumours induced are either acute forms or chronic granulocytic leukaemia, with the acute forms tending to predominate. The ICRP [I11] estimates the lifetime fatal probability coefficient to be 50 (10^{-4} Sv^{-1}) among a population of all ages from non-CLL after exposure to low doses. The risk at low doses is based on mathematical models since the studies have not shown a statistically significant increase in leukaemia incidence at marrow doses of less than about 400 mSv. A linear–quadratic dose–response model appears to be more appropriate than a linear non-threshold model and this has been used by the ICRP [I11], BEIR [N38, N43] and UNSCEAR [U12, U13] with allowances for dependencies on sex, age at exposure and time since exposure. The estimates made by these different groups of the excess leukaemia deaths in a population of 100,000 of all ages and both sexes exposed to a dose of 0.1 Gy are quite similar. The studies that have sufficient statistical power to permit the derivation of risks of radiation-induced leukaemia are shown in table B5. Overall, the risk to

children appears to be three to fivefold greater than that to adults. A number of epidemiological studies of children who have undergone CT scanning are currently under way and these may yield more information on the risks of radiation-induced leukaemia over the next several years.

Table B5. Estimates for leukaemia incidence and mortality rate from radiation exposure in children

Adapted from UNSCEAR 2006 Report (annex A, table 44) [U12]; only studies are listed for which quantitative estimates of risk were possible

Study		*Average ERR [a] at 1 Sv*	*Average EAR (10^4 PY Sv)$^{-1}$*
EXTERNAL LOW-LET EXPOSURES			
Incidence			
LSS [P47]			
Sex	Males	4.66 (3.07, 6.88)	4.14 (3.06, 5.39)
	Females	5.05 (3.24, 7.61)	2.41 (1.71, 3.23)
Age at exposure	<20 years	8.27 (4.95, 13.66)	2.79 (1.99, 3.74)
	0–40 years	3.59 (2.01, 5.97)	2.69 (1.70, 3.90)
	>40 years	3.98 (2.32, 6.45)	4.68 (3.10, 6.57)
LSS [H70]			
Age at exposure	<20 years	6.5 (4.0, 10.3) [b]	n.a
	20–39 years	3.9 (2.3, 6.1) [b]	n.a
	≥40 years	4.0 (2.1, 6.9) [b]	n.a
Paediatric CT examinations [P22] [b]		36 (5, 120) [d]	n.a
Paediatric CT examinations [M9]		39 (14, 70) [d]	n.a
Hodgkin's disease [K5] [c]		0.24 (0.04, 0.43) [b]	n.a.
UK childhood cancers [H33] [e]		0.24 (0.01, 1.28) [b]	n.a.
International childhood cancer [T47]		0.0 (0.00, 0.004)	n.a.
Mortality rate			
LSS [P51]			
Sex	Males	4.07 (2.75, 5.84)	3.23 (2.41, 4.18)
	Females	3.96 (2.57, 5.87)	<0 (<0, 291.33)
Age at exposure	<20 years	6.63 (4.21, 10.26)	<0 (<0, 271.86)
	20–40 years	3.07 (1.81, 4.87)	2.39 (1.56, 3.39)
	>40 years	3.15 (1.74, 5.24)	3.46 (2.12, 5.09)
Israeli tinea capitis [R37] [e]		4.44 (1.7, 8.7)	0.95 (0.4, 1.9)
Stockholm skin haemangioma [L42] [f]		1.6 (–0.6, 5.5) [b]	n.a.

Study	*Average ERR [a] at 1 Sv*	*Average EAR (10^4 PY Sv)$^{-1}$*
INTERNAL LOW-LET EXPOSURES		
Incidence		
Chernobyl-related exposure in Belarus, Russian Federation and Ukraine [D19]	32.4 (9.78, 84.0)	n.a.
Chernobyl-related exposure in Ukraine [N34]	2.5 (1, 5.4) [b,g,h]	n.a.
Chernobyl-related exposure in Ukraine [N35]	2.1 (1.2, 3.7) [b,d,g] 4.4 (1.3, 15)	n.a.

[a] *90% CI in parentheses.*

[b] *95% CI in parentheses.*

[c] *Risk estimates based on [L29].*

[d] *ERR Gy^{-1} for leukaemia plus myelodysplasia.*

[e] *Risk estimates based on the UNSCEAR 2000 Report [U9].*

[f] *Based on those with doses above 0.1 Sv.*

[g] *Odds ratio, not ERR at 1 Sv.*

[h] *Relative risk among those with doses of 10 mSv or more relative to those with less than 2 mSv.*

IV. THYROID CANCER

A. General

B38. Thyroid cancer represents about 1–2% of all cancers. It is approximately twice as common in females as in males, with the incidence increasing with age. The association of ionizing radiation exposure with thyroid cancer risk was first noted in a case–control study by Duffy and Fitzgerald [D49] and was confirmed within a few years by several other studies [C30, S81, W28], including that of the survivors of the atomic bombings in Japan [S95, W40]. Since then, the thyroid has been the subject of many investigations concerning the induction of neoplasms, both malignant and benign. X-rays and gamma radiation, and also internally deposited radionuclides (particularly radioiodines), may induce thyroid carcinoma.

B39. Robbins et al. [R30] have estimated that 9% of thyroid cancers in the general population may be attributable to radiation. In Western Europe, the incidence of thyroid cancer has also been rising which prompted some to question whether the Chernobyl accident was a cause; however, this supposition has not been borne out. The reason for the increased incidence may be improved diagnosis of clinically "occult" lesions. Studies ranging from the early case–control study by Astakhova et al. [A27] to the Ukrainian and Belarusian cohort studies [B60, T39, Z1] have confirmed radiation as the primary cause of the large increase in thyroid cancer rates among juveniles in Belarus and Ukraine.

B40. Radiation-induced thyroid cancer does not appear to have a different survival rate from that of sporadic thyroid cancer [B69]. In the United States of America, the five- and 10-year survival rates of thyroid cancer patients are 97% and 95%, respectively. In general, most thyroid cancers induced by radiation are well-differentiated papillary adenocarcinomas, with a small percentage being follicular

[N13]. Radiation-induced thyroid cancers do not usually include the anaplastic and medullary types; thus, the fatality rate of radiation-induced thyroid tumours may be even lower than for sporadic cancers.

B41. Although several cases of anaplastic thyroid tumours have been reported following radiation exposure [G8, K43], it is uncertain whether these were fortuitous or whether they were indeed radiation-induced. It is possible that they may have resulted from the degeneration of better-differentiated radiogenic tumours.

B42. The risk factors derived in various epidemiological studies are not always easy to compare because they include different age groups, ethnic backgrounds, primary diseases, and ratios of males to females in the population examined. Sources of information regarding radiation-induced thyroid cancer include the NCRP [N17, N18], BEIR [N38, N43] ICRP [I11], the UNSCEAR Committee [U10, U12], Shore [S65], and Nagataki [N2].

B43. The occult carcinoma, which is usually of a non-sclerosing papillary type, is not considered in radiogenic risk estimates because these occult tumours are of doubtful clinical significance and are usually discovered incidentally by pathologists. Martinez-Tello et al. [M8] have indicated that in an autopsy study of a non-exposed Spanish population, about 22% of completely sectioned thyroids contained occult papillary carcinomas. A prevalence of 8.8% occult papillary carcinoma has been reported by Furmanchuk et al. [F24] in a Belarussian autopsy series, and 18% in autopsies of non-irradiated persons in the Japanese atomic bombing study [S14].

B44. Since the Chernobyl accident, there has been great interest in a possible genetic or mutational signature (a genomic fingerprint) that might be associated with radiation-induced thyroid cancers. A large proportion of the childhood thyroid cancers occurring after Chernobyl were reported to be aggressive. Initial reports indicated that rearrangements of the tyrosine kinase domain of the *RET* proto-oncogene were found at a higher than expected rate of these rearrangements in thyroid tumours in the general population [B54, E3, T20]. The most frequently observed were *RET/PTC1* and *RET/PTC3* rearrangements; however, 30–50% of the papillary cancers did not have these findings. Currently, it appears that the genomic differences and aggressive nature of the tumours reported may represent the type of thyroid cancer that occurs in childhood rather than a radiation signature per se (but see [H43]). The mortality rate from these cancers is very low [S23, T19, W24]. An indication of *EML4-ALK* fusion gene rearrangements has also been seen in irradiated thyroid cancer cases [H13].

B45. The cell type of the childhood thyroid cancers occurring after the Chernobyl accident was also initially felt to be rather specific with a solid-follicular variant of papillary cancer being predominant from 1990 to 1995. This cell type, however, has decreased with time since exposure, and the proportion of papillary cancers composed mainly of papillae has been increasing with time [T41]. As of 2000–2001, the percentage of each type of papillary cancer was almost equal. It also appears that RAS, p53, BRAF, B-raf and NTRK1 mutations are not characteristic of the radiation-associated tumours [B12, H12, H50, L25, N32, S117].

B. Modifying factors

B46. The latent period from radiation exposure to the clinical development of thyroid neoplasms varies widely among studies. Following exposure to external radiation, the latent period has been reported to be anywhere between four–five years and up to 60 years, the maximum length of follow-up of relevant cohorts [A7]. The reported latent periods appear to be a function of the follow-up time of

the particular study, with several authors indicating an excess number of cancer cases occurring 40 or more years after irradiation [A7, F29, S7]. Any epidemiological study not conducted with a long enough follow-up period will estimate the mean latent period as likely to be short. There is also a suggestion that the latent period may increase with age at irradiation [C37, R10], although that study was based on a large series of clinical cases rather than systematic follow-up and time-to-event analyses of well-defined cohorts. Schneider et al. [S33] have reported that for children who received radiotherapy to the head and neck for benign conditions, the ERR at 10 mGy was about 0.02 at less than 10 years post-exposure, 0.04 at 10–25 years post-exposure, rose to a maximum of 0.08 at 25–29 years post-exposure and then declined to about 0.04 at 40 or more years post-exposure. On the basis of pooled data from five irradiated cohorts, including the Schneider cohort, Ron et al. [R43] reported that thyroid cancer risk peaked at about 15–19 years after irradiation but was still elevated beyond 40 years, as was also noted by another temporal modelling method [S69].

B47. The effect of dose fractionation or a low dose rate is difficult to evaluate because there is no major study with appreciable intrastudy variation in dose rate/fractionation. Therefore, comparisons have to be made between studies, and variation in a number of factors can affect such comparisons. The pooled analysis by Ron et al. [R43] systematically attempted to evaluate dose-fractionation effects and reported a factor of 0.7 for the risk from fractionated exposures compared to single exposures. However, the degree of fractionation was relatively small in most of the included studies. Studies of the risks associated with the use of ^{226}Ra applicators for skin haemangiomas by Lundell et al. [L40] and Lindberg et al. [L26] tend to suggest that a lower dose rate confers essentially as much risk as acute exposures. However, a study of the risks associated with the administration of ^{131}I for diagnostic purposes suggests little effect after a low-dose-rate exposure [H7]. Nevertheless, the substantial Chernobyl data generally indicate approximately the same risk as for comparable brief external exposures. This is discussed later in the section on internal exposure.

B48. Various studies reviewed later indicate that the thyroid is more radiosensitive in children and adolescents than in adults. For radionuclides, it is unknown whether this is due to differences in metabolism or concentration of radionuclides. Certainly, inhalation of a fixed amount of radioiodine results in a greater concentration in the infant thyroid than in the adult thyroid [B47]. Moreover, there is substantial evidence that the younger a person is at the time of exposure, the higher the risk of developing radiation-induced thyroid cancer in the future. Except at high therapeutic doses, exposures over the age of about 30 years from external radiation have not been found to significantly increase the risk of thyroid cancer.

B49. The best estimate of risk for persons exposed under 20 years of age to external radiation comes from a pooled analysis of five large cohort studies by Ron et al. [R43]. The ERR at 1 Gy was estimated to be 7.7 (95% CI: 2.1, 29) following exposures in childhood, although if the one study with a very high risk was excluded, or if exposure status was adjusted for in that study, the ERR was reduced to 3.8 (95% CI: 1.4, 9.9).

B50. Sex also appears to be a modifying factor. Several epidemiological studies indicate that females are more sensitive than males to radiation-induced thyroid adenomas and cancers. The EAR in females may be two–four times that in males [D15, M11, M47], but the ERR per unit dose is about the same for both sexes or only slightly higher in females. In the United States population, spontaneous thyroid carcinoma occurs in females approximately two and a half times more commonly than in males.

B51. Ethnic background may also be a significant modifying factor. This has been noted particularly in the studies of persons of Jewish ancestry [R33, S65]. Radiation risk for those with Jewish ancestry may be several times higher than that for non-Jewish populations [R39, S65] although not all reports have confirmed that [A7]. Persons of Jewish ancestry from North Africa, especially

Morocco and Tunisia, appear to be five or more times more sensitive than non-Jewish populations, and twice as sensitive as the Jewish children native to Israel or other Middle East countries. Whether this is due to a high prevalence of ataxia telangiectasia heterozygosity from an ataxia-telangiectasia mutated (ATM) founder mutation in the North African Jewish population is unknown [S7]. A report of Momani et al. [M47] involving a United States hospital study of siblings who were irradiated did not identify familial factors that modified the effects of radiation exposure, nor did a study of infants irradiated for enlarged thymus [S66], although there seems to be some radiation-associated familial clustering [P24].

B52. As to other risk factors, various studies have reported mixed results with regard to modification of the radiation-induced risk by age at menarche or first childbirth, gravidity, parity, oral contraceptive use, menopausal hormone use and obesity [A7, F12, K42, M21, P44, R36, S32, S66].

B53. Several authors have suggested that iodine deficiency may be a promoting factor in radiation-induced thyroid carcinogenesis because of a reduction in the level of thyroid hormone and its stimulatory effect on the cells. While this has been suggested in animal studies, at least two human studies indicate the opposite—that thyroid cancer can be associated with a high normal intake of iodine [F13, K42]. Some authors believe that Graves' disease influences the development and behaviour of thyroid carcinoma [M14]. Whether there is an association between thyroid cancer and goitre is not fully clear [R32].

B54. In Ukraine, Tronko et al. [T39] observed a higher thyroid cancer risk among those with goitre, but not in relation to low levels of iodine in the urine. Similarly, in Belarus, diffuse goitre or thyroid enlargement increased the radiation risk estimate, but low levels of iodine in the urine did not [Z1]. However, a study in the Russian oblast of Bryansk found that low iodine excretion levels were associated with a twofold greater thyroid cancer risk from radioiodine exposure [S48].

B55. A study by Cardis et al. [C3], discussed below, indicates that in areas of iodine deficiency, the radiation-related risk of cancer may be three times higher than in areas of normal iodine levels and that with iodine prophylaxis, the risk can be reduced by about a factor of three, but replication of those results would be desirable. On the other hand, the cohort study in Ukraine did not find a statistically significant modification of radiation risk in the case of either low iodine excretion levels or the use of stable iodine prophylaxis [B60].

B56. Researchers have suggested that one reason for the sensitivity of the thyroid to radiation carcinogenesis may be that TSH enhances the effect of exposure to ionizing radiation [R28]. They have also suggested that patients at risk be given prophylactic exogenous thyroxine. In at least a few cases, however, this treatment seems to have had little effect [S24]. Even if the thyroid hormone did affect the sensitivity of the thyroid gland to cancer induction, this would be unlikely to explain an age-at-exposure effect since serum thyroid hormone levels in children and adults are similar.

C. External exposure

1. Atomic bombing survivors

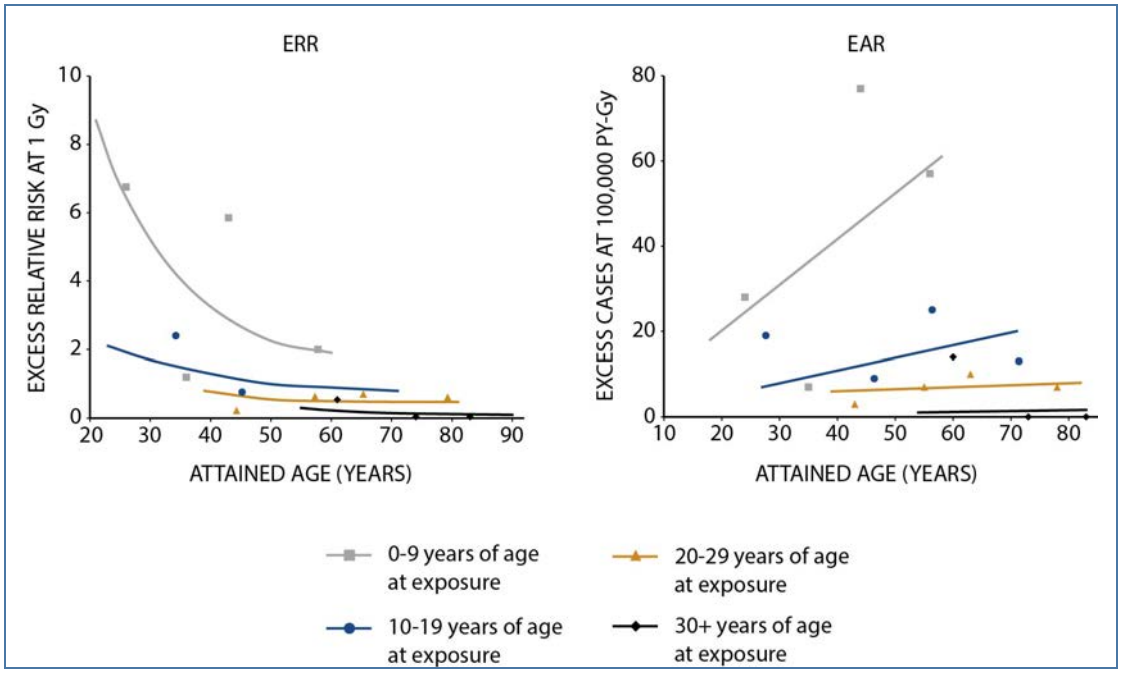
B57. Thyroid cancer was the first type of solid cancer to be found in excess among the survivors of the atomic bombings in Japan [P8, S95, W40]. The LSS mortality studies have not reported on thyroid cancer because of the rarity of death from thyroid cancer. The incidence of thyroid cancer increased with decreasing age at exposure and attained age. In the 1994 LSS incidence report, there were 225 thyroid cancer cases. The ERR at a dose 1 Sv was 1.2 (95% CI: 0.5, 2.1) with an EAR of 1.6 (95% CI: 0.8, 2.5) $(10^4 \text{ PY Sv})^{-1}$ [T23]. There was no significant difference in the ERR between males and females, although the risk decreased with age at exposure. At 0–9 years of age at exposure, the ERR was 9.5 Gy^{-1}; at 10–19 years of age, it was 3.0 Gy^{-1}; at 20–29 years of age, it was 0.3 Gy^{-1}; and at over 40 years of age, it was 0.2 Gy^{-1}. For the population 0–19 years of age at exposure, the ERR was 6.3 (95% CI: 5.1, 10.1) Gy^{-1} whereas for the population exposed over the age of 20, the ERR was not statistically significant at 0.3 (95% CI: <0, 12) Gy^{-1}.

B58. A more recent report of thyroid cancer incidence from 1958 to 1998 among the survivors of the atomic bombings was based on 471 thyroid cancers and showed a strong dose response with an ERR of 0.57 (90% CI: 0.24, 1.1) Gy^{-1} [P52]. The dose–response function indicated a radiation-related excess of 63 cancers. There was a negative age-at-exposure effect of -31% (90% CI: -59, 4) per decade of age at exposure, which implies that the risk is about 2.5 times higher for exposure at age 5 than at age 30. They did not report whether the radiation effect was statistically significant for exposures at ages 30 years and beyond. There also was a diminution in the ERR with attained age (age at risk), but the radiation risk was still elevated 40 or more years after exposure. The difference in risk between the sexes was not statistically significant: ERR ratio for females to that for males was 1.3 (90% CI: 0.6, 3.9). However, the EAR was greater for females than males, the EAR ratio being 3.6 (90% CI: 1.8, 9.5). This occurs because females have a higher baseline risk of thyroid cancer than males, so multiplying both the male and female baseline risks by about the same factor yields a greater absolute excess for females. The EAR averaged over the sexes was 1.2 (90% CI: 0.5, 2.2) $(10^4 \text{ PY Sv})^{-1}$, and it declined by 46% (90% CI: 68, 12) per decade of age at exposure, which indicates that the EAR would be about 4.7 times greater following exposure at age five compared to that at age 30. The change in EAR with attained age was not statistically significant.

B59. A pathological review of thyroid cancers in the LSS of atomic bombing survivors from 1958 through 2005 has now been reported [F29], including 371 thyroid cancers, but excluding microcarcinomas <10 mm in diameter. The ERR at 1 Gy, modelled for those exposed at age 10 and observed at age 60, was 1.28 (95% CI: 0.59, 2.70) and the EAR was 3.0 (95% CI: 1.4, 5.0) $(10^4 \text{ PY Sv})^{-1}$. The radiation risk decreased markedly with increasing age at exposure, such that there was little evidence of a radiation effect for those exposed at >20 years of age as the ERR was 0.27 (95% CI: <0, 1.07). They estimated that the ERR decreased by 53%, while the EAR decreased by 70%, per decade increase in age at exposure. The excess thyroid cancer risk among those <20 years old at exposure has persisted for over 50 years since exposure (figure B-V).

Figure B-V. Radiation and thyroid cancer incidence

Adapted from [F29]



2. Diagnostic radiology

B60. Inskip et al. [I39] conducted a study based on 484 thyroid cancers recorded in cancer registries covering the Uppsala region of Sweden for a 13-year period. The study included a search of hospital records for all diagnostic medical radiation procedures more than five years before diagnosis of thyroid cancer for the cases and a comparable period for the matched controls. For diagnostic exposures to the upper part of the trunk after age 20, there was a small (non-significant) diagnostic radiation-associated deficit of cases while for exposures before age 20, there was a small non-significant excess of cases.

3. Radiotherapy

B61. The external radiation doses to the thyroid in several major epidemiological studies were a few tens of milligrays to a few grays. Hempelmann et al. [H38] compared 2,872 patients who had received X-ray therapy for presumed thymic enlargement. The treatment was given in infancy, and the study population was compared to 5,055 non-irradiated siblings. The mean thyroid dose was 1.19 Gy with a wide range of doses (from 0.01 Gy up to >6 Gy for a few). The absolute risk derived was 2.7 cases annually per million persons exposed per 10 mGy. With Jewish subjects excluded, the absolute risk was lower, being 1.7 cases annually per million persons per 10 mGy (48 cases per million persons per 10 mGy). In 1993, Shore et al. [S66] reported on a study of this group with a mean follow-up time of 37 years. There were 37 thyroid cancers in the exposed group and five in the sibling controls. In the irradiated group, 33 cancers were papillary and four were follicular. The earliest cancer in this group was found six years after exposure, and the latest was at 49 years after irradiation. A linear dose–response model fit the data well, and the ERR at 1 Gy was 9.5 (95% CI: 6.9, 12.7). Jewish subjects

were noted to be at higher risk, as were women who were older at menarche or at first childbirth. In a recent update [A7], 50 thyroid cancers were identified in the irradiated group and 13 in the larger non-irradiated comparison group. After adjustment for several other risk factors, the ERR was 3.2 (95% CI: 1.5, 6.6) Gy^{-1}, with an EAR of 2.2 $(10^4\,PY\,Sv)^{-1}$. Although the ERR declined in longer periods, it was still elevated 58 years after irradiation.

B62. Maxon et al. [M11], examined 1,266 patients who had received external radiotherapy for an assortment of benign diseases in childhood. The mean thyroid dose was approximately 2.9 Gy. The male–female ratio in those who developed thyroid cancer was 0.6. The absolute risk factor derived from this study was 1.5 cases annually per million persons per 10 mGy.

B63. Ron and Modan [R32] examined Israeli patients who had been treated for tinea capitis with X-rays between 1949 and 1960; the estimated mean thyroid dose was 90 mGy. During irradiation, parts of the head, face, and neck were shielded with lead rubber sheeting, and the estimate of the dose depended critically on the children's maintaining a constant position. Nevertheless, statistical modelling of uncertainties suggested that the risk estimates would not be greatly affected by potential dosimetric uncertainties [L37, S26]. The ethnic background of this group was almost exclusively Jewish, and the absolute risk determined in this study was 13 cases annually per million persons per 10 mGy. A higher radiation risk was found in patients of Moroccan or Tunisian descent. There were 5,420 such subjects included. The absolute risk in the Moroccan and Tunisian subjects was 15 cases annually per million persons per 10 mGy and a lifetime risk of 140 cases per million persons per 10 mGy. Subjects from Israel, Asia, and other countries in North Africa had an absolute risk factor of seven cases annually per million persons per 10 mGy and a lifetime risk of 70 cases per million persons per 10 mGy. In an update of the Israeli tinea capitis group, Ron et al. [R39] estimated the ERR as 27 (95% CI: 15, 42) Gy^{-1} for childhood exposure. The absolute excess risk was 13 $(10^4\,PY\,Gy)^{-1}$. The risk was about twice as high among those irradiated before the age of five compared to those irradiated at ages 5–15 years. A statistically significant excess risk for thyroid cancer was found at doses between 50 and 100 mGy.

B64. In the most recent report on the Israeli tinea capitis patients, the median length of follow-up was 46 years [S7], with 103 thyroid cancer cases in the 10,834 irradiated subjects and 56 in the comparison group of 16,226 siblings or matched population controls. Nearly 10% of the irradiated subjects received more than one course of radiation treatment. The estimated doses ranged from 45 to 495 mGy, with a median of 87 mGy. A linear dose–response model provided an adequate fit to the data which was not improved significantly by adding a quadratic term, although there was some evidence of upward curvature. The ERR was 20 (95% CI: 12, 32) Gy^{-1} overall, and was about twice as high for those from North Africa as those from Israel or the Middle East. There was an age-at-exposure effect ($p = 0.02$), with the ERR of 34, 13 and 21 Gy^{-1} for irradiation at ages <5 years, 5–9 years and >9 years, respectively. The EAR was 9.9 (95% CI: 5.7, 15) $(10^4\,PY\,Sv)^{-1}$ overall, but was four times as high among females as males ($p = 0.001$). The risk coefficients were higher than those obtained in many other studies. It is unclear whether that was due to an underestimation of dose because of patient movement during radiotherapy, statistical fluctuations, an unusual sensitivity of this particular population, or undocumented X-ray treatments for scalp ringworm prior to immigration to Israel.

B65. A report by Shore et al. [S71] compared a group of 2,224 patients irradiated for tinea capitis at a mean age of eight in New York with 1,380 non-irradiated tinea capitis patients. The study, with a median follow-up of 39 years and an average thyroid dose of about 60 mGy [H24], found two thyroid cancers in the exposed group and none in the controls. A comparison of the two cancers in irradiated group with rates of thyroid cancer among the general population showed an SIR of 1.0 (i.e. 2.04 expected cancers). The comparison of irradiated and non-irradiated tinea capitis patients yielded an EAR estimate about six times lower than the Israeli study, so at face value the two tinea capitis

irradiation studies seem incompatible. However, the small number of cases in the New York study precludes a definite conclusion.

B66. A group of over 1,100 patients who were treated in Boston for lymphoid hyperplasia at an average age of seven years was located and asked to complete a questionnaire. A subset was clinically examined [P40]. The average length of follow-up was 29 years and the estimated mean thyroid dose was about 240 mGy. The analysis showed an ERR of 5.9 (95% CI: 1.8, 12) Gy^{-1} for thyroid cancer, based on 13 thyroid cancers (detected either by history or by screening and diagnostic examination) in the irradiated group and 2 in the unexposed group.

B67. A study performed in Chicago at Michael Reese Hospital initially followed up 2,189 persons who had received external radiotherapy to the head, neck, or chest prior to or during adolescence, predominantly for tonsillar hypertrophy [S31]. The absolute risk of cancer in this group was determined to be three–four cases annually per million persons per 10 mGy. The population included in this group may have contained a relatively high proportion of Jewish patients. The study was expanded to 4,296 X-irradiated subjects, including 2,634 for whom thyroid dose estimates and follow-up were possible. The mean age at treatment was four years, with an upper limit of 16 years, and the mean follow-up time was 33 years. The mean dose was 590 mGy. They documented 1,043 with thyroid nodules, including 309 with thyroid cancer [S33] of which 52% were <10 mm in diameter [B69]. When the estimates of thyroid cancer risk were compared for the time before screening and the time during which there were multiple screenings, there was no significant difference in the dose–response slopes, although the latter gave a smaller numerical risk estimate. The estimated ERR was 2.5 (95% CI: 0.6, 26) Gy^{-1} and the EAR was 3.0 (95% CI: 0.5, 17) $(10^4 \text{ PY Sv})^{-1}$ [R43]. They reported estimates of ERR of 3.6, 2.8 and 1.4 Gy^{-1} for treatments at ages <1 year, 1–4 years and 5–15 years, indicating a more than twofold gradient of risk over the age range 0–15 years.

B68. DeGroot et al. [D33] examined 416 patients who were irradiated at a mean age of seven years with a mean thyroid dose of 4.51 Gy. The study subjects volunteered for screening or were referred because of a suspected thyroid abnormality. Mean age at examination was 33.5 years and 41 thyroid carcinomas were detected. The average size was 1.7 cm, with 37% being less than 1 cm in size. Fifty-nine per cent of the tumours were multifocal, and 10 of 38 patients with cancer had normal radionuclide thyroid scans. Carcinoma occurred in 37% of single nodules and in 18% of multinodular glands in this population.

B69. Several studies reported on thyroid cancer incidence among patients who volunteered for thyroid screening because of a history of head and neck irradiation. Refetoff et al. [R15] reported the results of approximately 100 patients who had been irradiated during childhood or adolescence. Fifteen of these patients were subsequently subjected to operation, and seven cases of thyroid carcinoma were found. None of these were of the occult sclerosing papillary type; all were either papillary follicular or mixed in character. Paloyan et al. [P6] reported histological findings in 38 cancers found during operation on 70 such patients. Thirteen of the carcinomas were papillary, 8 were follicular and 17 were mixed papillary and follicular. DeGroot and Paloyan [D32] reported that among 50 patients seen for thyroid cancer, 20 had a prior history of neck irradiation. In addition, two thirds of patients who had had a history of neck irradiation and who had clinical thyroid abnormalities were later shown to have cancer. The ERR for the Chicago tonsillar radiation study was 3.0 (95% CI: 2.6, 3.5) and an excess incidence of cancers was seen at doses of about 0.5 Gy and above.

B70. Lundell et al. [L40] followed up a cohort of 14,351 infants given ^{226}Ra (81%) or X-ray (19%) treatment for skin haemangiomas during the 1920s through 1950s. On average, children had 1.5 treatments and received 260 mGy to the thyroid. The average age at treatment was six months, with a mean follow-up of 39 years. They found 17 thyroid cancers, which yielded an SIR of 2.3 (95% CI: 1.3,

3.7). Sixteen of the 17 cancers were among those treated with ^{226}Ra. A dose–response analysis showed an ERR of 4.9 (95% CI: 1.3, 3.7) Gy^{-1} and an EAR of 0.9 (95% CI: 0.2, 1.9) $(10^4 \text{ PY Sv})^{-1}$.

B71. Lindberg et al. [L26] followed up another cohort of 11,800 infants treated with ^{226}Ra for skin haemangioma between 1930 and 1965. Their median age at treatment was five months and the mean length of follow-up was 31 years. The estimated median thyroid dose was 120 mGy. Fifteen cases of thyroid cancer were observed, giving an SIR of 1.88 (95% CI: 1.05, 3.1). The ERR was 7.5 (95% CI: 0.4, 18) Gy^{-1}; the EAR was 1.6 $(10^4 \text{ PY Sv})^{-1}$.

B72. For comparison, a Swedish study of over 8,100 adults who received cervical spine radiotherapy (with an average thyroid dose of about 1 Gy) had a much lower risk estimate: an ERR of 0.6 (95% CI: 0.0, 1.4) Gy^{-1} [D4]. Most (15 out of 22) of the thyroid cancers were diagnosed more than 15 years after exposure.

B73. Radium applicators were used in some countries for nasopharyngeal irradiation to reduce the size of adenoid tissue. This was often used in children to reduce the incidence of otitis media and for submariners to reduce the potential for barotraumas [K36]. A report by Ronckers et al. [R48] on cancer incidence among 4,339 (89% under age 20) who received nasopharyngeal irradiation found an estimated thyroid dose of 15 mGy. After a mean follow-up of 31 years, they reported four thyroid cancers, giving an SIR of 2.8 (95% CI: 0.8, 7.2). A study of 904 children treated with radium for adenoid hypertrophy by Yeh et al. [Y5] found a non-significant excess of thyroid cancer based on two cases with a relative risk of 4.2 (95% CI: 0.4, 45).

B74. Thyroid nodules, both benign and malignant, have been reported after high-dose external radiotherapy. Hallquist et al. [H10] reviewed 1,056 cases of thyroid cancer. Thirty-seven of these had had a previous cancer and ten of these had received radiotherapy. The odds ratio was non-significantly increased at 1.1 (95% CI: 0.5, 2.8) and the thyroid doses ranged from 3 to 40 Gy. Van Daal et al. [V1] have followed up 605 persons treated with radiotherapy for benign diseases of the head and neck 16 to 46 years earlier. Seven thyroid carcinomas were found in this group, with a mean latency of 37 years. The mean dose to the thyroid was 11.1 Gy. The female–male ratio was 2.5, and average age at irradiation was ten years.

B75. De Jong et al. [D25] reported a retrospective analysis of thyroid surgery of 110 persons who had received childhood radiotherapy for acne. Of this highly select sample, 31% were found to have thyroid cancer. Such studies, unfortunately, cannot be used to develop risk estimates, owing to patient selection by a number of unknown factors.

B76. Several other reports of the late effects after childhood radiotherapy revealed that the frequency of thyroid cancer ranks second or third behind bone and soft tissue sarcomas. Mike et al. [M37] found 17 thyroid cancers in 15,000 children who had received radiotherapy for other cancers. Increases were noted mostly for patients who had been treated for Hodgkin's disease, neuroblastoma, or Wilms' tumour [K9, T48]. Hancock et al. [H18] reviewed 1,677 patients who had received radiotherapy for Hodgkin's disease. Forty-four patients developed thyroid nodules; six of these proved to be papillary cancers. The risk of thyroid cancer was 1.7%, and the risk was 15.6 times higher than that expected in a normal population. In the Late Effects Study Group [T49], the mean thyroid dose was 12.5 Gy and the mean age at exposure was seven years (range 0–18 years). There was a 53-fold increased risk of thyroid cancer compared to the general population rate in the 9,170 children who had survived more than two years (up to 48 years) after treatment for another cancer. Sixty-eight per cent of the cancers arose within the radiation field. The risk increased with dose and did not decrease even at doses as high as 60 Gy. The ERR was estimated to be 4.5 (95% CI: 3.1, 6.4) Gy^{-1}, but a later analysis as part of a systematic pooled study of thyroid cancer found an ERR of 1.1 (95% CI: 0.4, 29) Gy^{-1} [R43].

B77. A Nordic study by Sankila et al. [S21] of over 1,600 patients treated for Hodgkin's disease estimated a similar ERR of 0.8 (95% CI: 0.4, 1.5) Gy^{-1}.

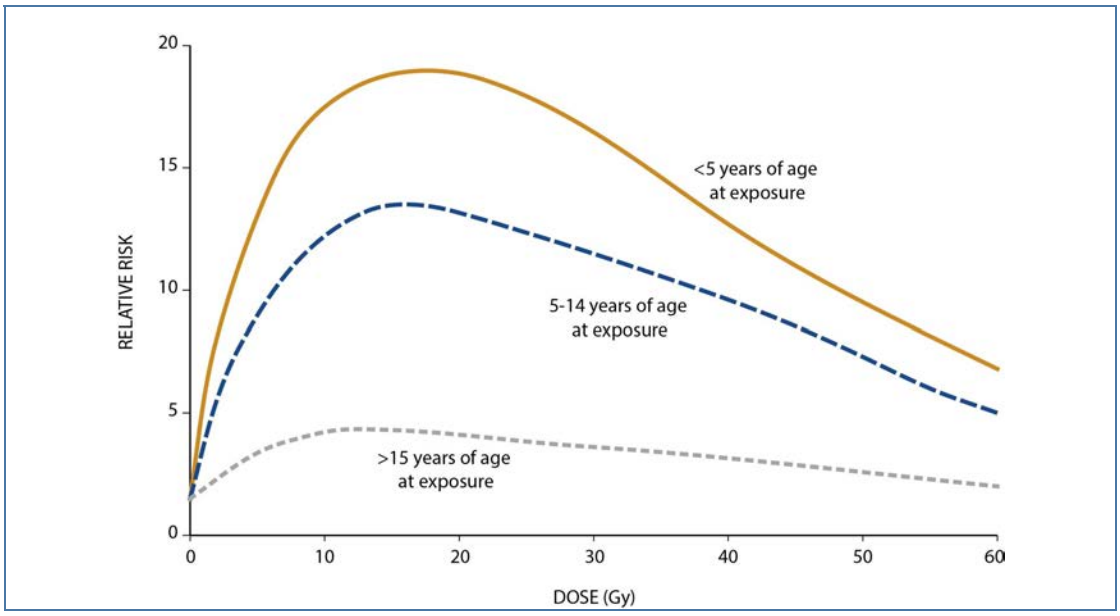
B78. A study reported by de Vathaire et al. [D28] of 4,096 children treated for cancer in France and the United Kingdom with a mean follow-up of 15 years was also consistent with an ERR in the range 4–8 Gy^{-1}. In a small study by Cohen et al. [C32], there was a high incidence of thyroid cancer (eight cases among 113 children), perhaps because of annual screenings with ultrasound and palpation. Six were papillary and two were follicular, and they appeared 3.1–15.7 years post-treatment.

B79. The long-term risk of thyroid cancer associated with radiation treatment was quantified among 12,500 five-year survivors of a childhood cancer (leukaemia, Hodgkin's lymphoma and non-Hodgkin's lymphoma, CNS cancer, soft tissue sarcoma, kidney cancer, bone cancer, neuroblastoma) diagnosed between 1970 and 1986 in the CCSS and followed up to 2005 [B26]. There were 119 subsequent pathologically confirmed thyroid cancer cases, and individual radiation doses to the thyroid gland were estimated for the entire cohort. Thyroid cancer risk increased linearly with radiation dose up to approximately 20 Gy, where the relative risk peaked at 14.6-fold (95% CI: 6.8, 31.5). Age at exposure modified the ERR linear-dose term (higher radiation risk with younger age, p <0.001), while sex (higher radiation risk among females, p = 0.008) and time since exposure (higher radiation risk with longer time, p <0.001) modified the EAR linear-dose term [B26]. A follow-up of 14,359 patients in the CCSS by Friedman et al. [F17] found an observed/expected (O/E) ratio of 128/12 and an SIR of 10.9 (9.1, 12.9) for thyroid cancer with a median time to diagnosis of 18.9 years.

B80. Veiga et al. [V15] pooled four studies that included 187 primary thyroid cancer cases among 16,757 childhood cancer survivors. Radiation dose-related thyroid cancer risk increased approximately linearly up to about 10 Gy, plateaued at about 10–15-fold risk for thyroid doses of 10–30 Gy, then declined but was still elevated at doses >50 Gy (figure B-VI). The fitted RR was 13.7 (95% CI: 8, 24) at 10 Gy. The radiation excess RR increased with decreasing age at exposure (p<0.01), but did not vary by attained age, time since exposure, or sex.

Figure B-VI. Modelled relative risk for thyroid cancer incidence by radiation dose after radiotherapy at various childhood ages, based on a pooled analysis of data from four cohorts

Adapted from [V15]



B81. In a study of over 19,200 patients who had received allogenic bone marrow transplants reported by Curtis et al. [C55], the absorbed fractionated whole body dose was about 12 Gy and the median age was 25 years. There was a statistically significant increase in thyroid cancer with an observed over expected ratio of 6.6 mostly occurring more than ten years after treatment. An observed over-expected ratio of ten was found by Bhatia et al. [B24] that, considering their absorbed doses were in the range 10–12 Gy, would yield an ERR of about 1.0 Gy^{-1}. Socie et al. [S93] reported on over 3,100 children following bone marrow transplantation and reported five cases of papillary carcinoma, with four of the five occurring more than five years post-radiation.

D. Internal exposure

B82. The major sources of human data concerning internal thyroid irradiation are: *(a)* patients receiving ^{131}I (and occasionally ^{135}I) for therapeutic purposes; *(b)* those receiving ^{131}I for diagnostic purposes; and *(c)* persons receiving mixtures of radioiodines in the environment.

1. Nuclear medicine

B83. Patients are sometimes administered radioiodine for diagnostic purposes. Hahn et al. [H4] followed up about 800 of 2,200 children who had received ^{131}I for diagnostic purposes and had an average thyroid dose of 1 Gy, and 1,100 evaluated for thyroid disease without exposure to radioiodine. The median age at exposure was 14.9 years. There was no increase in thyroid cancer later in life and the reported relative risk was 0.86 (0.14, 5.13). Possible participation biases cannot be ruled out in that only about 40% of eligible subjects participated.

B84. For up to 40 years, Hall et al. [H7] followed up 34,000 patients who had been given ^{131}I for diagnostic purposes. These had previously been reported on by Holm et al. [H57]. The mean thyroid dose was estimated as 1.1 Gy. They observed 67 thyroid cancer cases while the expected number from population rates was 50, giving an SIR of 1.35 (95% CI: 1.05, 1.7). However, subsequent excess cancers were seen only among those who had been referred for diagnostic examination for a suspected thyroid tumour, and there was no dose response. Among those irradiated before age 20, three thyroid cancers were observed whereas 1.8 would be expected. This provided a risk estimate several times lower than that obtained from the study of the survivors of the atomic bombings.

2. Radionuclides in the environment

B85. *Fallout from testing nuclear weapons.* Rallison et al. examined 5,179 children who had been exposed to fallout from the testing of nuclear weapons in the western United States during 1965–1970. The mean thyroid dose was estimated at that time to be 0.46 Gy [R4]. No significant difference between irradiated and non-irradiated subjects was identified. In 1985–1986, a re-examination of about 2,500 of the cohort was conducted [K27], and an improved dosimetry led to an estimated average thyroid dose of 0.17 Gy. Altogether, there were eight cases of thyroid cancer. This leads to an ERR of about 7.9 Gy^{-1} (lower 95% bound of 0.0, p = 0.10) which is substantially higher than risks obtained from the Swedish studies of patients exposed to ^{131}I for diagnostic purposes where the average thyroid dose was 0.56 Gy and the ERR was 0.4 Gy^{-1}, but the risk is similar to that seen in Chernobyl studies.

B86. Lyon et al. [L44] conducted a dosimetric and diagnostic reassessment of the above Utah thyroid data. After further cleaning of the dataset, correction of the dosimetry algorithm and a blinded review of the diagnoses using current criteria, they re-analysed the data. For the eight thyroid cancers, they reported an ERR of 0.8 Gy^{-1} (lower bound of 0.0, p = 0.10). For total nodules and neoplastic nodules, they reported large, statistically significant risk estimates. However, the original data had several limitations having to do with incomplete blinding and comparability of the examiners, and to uncertainties and possible biases in the dietary recall which was central to the dose estimates.

B87. Machado et al. [M2] compared thyroid cancer mortality in southwestern Utah with that in the rest of Utah and the rest of the United States. The odds ratio in both cases was non-significantly reduced at 0.4 (90% CI: 0.08, 2.00), suggesting less thyroid cancer mortality in the areas receiving heavier fallout. Gilbert et al. [G11] examined mortality from thyroid cancer across the continental United States compared to areas felt to have been exposed to fallout from the testing of nuclear weapons in Nevada. The result was a negative ERR in the potentially-exposed group which was not statistically significant and the risk did not increase with total cumulative dose or dose received at ages 1–15 years. A non-significant positive association was suggested for those exposed at less than one year of age with a mortality ERR of 10.6 (95% CI: -1.1, 29) Gy^{-1} and an incidence ERR of 2.4 (95% CI: -0.5, 5.6) Gy^{-1}.

B88. In 1954, the residents of the Marshall Islands were exposed to fallout that resulted in both external irradiation and ingestion of radioiodine. Nine thyroid tumours have been identified in 243 exposed subjects. The estimated risk was 145 (70 to 270) cases per 10,000 persons per gray. An increased risk in children could not be supported by the data, although the confidence limits of the statistics were quite wide. All the cancers occurred in females, again suggesting a higher induction rate in females than males. No thyroid tumours were observed in 504 unexposed subjects [C42]. The major contributions to dose were from the short-lived radioisotopes of iodine (^{132}I, ^{133}I and ^{135}I) with only about 10–15% of the dose from ^{131}I. Conard et al. suggested that the effects of the shorter-lived isotopes of iodine appear to be more like those predicted from external radiation exposure than from ^{131}I, although the exact types of exposures and amount of exposure in the Marshall Islands is somewhat difficult to ascertain.

B89. A Scandinavian study of thyroid cancer by Lund and Galanti [L38] appears on initial inspection to indicate an increase in thyroid cancer in Norway and Sweden due to fallout from the testing of nuclear weapons. The authors compared the incidence of thyroid cancer in children born in the period 1951–1962 (the exposed cohort) with that in cohorts born prior to or after that period. They found a borderline but significant RR of 1.7 (95% CI: 1.0, 3.0) for ages 7–14 years, but no excess risk at older ages. They acknowledged there may be other explanations for the results than exposure to fallout. Furthermore, they did not have any data on the different levels of dose to which the cohorts had been exposed.

B90. *Hanford and Mayak.* An analysis of the effects of discharges of radioiodine from the Hanford nuclear facility in the United States of America included 3,447 subjects who were born between 1940 and 1946 and resided in the region around the Hanford plant. Their mean dose was 174 mGy. This carefully conducted study reported by Davis et al. [D17] found 19 thyroid cancers, but it did not find a significant increase in thyroid cancer based on a standardized thyroid screening protocol. The estimated ERR was 0.7 (95% CI: <0, >500) Gy^{-1}, and the relative risk detectable with an 80% or better power at 170 mGy was 2.14, which means that the study had low statistical power. A study of residents near the Mayak facility suggested an increase in thyroid cancer risk, potentially associated with radioiodine releases, but no excess of childhood thyroid cancer was found [K46].

B91. *Chernobyl*. After the Chernobyl accident, there was an examination of the incidence of thyroid cancer in the areas affected by release of radioactive material. The four components of exposure of the thyroid were: *(a)* internal irradiation from intakes of ^{131}I; *(b)* internal irradiation from intakes of short-lived radioiodine (^{132}I, ^{133}I and ^{135}I) and of short-lived radiotellurium (^{131m}Te and ^{132}Te); *(c)* external irradiation from radionuclides deposited on the ground (predominantly ^{137}Cs and ^{134}Cs); and *(d)* internal irradiation from intakes of long-lived radionuclides (including radiocaesium). The first component gave more than 80% of the total thyroid dose and was predominantly due to the ingestion of fresh milk. The estimated release of ^{131}I was about 1.8 10^{18} Bq (about 45 million curies). The median thyroid dose in the most contaminated regions of both Belarus and Ukraine was about 0.3 Gy with a substantial fraction of doses exceeding 1 Gy.

B92. As of 1989, no definite increase in thyroid cancer rates had been seen, in part, perhaps, owing to the lack of a reliable pre-accident tumour registry [I2]. In 1991 and 1992, several reports were published of a markedly increased incidence of thyroid cancer in children in Belarus and to some extent in Ukraine [B18, K21]. These reports were unusual because the latent period was shorter than those reported in other studies of the incidence of thyroid cancer and because no increase had been found at that time in contaminated areas of the Russian Federation. As of 2000, however, many additional descriptive studies [I44, P55, S58, T37, T40, T45], two ecological studies by Jacob et al. [J3, J4] and one case–control study by Astakhova et al. [A27] had indicated a clear increased incidence of childhood thyroid cancer. More than 2,000 cases were diagnosed in the three affected countries in those under the age of 18 at the time of exposure. Many of the studies published after 2000 continue to report an increased SIR and the number of thyroid cancer cases in 2008 was estimated to be ~6,000. Evaluation of the dose–response relationship is complicated by the fact that in most studies, very few of the persons who had developed thyroid cancer had had measurements made of the activity in the thyroid shortly after the accident. As a result, most estimates of dose need to be based on dose reconstruction using caesium deposition as a surrogate for radioiodine exposure. In some cases, an average of the thyroid measurements in a particular settlement can be used.

B93. In a carefully conducted ecological study, Jacob et al. [J5] examined ^{131}I-associated risks of thyroid cancer in over 1,000 settlements in Ukraine and Belarus using the average of the thyroid measurements made in those settlements. They considered only settlements in which ten or more measurements had been made. The analysis was based on nearly 1,100 thyroid cancers. They estimated a linear ERR coefficient at 1 Gy of 18.9 (95% CI: 11, 27), but with a concomitant quadratic coefficient of -1.03 (95% CI: -1.46, -0.60) Gy^{-2}. The linear EAR coefficient was 2.7 (95% CI: 2.2, 3.1), combined with a quadratic coefficient of -0.145 (95% CI: -0.17, -0.12). The negative curvatures occurred primarily because of a downturn in risk at doses above 1 Gy. They reported that both the ERR and EAR varied inversely with age at exposure.

B94. The risks from ^{131}I exposure have been examined in detail in a case-control study by Cardis et al. [C3] of childhood thyroid cancer following the Chernobyl accident. The study included 276 thyroid cancer patients and 1,300 controls. Individual thyroid dose estimates were reconstructed, based primarily on reported location, milk intake, other lifestyle habits and whether they underwent stable iodine prophylaxis. Unfortunately, it was not possible to keep interviewers blinded as to case–control status because of visible thyroid surgery scars. The participation rates were much better for cases than controls, which might be another source of bias. Excess risk was identified at all doses above 0.2 Gy. At thyroid doses in excess of 2.0 Gy, the risk plateaued. The odds ratio at 1 Gy was between 5.5 (95% CI: 3.1, 9.5) and 8.4 (95% CI: 4.1, 17.3), depending on the risk model used. The risk is similar to that reported by Davis et al. [D18] in a smaller case–control study in the Bryansk oblast in the Russian Federation, and also was approximately the same as that seen with published studies of external exposure [R43].

B95. The prevalence of thyroid cancer at the first screening of a fixed cohort of 13,000 children exposed to radioiodine in Ukraine at ages 0–18 years was examined [T39]. The estimates of dose to the thyroid were based on individual measurements of ^{131}I in the thyroid made soon after the accident along with dosimetric data obtained by questionnaire. Thyroid cancers were detected by ultrasound or palpation, with fine needle aspiration for suspected cancer. A total of 45 thyroid cancer cases were detected—43 papillary and two follicular cancers. The dose response was approximately linear and showed an ERR of 5.3 (95% CI: 1.7, 28) Gy^{-1} for prevalent thyroid cancers. Those exposed at older ages had lower ERRs than those exposed at younger ages but the difference was not statistically significant. The ERRs were 9.1, 7.0 and 3.4 Gy^{-1} for those exposed at ages 0–4, 5–9 and 10–18 years, respectively. This prospective cohort study is subject to less bias than the prior case–control studies because the estimates of individual dose were based on direct measurements of activity in the thyroid, potential recall or interviewer bias was avoided, and uniform screening of all study subjects across the dose range was undertaken.

B96. Screening for thyroid cancer in this cohort has continued. After four screenings at approximately two–three year intervals, 65 additional incident thyroid cancers were detected—61 papillary, three follicular and one medullary [B60]. This gave an ERR of 1.9 (95% CI: 0.4, 6.3) Gy^{-1} for incident thyroid cancers with an approximately linear dose response, and an EAR of 2.2 (95% CI: 0.04, 5.8) (10^4 PY Gy)$^{-1}$. The risk estimates are somewhat lower than, but statistically compatible with, those found for external radiation exposure of children. A non-significant age-at-exposure effect was observed, with ERRs of 7.4, 1.6 and 0.7 Gy^{-1} for exposures at ages of 0–4, 5–9, and 10–18 years, respectively.

B97. A fixed cohort of nearly 12,000 Belarusians who were exposed at ages 0–18 years to radioiodine from the Chernobyl accident has been followed up with systematic screening for thyroid disease [Z1]. Measurements of ^{131}I in the thyroid of members of the cohort had been made shortly after the accident; a questionnaire was used to obtain additional dosimetric information. Estimated thyroid doses ranged from nearly 0 to 33 Gy with a mean dose of 0.56 Gy; since the dose response seemed to flatten out at higher doses, the primary risk estimates were based on the dose range 0–5 Gy. The estimated excess odds ratio was 3.2 (95% CI: 2.1, 73) Gy^{-1} based on the thyroid cancers previously diagnosed (n = 48) and those found through screening (n = 85). No age-at-exposure differences were found over the range 0–18 years.

B98. The role of iodine deficiency, iodine prophylaxis (iodine prophylaxis was used following the accident and also as a public health measure because goitre was endemic in the area) and screening bias remain possible confounding issues in risk estimation [R41]. Shakhtarin et al. [S48] and Cardis et al. [C3] have indicated that the ERR at 1 Gy was two- to threefold higher in areas of severe iodine deficiency. Ultrasound and physical screening of the general population appear to have had minimal impact on the studies of the general population. During the period 1996–2000, screening found only 15% of the thyroid cancer cases in the most contaminated regions of Ukraine. In Gomel, Belarus, the percentage found by screening seems to be greater, at least early on. Specifically, Astakhova et al. [A27] found appreciably higher odds ratios with general-population controls than with screening-matched controls (OR of 10.4 versus 7.4, respectively, for rural study subjects, and 5.1 versus 1.5, respectively, for urban subjects).

B99. The risk in children under the age of 10 has been reported by Heidenreich et al. [H37] to be about three times higher than in older children. A recent analysis of over 1,000 thyroid cancer cases in the regions contaminated by ^{131}I from the Chernobyl accident found that the risk was three to six times higher for those exposed at age five than for those exposed at age 15, with the ratio depending on the statistical model that was used [W12].

E. Summary

B100. Excess thyroid cancer risk has been seen following childhood exposures to the atomic bombings, Chernobyl fallout, and radiotherapy. The excess risk in children compared to that in adults is not possible to quantify since those exposed as adults appear to have little or no subsequent risk of radiation-induced thyroid cancer. The ERR for those irradiated in childhood derived from the major studies of external irradiation ranges from about 3 to 20 Gy^{-1}. A pooled analysis indicates a risk of about 7.7 Gy^{-1}; with a statistical adjustment to the one study that seemed to be an outlier, the pooled risk was reduced to 3.8 Gy^{-1}. There is no clear evidence from the studies of medical irradiation as to whether dose fractionation or a low dose rate is associated with a lower risk per unit dose than the same dose given acutely. However, the data from the populations exposed as a consequence of the Chernobyl accident generally show that exposure to radioiodine (mostly ^{131}I) carries risks similar to those from external, acute exposures. The studies from which risk estimates for thyroid cancer following childhood exposure can be derived have been summarized by the UNSCEAR 2006 Report [U12] and are updated for this report (see table B7).

Table B7. Age differences and risk estimates for thyroid cancer incidence and mortality from studies of childhood radiation exposure in the LSS for an exposed group including survivors with organ doses of 0.005 Sv (weighted thyroid dose) or more for incidence or mortality

Extracted from UNSCEAR 2006 Report (annex A, table 40) [U12] with updated and added studies. Studies listed are those for which quantitative estimates of risk could be made

Study		*Average ERR [a] at 1 Sv*	*Average EAR [a] (10^4 PY Sv)$^{-1}$*
Incidence			
LSS [P52]			
Age at exposure	<20 years	3.93 (2.57, 5.81)	3.07 (2.14, 4.14)
	20–40 years	0.99 (0.34, 1.93)	1.46 (0.49, 2.69)
	>40 years	0.29 (<0, 0.95)	0.86 (<0, 2.84)
All		1.59 (1.10, 2.19)	2.30 (1.67, 3.02)
LSS [F29][j]			
Age at exposure	<20 years	1.36 (0.59, 2.7)	3.0 (1.4, 5.0)
	≥20 years	0.27 (<0, 1.07)	
TB, adenitis screening [H23, S65]			
Age at exposure	<20 years	36.5 (16, 72) [b]	7.7 (3.3, 15) [b]
	>20 years	1.2 (0.1, 3.7) [b]	0.7 (0.1, 2.4) [b]
Israeli tinea capitis [S7] [c]		20 (12, 32) [b]	9.9 (5.7, 15) [b]
New York tinea capitis [S65, S71]		–0.67 (-29.96, 86.41) [b,j]	1.5 (0, 9.4) [b]
Rochester thymic irradiation [A7] [e]		3.2 (1.5, 6.6) [b]	2.2 (1.4, 3.2) [b]
Childhood cancer [R43, T49] [f]		4.5 (3.1, 6.4) [b] 1.1 (0.4, 29) [k]	0.4 (0.2, 0.5) [b]
Stockholm skin haemangioma [L40]		4.9 (1.3, 10)[j]	0.9 (0.2, 1.9)[j]
Gothenburg skin haemangioma [L26]		7.5 (0.4, 18.1)[j]	1.6 (0.09, 3.9)[j]

Study	*Average ERR [a] at 1 Sv*	*Average EAR [a] (10^4 PY Sv)$^{-1}$*
Lymphoid hyperplasia screening [P40, S65] [e,g]	5.9 (1.8, 12) [b]	9.1 (2.7, 18) [b]
Thymus adenitis screening [M11, S65]	4.5 (2.7, 7.0) [b]	1.2 (0.7, 1.8) [b]
Michael Reese, tonsils [S33] [h]		
<1 year	3.6	
1–4 years	2.8	
5–15 years	1.4	
All	3.0 (2.6, 3.5) [b]	37.6 (32, 43) [b]
Tonsils/thymus/acne screening [D32, S65]	12.0 (6.6, 20) [b]	3.5 (2.0, 5.9) [b]
Pooled external-irradiation study	7.7 (2.1, 28.7) [j] (all studies)	4.4 (1.9, 10.1) [j]
LSS Israeli tinea capitis Rochester thymic irradiation Lymphoid hyperplasia screening Michael Reese, tonsil [R43]	3.8 (1.4, 10.7) [l] (excluding Israeli study)	
Pooled childhood-cancer radiotherapy studies [V15]	2.2 (1.2, 4.3) [j]	1.3 (0.9, 1.8)
Russian Federation–Belarus Chernobyl case–control study [C3]	4.9 (2.2, 7.5) [n]	n.a.
Ukraine–Belarus Chernobyl cohort study [J5]	18.9 (11.1, 26.7) [i]	2.66 (2.19, 3.13) [i]
Ukraine cohort study [B60, T39]		n.a.
Age at exposure 0–4 years [n]	9.1 (1.3, 85) 7.4 (<1.7, n.a.)	
5–9 years (5–11 years)	7.0 (1.8, 33) 1.6 (<0, 8.5)	n.a.
10–18 years (12–18 years)	3.4 (0.7, 20) 0.7 (<0, 6.3)	n.a.
All	5.3 (1.7, 28) 1.9 (0.4, 6.3)	n.a. 2.2 (0.04, 5.8)
Belarus cohort study [Z1] [d]		
Age at exposure 0–4 years	4.0 (1.0, 15)	n.a.
5–11 years	2.0 (0.4, 6.2)	n.a.
12–18 years	1.4 (n.a., 5.0)	n.a.
All	2.2 (0.8, 5.5)	n.a.
Utah fallout study [K27, L44]	0.8 (0, n.a.) [m]	n.a.
United States fallout study [G11]	2.4 (–0.5, 5.6)	n.a.
Hanford fallout study [D17]	0.7 (<0, >500)	n.a.

Study		*Average ERR [a] at 1 Sv*	*Average EAR [a] (10^4 PY Sv)$^{-1}$*
Mortality			
LSS [P50]			
Age at exposure	<20 years	1.67 (<0, 7.67)	<0 (<0, 12.88)
	20–40 years	<0 (<0, 0.87)	<0 (<0, 0.23)
	>40 years	<0 (<0, <0)	<0 (<0, 0.01)
All		<0 (<0, 0.42)	<0 (<0, 43.97)

[a] *90% CI in parentheses derived from fitting models for the LSS detailed in [P52], and from published data for the other studies unless otherwise stated.*

[b] *Estimates based on UNSCEAR 2000 Report (annex I) [U10].*

[c] *Doses to the thyroid in this study may be much more uncertain than doses to organs directly in the X-ray beam.*

[d] *Thyroid cancers detected at screening.*

[e] *Known dose. Person-years and expected number of cases estimated from data given in reference [S65].*

[f] *Based on cohort members with 15 or more years of follow-up and population-expected rates.*

[g] *This was a study of nodular disease, and cancer cases were not confirmed.*

[h] *Study includes no unexposed controls; estimates of the number of expected cases were computed using the fitted ERR reported by Schneider et al. [S33]. The large EAR in this study illustrates the impact of screening on thyroid cancer risk estimates. A special thyroid screening programme in this cohort was initiated in 1974 which led to a large increase in the number of cancer cases detected among both cases and controls.*

[i] *Linear coefficient of linear-quadratic model fit, 95% CI.*

[j] *95% CI in parentheses.*

[k] *The publication gave an ERR estimate of 4.5, while the pooled analysis by Ron et al. [R43] produced an estimate of 1.1.*

[l] *The value of 3.8 is based on a model that allowed for a non-zero intercept in the Israeli tinea capitis exposed group, i.e. an overall difference between the exposed and non-exposed groups, perhaps because of a surveillance effect.*

[m] *Based on only 8 thyroid cancer cases.*

[n] *Fitted using linear-quadratic model for odds ratio over full dose range, 95% CI.*

V. BREAST CANCER

B101. Breast cancer accounts for 32% of all malignancies in women but less than 0.2% in men. It is the third most common cancer in the world and represents 9% of the global cancer burden. It is the most common cancer in females. Data concerning risk factors for breast cancer following radiation exposure come primarily from three major population groups. These groups have been extensively studied and include the survivors of the atomic bombings, patients who have had exposure to diagnostic radiology, and persons who have had radiotherapy to the breast. Epidemiological studies of radiation-induced breast cancer are of special interest with regard to the effects of dose rate upon the process of radiation carcinogenesis and age-at-exposure differences. The majority of studies indicate that breast cancer may be induced with a reasonably high frequency after radiation exposure of women who are under the age of 40 at exposure. Preston et al. [P48] have analysed the pooled dose–response data on radiation and breast cancer risk from eight studies, taking into account the age at exposure. The authors indicated that they thought the best statistical fit to the available data was a dose–response curve of approximate linearity. Although there may be a small element of curvilinearity, with the available data, it appears that risk estimates based on linearity of the dose–response curve are not likely to be far wrong.

A. Modifying factors

B102. In general, the results of population studies have provided only suggestions about a number of factors that modify radiation risk. Those that might increase radiation risk are irradiation at the time of menarche [B36] or the time of the first pregnancy [B36, S61]; nulliparity [B36, B65], obesity [V10]; family history of breast cancer [B36, R50]; and history of benign breast disease [S61]. Those that might result in decreased radiation risk are early age at first full-term pregnancy; several childbirths; and breast feeding [L3]. However, the results should be interpreted cautiously since most of the findings regarding factors that modify radiation risk are marginal and the results of attempts to replicate the modifying effects in multiple studies have been inconsistent [H49]. Low statistical power of the studies may have contributed to the inconsistency. Genetic factors may modify radiation risk. There is a suggestion that carriers of *ATM* gene mutations may be at heightened radiation risk for breast cancer [B16] while the data regarding *BRCA1/BRCA2* mutations and radiation exposure are mixed [B17, B64].

B103. Time after exposure may have a weak effect on the expression of risk. Earlier data suggested that the relative risk may increase for 15 years after exposure and then decrease [S56], but more recent incidence data from the study of the survivors of the atomic bombings indicated no significant modification of the relative risk with time since exposure ($p = 0.13$) [T23]. The effect of time since exposure was not examined in the most recent update on breast cancer incidence [P52]. Two strong modifying factors observed repeatedly are age at exposure and age at risk (attained age). A pooled analysis of eight studies found that a model using both age at exposure and age at risk fit the data better than one using age at exposure and time since exposure [P48].

B. External exposure

B104. In many studies of breast cancer, risk decreases markedly with increasing age at exposure. In fact, the studies of patients receiving multiple fluoroscopies in Massachusetts and Canada showed little if any detectable risk in women exposed over the age of 40 [B38, H67]. Studies of the survivors of the atomic bombings showed only a low risk after exposure above this age [L5, P52].

B105. In a pooled analysis of the data from eight studies using a smoothed model, the estimated ERRs at 1 Gy for those exposed at ages 5, 25 and 45 years were 1.10, 0.86 and 0.65, respectively [P48] (table B8). The corresponding EARs were 19.0, 13.4 and 8.8 per 10,000 person-years per gray, respectively. However, those analyses were based on a compilation of studies of subjects with disparate limited ages at exposure and with special medical conditions that might modify the risk, so the results may not be comparable across the age range.

Table B8. Radiation risk for breast cancer incidence and mortality by age at exposure

Studies listed are those for which quantitative estimates of risk could be made

Study and type of risk metric	*Age-at-exposure group [a] (years)*			
	Youngest	*Intermediate*	*Older/Oldest*	*Oldest*
8-study pooled data [P48] — incidence, ERR [b,c]	Age 5 1.10	Age 25 0.86	Age 45 0.65	
8-study pooled data [P48] — incidence, EAR [b,e]	Age 5 19.0	Age 25 13.4	Age 45 8.8	
A-bomb incidence, ERR [P48] [b,c]	Age 5 2.6	Age 25 1.8	Age 45 1.1	
A-bomb incidence, EAR [P48] [b,e]	Age 5 21.1	Age 25 11.6	Age 45 4.9	
A-bomb mortality, ERR [P50] [b]	Age 5 2.1	Age 15 1.4	Age 30 0.79 (90% CI: 0.29, 1.5)	Age 45 0.4
A-bomb mortality, EAR [P50] [b]	Age 5 4.7	Age 15 3.1	Age 30 1.6 (90% CI: 1.2, 2.2)	Age 45 0.7
A-bomb mortality, ERR [O25] [b]	Age 5 2.3	Age 15 1.6	Age 30 0.9 (95% CI: 0.3,1.8)	Age 45 0.4
A-bomb mortality, EAR [O25] [b]	Age 5 6.4	Age 15 4.3	Age 30 2.3 (95% CI: 1.0,3.8)	Age 45 0.8
A-bomb incidence, ERR (as reported in) [U12]	Age <20 1.89 (0.38, 2.50)	20–40 1.31 (0.86, 1.87)	>40 0.62 (0.04, 1.51)	
A-bomb mortality, ERR (as reported in) [U12]	Age <20 2.94 (1.63, 4.86)	20–40 1.01 (0.31, 2.06)	>40 <0 (<0, 0.99)	
A-bomb incidence, EAR (as reported in) [U12]	Age <20 8.78 (6.54, 11.28)	Age 20–40 6.97 (4.71, 9.54)	Age >40 2.49 (0.02, 5.82)	
BEIR VII — incidence, EAR [N43] [b,c]	Age 5 32.8	Age 15 19.9	Age 30 9.4	Age 45 4.4
Canada multiple fluoroscopy and A-bomb — mortality, ERR [H67] [b]	Age 5 1.5	Age 15 0.5	Age 30 0.11	Age 45 0.02
Canada multiple fluoroscopy and A-bomb — mortality, EAR [H67] [b,d]	Age 5 4.7	Age 15 2.6	Age 30 1.0	Age 45 0.3
Massachusetts multiple fluoroscopy—incidence, ERR [B38]	Age 0–14 1.76	Age 15–19 0.90	Age 30–39 0.16	Age ≥40 0.06
Rochester thymus irradiation — incidence, ERR [A6]	Infancy 1.10 (0.61, 1.86)			
Skin haemangioma irradiation — incidence, ERR [E10]	Early childhood 0.25 (0.14, 0.37)			
Hodgkin's disease — incidence, relative risk, RT (not per Gy) [H20]	Ages <20 33 (12, 73)	Ages 20–29 11 (6.4, 18)	Ages ≥30 0.7 (0.1, 1.9)	
Hodgkin's disease — incidence, SIR (not per Gy or limited to RT) [V10, V9]	Ages ≤20 17 (8, 32)	Ages 21–30 5.6 (2.9, 9.8)	Ages 31–39 2.4 (0.9, 5.2)	

Study and type of risk metric	*Age-at-exposure group [a] (years)*			
	Youngest	*Intermediate*	*Older/Oldest*	*Oldest*
Hodgkin's disease —incidence, SIR (not per Gy) [B25]	Ages 0–15 56 (40, 76)			
Hodgkin's disease—incidence, SIR (not per Gy or limited to RT) [M32]	Ages ≤16 22 (13, 34)	Ages 17–20 12 (8, 17)		
Hodgkin's disease—incidence, SIR (not per Gy or limited to RT) [D43]	Ages ≤20 14.2 (11, 19)	Ages 21–30 3.7 (2.9, 4.7)	Ages 31–40 1.2 (0.8, 1.7)	Ages >40 1.2 (1.0, 1.5)
Hodgkin's disease — incidence, SIR, RT (not per Gy) [S118]	Age <25 14 (6, 29)	Age 25–44 1.6 (0.5, 3.7)	Age ≥45 1.5 (0.4, 3.8)	
Hodgkin's disease — incidence, odds ratio, RT (not per Gy) [T35]	Age 13–17 4.2 (1.1, 22)	Age 18–21 2.1 (0.7, 8.3)	Age 22–25 2.0 (0.3, 17)	Age 26–30 2.9 (1.0, 11)

[a] *Numbers in parentheses represent 95% confidence intervals, unless designated otherwise.*

[b] *Estimates derived from the smoothed statistical model for age at exposure given in the publication, not estimates calculated for each individual age-specific data point.*

[c] *ERR at 1 Gy.*

[d] *EAR per 10,000 person-years per gray.*

[e] *Estimated as of attained age 60.*

1. Atomic bombing survivors

B106. Wanebo et al. [W13] identified a statistically significant excess of breast carcinoma among females in Hiroshima and Nagasaki in 1968. A number of updates permitting a better assessment of the magnitude and time course of risk have been published since then [J1, L5, T30, T28, T29, W5]. In an analysis of the survivors, who had a large range of ages and were unselected for medical conditions, the ERRs were 2.6, 1.8 and 1.1 after exposure at ages 5, 25 and 45 years, respectively, and the corresponding EARs were 21.1, 11.6 and 4.9 $(10^4\,\text{PY Gy})^{-1}$ at 1 Gy [P48]. In summary, the risks in the survivors of the atomic bombings obtained from these data were 2.5–4 times greater after exposure at five years of age 5 than after exposure at over 45.

B107. Land et al. [L5] performed a careful analysis of age-at-exposure effects on female breast cancer risk. They found that the ERR at 1 Sv was greater for exposures before age 20 than that after age 20. They did not find a significant variation in risk within the age-at-exposure range 0–19 years, although there was some indication that risk might be higher after exposure in early childhood (see figure B-VII). McDougall et al. [M17] also found similar risk estimates for those irradiated in early childhood and around the time of puberty.

B108. In the most recent examination of updated breast cancer incidence data, Preston et al. [P52] found that the ERR was comparable for all ages at exposure once attained age (age at risk) was included in the model (figure B-VIII). But without an adjustment for attained age, the ERR was -19% (90% CI: -33, -4) per decade of age at exposure. The EAR was appreciably higher for those exposed in childhood than for those exposed later in life at any given attained age (figure B-VIII).

B109. A number of reports have indicated that radiation exposure during early childhood may result in breast cancer in very young women [I32]. Land et al. [L2] evaluated this possibility in some detail. Among the survivors of the atomic bombings who were exposed at ages 0–19 years, they found that the ERR at 1 Gy was very high before the age of 35, being 13.5 (95% CI: 4.4, 64), compared to a twofold ERR at 1 Gy for cancers occurring after age 35 [L2] (figure B-IX). A more recent analysis of updated

data on the survivors of the atomic bombings showed that, even after allowing for an overall age-at-exposure effect, the ERR at 1 Gy was still 4.5 times greater before the exposed persons attained age 35 than that after that age. The EAR was 3.5 times greater than expected before age 35 [P52]. That excess is largely attributable to those exposed before age 20.

Figure B-VII. Estimated excess relative risk at 1 Sv for breast cancer incidence, by 5-year intervals of ages at exposure

Adapted from [L5]. The panel shows a non-parametric isotonic regression model with 90% confidence limits

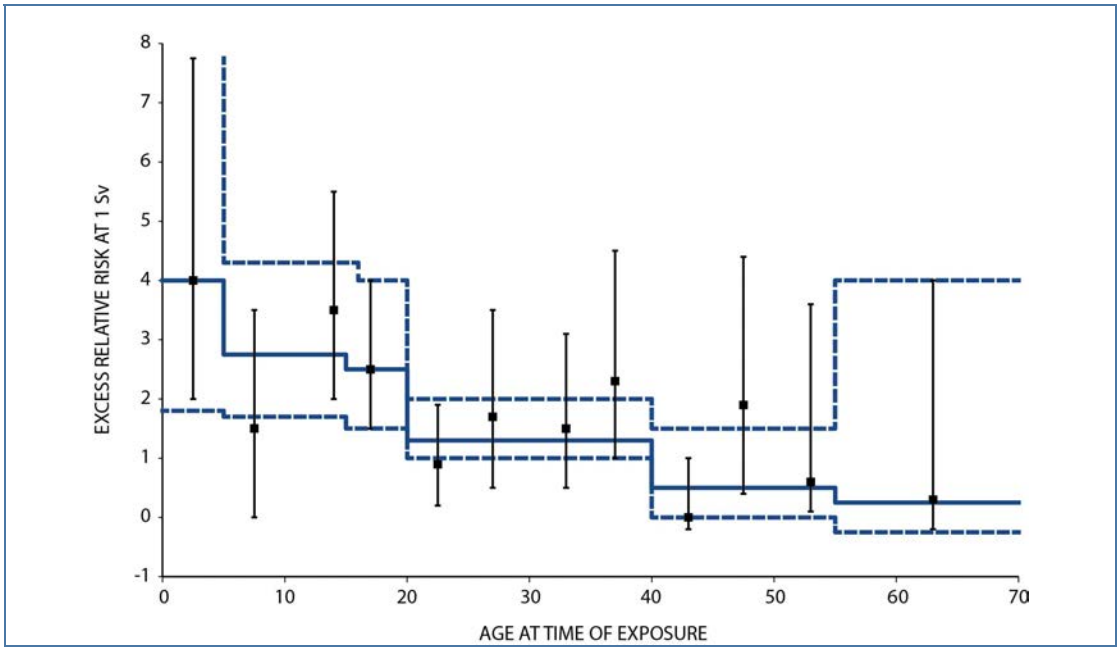


Figure B-VIII. Variation in radiation-associated excess breast cancer risk by age at exposure and attained age for an effect-modification model

Adapted from [P52]. In this model the excess risks are proportional to a log linear function of age-at-exposure and a power of attained age

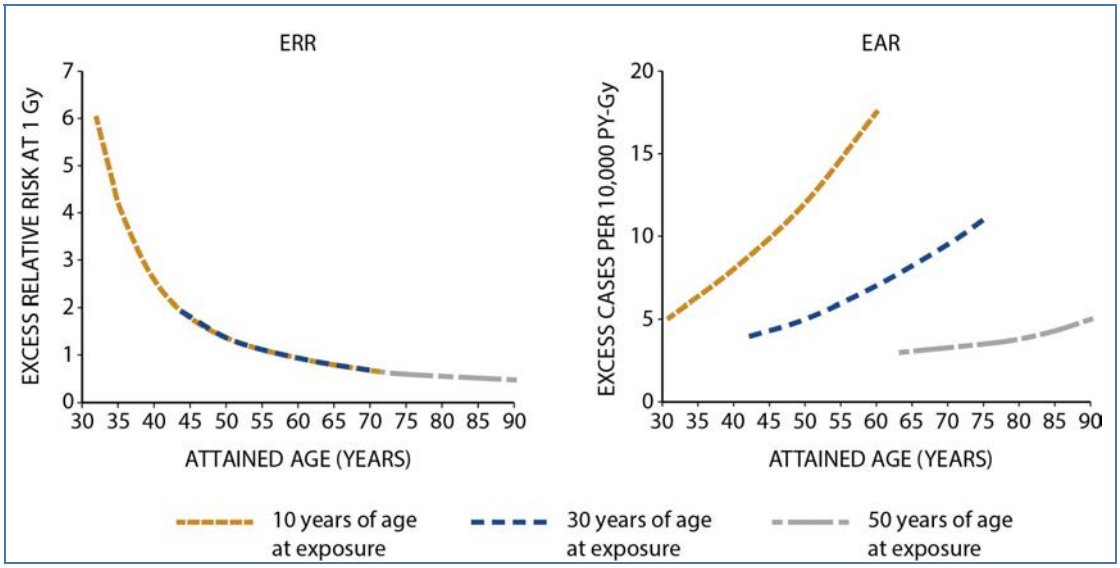
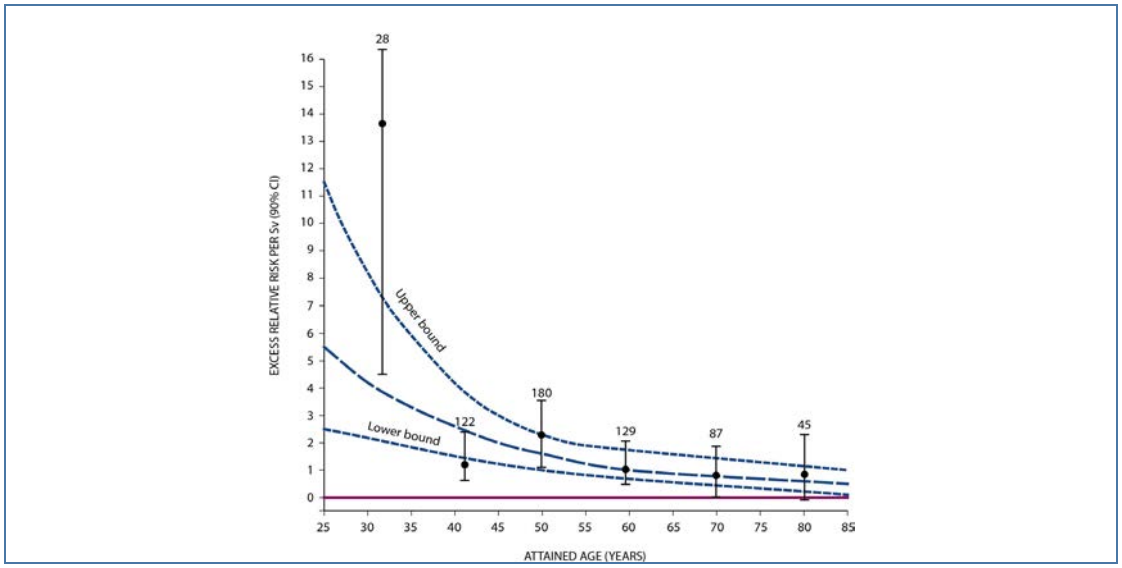


Figure B-IX. Heightened breast cancer risk at young ages

Adapted from [T30]. Modelled ERR per sievert by intervals of attained age. Estimates and 90% confidence limits were adjusted for city, age at exposure and time period. The corresponding total number of cases appears above the upper confidence limit for each interval of attained age



B110. A high risk of radiation-induced breast cancer from exposure at an early age was also found by van Leeuwen et al. [V9] in a study of survivors of Hodgkin's disease. For those exposed before age 20, they reported a relative risk of 61 (95% CI: 25, 127) for breast cancer occurring before age 40, but only 5.4 (95% CI: 0.7, 20) for breast cancer at ages 40–49. For those exposed after age 20, no differential was seen for the attained ages of less than 40 compared to those of more than 40.

B111. The Committee independently analysed breast cancer incidence and mortality by age at exposure [U12]. For breast cancer incidence, they derived an ERR at 1 Sv for exposure at ages <20, 20-40 and >40 years of 1.89 (95% CI: 1.4, 2.5), 1.31 (0.9, 1.9) and 0.62 (0.04, 1.5), respectively, while for breast cancer mortality, the respective risk estimates were 2.94 (1.6, 4.9), 1.01 (0.3, 2.1) and <0 (<0, 1.0). The EARs for the incidence of breast cancer were 8.78 (6.5, 11.3), 6.97 (4.7, 9.5) and 2.49 (0.02, 5.8) $(10^4 \text{ PY Gy})^{-1}$. Thus a higher risk of breast cancer was evident from exposure at young ages.

B112. The BEIR VII committee adapted the risk estimates from the pooled analysis of [P48] using an EAR model because that was considered to be better than the ERR model for the transfer of risk from the Japanese to the United States population [N43]. Their best-fitting model took into account both age at exposure and attained age (age at risk). For an attained age of 60 years, the EAR per 10,000 person-years per gray ranged from 32 to 4 for exposures at ages 5 to 45, respectively (table B8) [N43].

2. Background radiation, fallout and populations living near nuclear plants

B113. There are conflicting reports regarding breast cancer risk after the Chernobyl accident. One study reported excess risks among females in the exposed areas of Belarus (RR = 2.2; 95% CI: 1.5, 3.3), and Ukraine (RR = 1.8; 95% CI: 1.1, 2.9) with some indication that the risk may have been higher among those exposed when young (but this was not formally tested) [P62]. Another study reported an excess incidence of breast cancer among female Chernobyl clean-up workers, but not among Chernobyl evacuees or residents of contaminated areas [P60]. A third study reported no radiation-associated

excess of breast cancer in a highly exposed oblast in Belarus compared to a minimally exposed oblast [D10].

B114. Bauer et al. [B7] reported a significant dose–response trend (p = 0.004) for breast cancer mortality in the female population downwind of the Semipalatinsk atomic bomb testing site in Kazakhstan, with a relative risk in the exposed group, compared to the unexposed, of 1.85 (95% CI: 1.1, 3.2). However, effect modification by age at exposure was not examined. A study of residents near the Techa River in the Russian Federation showed a dose-dependent elevated risk for breast cancer [O18]. Because of a relatively small number of breast cancers (n = 109) and the relatively low distribution of breast doses, radiation modifying effects of various other factors were not statistically significant, but they noted that women who were under age 10 at first exposure appeared to have the highest excess breast cancer risk. Other studies of background radiation [N4, Z5] or radioactive fallout [H28, H29] have not studied breast cancer incidence or mortality.

3. Diagnostic radiology

B115. In 1965, MacKenzie [M3] reported the occurrence of excess breast cancer incidence among female patients exposed to multiple fluoroscopic examinations for treatment of pulmonary tuberculosis by artificial pneumothorax. The patients studied were treated in a Nova Scotia sanatorium. The dose to the breast was generally higher than that to the rest of the body because the patients receiving fluoroscopy were turned to face the radiation source. When the pneumothorax treatment was unilateral, the cancer usually developed on the side that received the majority of the radiation exposure from the treatment [M62]. An additional follow-up of this group was reported somewhat later by Myrden and Quinlan [M61]. There were 256 patients exposed during pneumothorax treatment, 32 of whom developed breast cancer. The control group comprised 535 patients with pulmonary tuberculosis who had not been treated with pneumothorax. Seven members of the control group developed breast cancer. The doses were estimated to be between 0.04 and 0.20 Gy for each examination, and the numbers of fluoroscopic examinations often exceeded 100. The average dose to the breast was estimated to be between 6 and 12 Gy. The Committee has previously estimated the excess cancer incidence rate to be between 20 and 200 cases per million persons per 10 mGy [U6].

B116. In a large study of about 30,000 Canadian patients, Miller et al. [M39] reported similar findings, but they indicated that when the females were between 10 and 14 years of age at exposure, the ERR was 3.5 Sv^{-1} and the absolute risk was 6.1 $(10^4 \text{ PY Sv})^{-1}$. The radiation effect appeared to peak between 25 and 34 years after exposure. Of interest was that patients treated in Nova Scotia (where the women faced the radiation beam) had a three times higher relative risk per unit dose than women treated in other provinces. One of the major problems associated with these studies is the exact determination of the fluoroscopic dose, and also the effect of disease and nutritional status on the patients.

B117. The most recent report on the Canadian multiple fluoroscopic examination study, based on the mortality experience from 1950 to 1987, included 103 breast cancer deaths in the Nova Scotia series and 578 in other provinces [H67]. The doses to the breast ranged from less than 0.01 Gy to greater than 10 Gy. The dose–response analyses were conducted in parallel with the data from the survivors of the atomic bombings for the purpose of comparison. The authors reported a statistically significantly higher radiation risk for those exposed before the age of 10 than after that age in the fluoroscopy study. Their model, treating age at exposure as a continuous variable (using the year of age (e.g. 5, 6, 7, 8) rather than age bands) showed estimates of excess relative risk at 1 Gy of 1.5, 0.5, 0.11 and 0.02 after exposure at ages 5, 15, 30 and 45, respectively, based on the combined data for the Canadian multiple-

fluoroscopy and atomic-bombing survivor cohorts. The excess relative risk estimates for the fluoroscopy series (with combined fluoroscopy and atomic-bombing survivor cohort estimates in parentheses) were 1.25 (1.41), 0.17 (1.44), 0.37 (0.44), 0.22 (0.24), 0.04 (0.05) and <0.0 (<0.0) for specific age bands of exposure of 0–9, 10–14, 15–19, 20–29, 30–39 and >=40, respectively.

B118. Boice et al. developed a cohort of former female patients at Massachusetts tuberculosis sanatoria where some had been treated with pneumothorax that entailed multiple fluoroscopic examinations to monitor the condition of the lung. Over successive reports, the irradiated cohort was increased from about 1,047 to 2,573 patients in the most recent report [B38, D14, H68]; the control group comprised 2,367 patients without any fluoroscopic examinations. The patients with pneumothorax had an average of 88 fluoroscopic examinations with an estimated mean cumulative dose to the breast of 790 mGy [B38]. The groups were followed up for an average of 30 years after their exposure had ended. There were 147 breast cancers cases in the irradiated group, an excess of 33, a small deficit was seen in the unexposed group. The overall ERR at 1 Gy was 0.61 (95% CI: 0.30, 1.01) and the EAR was 10.7 (95% CI: 6.0, 15.8) $(10^4 \text{ PY Gy})^{-1}$. The values of ERR at 1 Gy ranged from 1.76 and 0.90 when first treated at ages 0–14 or 15–19 years, respectively, to 0.16 and 0.06 when treated at ages 30–39 or >39 years, respectively. The inverse age-at-exposure trend was statistically significant ($p = 0.03$).

B119. Ronckers et al. examined breast cancer incidence among 3,010 women who received multiple radiological examinations at young ages between 1912 and 1965 in the course of treatment for scoliosis [R50]. The dose to the breast per examination was estimated to be 11 mGy on average, and the estimated mean cumulative dose to the breast among those with exposure was 132 mGy (range of estimated doses of 0 to 1,110 mGy). They received an average of 26.8 radiographs over the mean span of 6.1 years. Exposures were received mainly between the ages of menarche and first childbirth (or similar ages for nulliparous women). A total of 78 women developed invasive breast cancer. The estimated ERR at 1 Gy was 2.86 (95% CI: -0.07, 8.6; $p = 0.06$) based on a dose–response analysis. The authors suggested that this risk, which was nominally higher than that found among the survivors of the atomic bombings, may have occurred because the doses to the breast had been underestimated, although the relatively young age at exposure may have contributed as well, and the confidence interval includes a wide range of risk estimates.

B120. A notable feature of both the fluoroscopic-examination studies and the scoliosis study was the lack of diminished risk after highly fractionated exposure compared to that seen after acute, single exposures (such as those received by the survivors of the atomic bombings), although the confidence bounds on the risk estimates were fairly wide. Parallel analyses of the survivors of the atomic bombings with both the Canadian [H67] and Massachusetts [L30] fluoroscopy cohorts confirm the comparability of the risk associated with highly fractionated and single-acute exposures.

4. Radiotherapy for benign disease

B121. An increased risk of breast cancer in girls treated for presumed thymic enlargement in infancy has been reported by Hildreth et al. [H48, H46]. The 1,201 girls treated were compared to their 2,469 non-irradiated siblings. An increased risk was identified even in the group that had received doses of 0.01 to 0.49 Gy. The strengths of this study are that individual dosimetry was available, there was a long follow-up, and there was a sibling control group. The study also was able to evaluate the effects of dose fractionation to a limited degree, and a dose–response analysis could be performed. The weaknesses are that the size of the treatment fields varied, so the dosimetry for some sites is uncertain and the questionnaire follow-up may have caused some under-ascertainment of cases. In the most

recent update of this series, among the 1,120 women irradiated in infancy, there were 96 cases of breast cancer, while among the 2,382 unexposed women there were 57 cases of breast cancer after a mean follow-up of 57 years [A6]. The mean dose to the breast was 0.71 Gy (range from 0.02 to 14.4 Gy); 89% received only one or two treatments and 11%, three or more. A variety of risk factors were examined but none proved to confound the radiation-breast cancer association. The dose–response ERR for breast cancer was 1.10 (95% CI: 0.61, 1.86) Gy^{-1}, indicating a high breast cancer risk among those receiving radiation exposure in early childhood.

B122. Furst et al. [F25] followed up a cohort of children who had been treated for skin haemangiomas between 1920 and 1959 and reported an excess incidence of breast cancer related radiation exposure. Holmberg [H60] updated and combined two cohorts that included 17,202 women who had been irradiated for skin haemangiomas between 1920 and 1965 at a mean age of six months. The doses to the breast ranged from 0 to 35.8 Gy; 89% of the children had been treated with ^{226}Ra applicators and 11% with X-rays. There were 307 cases of breast cancers. A linear dose–response model, with adjustment for fertility pattern and menopausal status, showed an ERR at 1 Gy of 0.33 (95% CI: 0.17, 0.53). In the most recent report of this combined cohort, 678 cases of breast cancer were observed through 2004 [E10]. They reported mean and median absorbed doses to the breast of 0.29 and 0.04 Gy, respectively. At age 50, the ERR was 0.25 Gy^{-1} (95% CI: 0.14, 0.37) and the EAR was 3.1 (95% CI: 1.7, 4.3) $(10^4$ BreastY $Gy)^{-1}$.

B123. In the Rochester study of radiation treatment for acute postpartum mastitis, the treatment occurred over an age range of approximately 15–40 years [S64]. Within this age range, there was no evident differential in risk by age at exposure, but there were relatively few with exposure before age 18, and the data were complicated by the fact that the breasts were highly stimulated by hormones at the time of the radiation treatment.

5. Radiotherapy for malignant disease

B124. A number of studies examining the risk of breast cancer after the treatment of various childhood malignancies have been performed. The common theme in these reports is the radiation exposure to developing breast tissues, as can occur after radiation therapy for Hodgkin's lymphoma, Wilms' tumour (when breast tissue is in the abdominal field or the chest is irradiated for pulmonary metastases), sarcomas, etc. Relevant variables include the radiation dose both to breast tissues and to the ovaries (the latter relating to oestrogen secretion), pregnancy history, patient age, and genetic variations relating to the primary (initial) malignancy [H39].

B125. A breast cancer excess has been reported in the British CCSS [R19]. An SIR of 2.2 (95% CI: 1.8, 2.7) was found, but a breakdown was not given specifically for those who received radiotherapy. The American CCSS also found an excess of breast cancer (SIR of 9.8; 95% CI: 8.4, 11.5) but did not provide a breakdown by radiotherapy status [F17].

B126. Follow-up studies after treatment for Hodgkin's lymphoma with mantle radiotherapy have indicated at least a fourfold increase of breast cancer risk, with doses to the breast varying from 4 to 40 Gy, depending upon the technical factors and positioning. Janjan and Zellmer [J12] have indicated a dose response that is between a linear and cell killing model. Some authors [D35] believe that the increased risk in young females receiving treatment justifies routine mammographic screening before the age of 35. In general, the EAR increases dramatically more than 15 years after therapy. In a study of 885 women treated for Hodgkin's disease, Hancock et al. [H20] found 25 patients who had developed breast cancer. The estimated relative risk was 4.1 (95% CI: 2.5, 5.7). The relative risk in women treated

under 15 years of age was extremely high, being 33 (95% CI: 12, 73). For women who were over 30 years of age at exposure, there was no elevation of risk, the relative risk was 0.7 (95% CI: 0.1, 1.9). A United States study by Bhatia et al. [B25] of survivors of Hodgkin's disease in childhood found an SIR for breast cancer of 52 (95% CI: 40, 76). A Dutch cohort study by van Leeuwen et al. [V9]; reported an SIR of 17 (95% CI: 8, 32) for paediatric cases but this was reduced to 2.4 (95% CI: 0.9, 5.2) for women treated after the age of 30. This study is also of interest because it suggests that known protective factors for breast cancer (e.g. multiple births) also reduce the risk of radiation-induced breast cancer to the same degree as those that are not treated with radiation.

B127. A pooled study of European and United States survivors of Hodgkin's disease in childhood by Metayer et al. [M32] found SIRs of 22 for women treated prior to age 17, and 12 for those treated at ages 17–20. An enlarged pooled study over a broad range of ages by Dores et al. [D43] included 13,877 female patients who had had Hodgkin's disease with about 35% having ≥10 years of follow-up and 234 subsequent breast cancers. Those treated before age 21 had a large relative risk (SIR = 14.2; 95% CI: 10.7, 18.5) of subsequent breast cancer, while there was little risk for those treated at ages 31–50 (SIR = 1.4; CI: 1.1, 1.8) and none when treated after age 50 (SIR = 1.05; CI: 0.8, 1.4).

B128. The volume of tissue irradiated and dose are primary determinants in the occurrence of breast cancer. Mantle (chest) radiotherapy for Hodgkin's lymphoma is associated with an odds radio of 2.7 (CI: 1.1, 6.9) compared with similarly dosed mediastinal irradiation since the former includes the axilla wherein lies additional breast tissues. However, emerging data indicate that females treated with low-dose, involved-field radiation (i.e. lower radiation doses and fields that do not necessarily include axillary tissues) still exhibit excess breast cancer risk [O1]. As previously stated, for female patients treated with radiation exposure to the chest for Hodgkin's lymphoma before age 16 years, the cumulative incidence of breast cancer approached 20% by age 45 years [B25]. In a case–control study conducted as part of the CCSS that included 6,647 women who were five-year survivors of childhood cancer (all initial cancer types included), 120 patients (65% of whom were initially diagnosed with Hodgkin's lymphoma) were identified with breast cancer. The patients were matched with 464 sibling control patients. The odds ratio for breast cancer increased linearly with radiation dose, reaching a statistically significant value of 7.1 for doses of 11.4–29.9 Gy and 10.8 for doses of 30–60 Gy relative to no radiation exposure. The risk associated with breast irradiation was sharply reduced among women who received a dose of 5 Gy or more to the ovaries, with an excess odds ratio of 0.36 Gy^{-1} for those who received ovarian doses of less than 5 Gy and 0.06 for those who received higher doses. In this and other studies, the latency period after chest radiation ranged from 8 to 10 years, and the risk of subsequent breast cancer increases in a linear fashion with radiation dose (p for trend <0.001) [I40].

B129. Radiation-induced breast cancer has been reported to have more adverse clinicopathological features compared with breast cancer in age-matched population controls [D44]. The incidence of bilateral breast cancer seems to be increased in women treated with radiation exposure of the chest for paediatric or young adult cancer. From the large CCSS cohort, Kenney et al. [K25] reported bilateral disease in 17% of breast cancer cases: 5% were synchronous and 12% were metachronous. Other studies specific to Hodgkin's lymphoma also provide information about bilateral cancer [C59]. Of 219 women with breast cancer, 12.8% had bilateral disease (5.5% were synchronous and 7.3% were metachronous). In contrast, in population-based studies of the general population, 3–5% of women had bilateral disease; 1–3% were synchronous and 1–4% were metachronous. However, the population at risk for breast cancer after radiation exposure of the chest is still relatively young, so the percentage of cases with metachronous disease will probably increase over time.

6. Radiation and male breast cancer

B130. Male breast cancer following radiotherapy for benign conditions has occasionally been reported as individual cases [L33, O15], but most cohorts that have been exposed to radiation have had too few cases for analytical studies to be conducted. In the study of the Japanese survivors of the atomic bombings, nine male breast cancer cases were observed among the exposed persons and three among the unexposed, making a relative rate of 3.6 [R46]. A dose–response analysis showed an ERR of eight (95% CI: 0.8, 48) Gy^{-1}. The risk was about twice as high among those exposed before age 15 compared to those exposed after that age, but the small numbers precluded a formal statistical analysis. Thomas et al. [T18] suggested that male breast cancer could be increased by radiation exposure of the chest. However, this study had significant limitations since "exposure" was determined by personal interview after the breast cancer had occurred, and such studies may be subject to significant recall bias. In addition, given the very low dose distribution from X-ray exposure of the chest, a detectable radiation risk is not plausible with a sample size of less than 300 cases.

C. Internal exposure

B131. In a study of mortality among about 28,000 female patients treated for hyperthyroidism, mainly in the United States of America, only 3% were under age 20 at the time of treatment [R44]. Among those treated with ^{131}I, 248 breast cancer deaths were observed; the SMR was 1.10 (95% CI: 0.97, 1.2). There was a slight (non-significant) suggestion of a dose response in relation to the activity of the administered ^{131}I. In a similar study in Sweden [H6], 94 breast cancers deaths were observed—the SMR was 0.9 (95% CI: 0.7, 1.1)—among about 8,700 women treated with ^{131}I for hyperthyroidism. However, relatively few were under age 40 at treatment.

B132. A study of 5,260 Swedish, French and Italian female thyroid cancer patients, nearly half of whom had been treated with ^{131}I, some with additional external beam radiotherapy, found a suggestion of an increase in breast cancer incidence in the group exposed to ^{131}I; the SIR was 1.2 (95% CI: 0.9, 1.6; 54 cases) [R62]. However, there was no trend of increasing breast cancer risk with the administered quantity of ^{131}I, either for those who also received external radiotherapy or for those who did not. There was a suggestion of an increase in breast cancer risk among those exposed before age 20 (five cases of breast cancer in 344 patients), but the fraction of those with ^{131}I treatment was not reported and the number was too small for analysis. Other studies [D27, E8, G13, H5] of patients treated with ^{131}I for thyroid cancer had only small numbers of breast cancer cases.

D. Summary

B133. Female breast cancer can be induced by radiation. The difference in risk from exposure in childhood compared to that in adulthood depends upon the model used to analyse the data. Much of the published data indicate that age at exposure is an important factor in determining the risk of radiation-induced breast cancer. A number of studies attest that the highest risk occurs when age at exposure is less than about 18 years. The increased risk in those exposed as children compared to adults appears to be a factor of about three to five. At ages over 40 at exposure, the risk appears to be minimal or too small to be detectable in most low-dose studies. The minimum latent period may depend upon the age at exposure, with longer latent periods in the groups exposed at younger ages, although the findings of

the studies of the survivors of the atomic bombings in Japan [L2] and Hodgkin's disease in the Netherlands [V9] of a high risk at young ages (before age 35 or 40) suggests that there might be a susceptible subpopulation prone to early breast cancer risk. However, consistent findings from a number of studies suggest that after the minimum latent period, the risk of radiation-induced breast cancer persists for the remaining lifetime, much as it appears for other solid cancers [P52].

B134. Most data support a linear dose–incidence model for doses to the breast of up to about 3 Gy. At higher doses, the risk may reach a plateau and then decrease. Many studies of groups exposed to doses less than 0.2 Gy do not show an increased risk, which may reflect inadequate statistical power. There are a number of potential confounding variables that should be considered in an analysis of data, especially length of follow-up and ages at follow-up, and sometimes potential for cell killing. There is some evidence that radiation may act additively with regard to the different baseline incidence rates for the Japanese and western population. The limited data regarding modification of the radiation effect by reproductive and other breast cancer risk factors have tended to be inconsistent and do not suggest any major radiation-risk modification. The literature on genetic radiation-risk modifiers has mixed results and often methodological limitations.

B135. Risk estimates for population exposure have been summarized in detail by the Committee in the UNSCEAR 2008 Report [U12]. Although it is generally felt that the risks at low doses and dose rates are a factor of 1.5 to 2 lower than those observed at high acute doses, two sets of direct comparisons of single and highly-fractionated exposures have suggested there is little, if any, justification for such a reduction regarding breast cancer. Radiation risk factors for breast cancer have been summarized in the UNSCEAR 2006 Report [U12]. Variations in radiation-associated risk with regard to age at exposure are summarized in table B8.

VI. STOMACH CANCER

B136. In 1980, stomach cancer was considered to be the single most common form of cancer in the world, accounting for about 10–11% of all new cases [I5]. The highest incidence areas are Japan, Korea, and parts of China. Diet probably has an impact on the incidence of stomach cancer, with higher nitrate, nitrosamines, and salt intake associated with higher risk. Persons with blood type A and those who have had gastric surgery have also been shown to be at increased risk in some studies [H45]. Ninety-five per cent of malignant stomach tumours are adenocarcinomas. The most common sites are the lesser curvature and antral portions of the stomach. A report on the atomic bombing survivors by Ito et al. [I41] has suggested that the frequency of poorly differentiated adenocarcinoma was somewhat higher in the group exposed to more than 0.01 Gy than in a no-exposure group.

A. External exposure

1. Atomic bombing survivors

B137. The 1994 LSS incidence study of the atomic bombing survivors, which included 40,759 persons with >=10 mGy and 39,213 controls with <10 mGy, found a statistically significant increase

for cancer of the stomach [T24]. During 1958–1987, 1,307 cancers were observed versus 1,222 expected (an excess of 85 cases) in 792,500 person years of observation for those who received 0.01 Sv or more. A linear dose response fitted the data. The ERR at 1 Sv was estimated to be 0.32 (95% CI: 0.16, 0.50), and the EAR was 4.8 $(10^4 \text{ PY Sv})^{-1}$. They reported that the ERR estimate decreased with increasing age at exposure (p = 0.03), with ERR Sv^{-1} estimates of 0.65, 0.69, 0.43 and 0.12 for those exposed at ages 0–9, 10–19, 20–39 and >=40, respectively. The ERR at 1 Sv was 0.18 for males of all ages and 0.51 for females [T24].

B138. The LSS mortality study data for the period from 1958 to 1987 [P33] also demonstrated a statistically significant increase in cancer of the stomach. Compared with the 1,107 expected (an excess of 56), 1,163 stomach cancer deaths were observed in 1,203,100 person years of observation for the 41,000 persons who received 0.01 Sv or more. In this study the ERR at 1 Sv was estimated to be 0.2, and the EAR was 1.9 $(10^4 \text{ PY Sv})^{-1}$. In the 2003 update studies of the mortality of atomic bombing survivors during the period 1950−1997, Preston et al. [P50] had a cohort of 86,572 persons with an average external dose of 0.23 Sv. In males, there was a statistically marginally significant excess of stomach cancer at dose levels of 1 Sv with an ERR of 0.20 (90% CI: 0.04, 0.39). In females, there was a statistically significant excess at dose levels of 1 Sv with an ERR of 0.65 (90% CI: 0.40, 0.95).

B139. In the latest report on cancer incidence among the LSS survivors [P52] for the period 1958–1998, an approximately linear dose response was seen. When both age at exposure and attained age (age at risk) were modelled, the ERR model gave no clear indication of more risk after exposure at younger ages (change of -13% per decade of age, 90% CI: -35, 15; p = 0.4). For the EAR model there was no indication of an age-at-exposure trend (EAR = -2%; 90% CI: -26, 29). The updated cancer mortality data [O25] likewise showed no significant effect variation by age at exposure: an ERR model change of -18% per decade of age (95% CI: -47, 20), and an EAR model change of 18% per decade (95% CI: -18, 62).

2. Medical radiation uses

B140. The studies of radiotherapy for benign conditions that have evaluated stomach cancer—treatment for ankylosing spondylitis, benign gynaecological disorders, or peptic ulcer—have mainly described effects associated with adult exposures and so are not informative regarding risks from childhood radiation exposure.

B141. A study of patients given multiple fluoroscopic examinations of the lung in conjunction with pneumothorax treatment for tuberculosis contained a large number examined before age 20 but did not report an excess of stomach cancer mortality (sex-averaged SMR = 0.8) [D15]. However, the estimated mean stomach dose was only about 60 mGy, so the lack of an excess was not surprising. Similarly, a study of girls who received multiple radiographs for scoliosis showed no excess of stomach cancer [B26]. Again, the mean stomach doses were probably low, though the stomach doses per se were not estimated (mean lung dose of 41 mGy).

B142. Dores et al. [D43] reported on the follow-up of 32,000 patients treated for Hodgkin's lymphoma. They found an increasing risk of subsequent stomach cancers for younger ages at exposure (observed/expected ratio O/E = 13.8, 7.1, 3.1 and 1.1 for those diagnosed at ages <=20, 21–30, 31–50 and >50 years). However, the results were not broken out by radiotherapy alone versus multiple therapies.

B143. Van Leeuwen et al. [V7] reported on second cancer risk in 1,909 testicular cancer patients and found a significantly increased relative risk for stomach cancer of 3.7 (95% CI: 1.8, 6.8). Similar

findings were reported by Travis et al. [T36], who examined long-term survival and second cancers in over 40,000 testicular cancer patients almost all of whom received infradiaphragmatic radiotherapy and in whom the relative risk for stomach cancer was significantly increased.

B. Internal exposure

B144. Hall et al. [H5] found a suggestion of excess stomach cancer (O/E = 7/4.0) among patients given ^{131}I therapy for thyroid cancer, with a mean stomach dose of 2.1 Gy but no information is available specifically related to childhood exposure.

C. Summary

B145. Risk estimates for stomach cancer can be derived from certain epidemiological studies. From the atomic bombing survivor data, there appears to be a higher ERR in females than in males, but this is not seen in all studies. There also appears to be a decrease in relative risk with age at exposure of over 30 years [U12].

B146. The UNSCEAR 2006 Report [U12] summarized radiation risk factors for stomach cancer that could be derived from epidemiological studies (table B9). The updated information from the Japanese LSS and the peptic ulcer radiotherapy study continue to show a positive dose-response relationship. The LSS data provide weak evidence that the ERR may decrease with increasing age at exposure but the EAR does not. Likewise, the very limited evidence from other studies does not support an increased sensitivity among those exposed at young ages.

Table B9. Risk estimates for stomach cancer incidence and mortality from studies of childhood radiation exposure

Updated and adapted from UNSCEAR 2006 Report (annex A, table 22) [U12]. Studies listed are those for which quantitative estimates of risk could be made

Study		*Average ERR [a] at 1 Sv*	*Average EAR [a] (10^4 PY Sv)$^{-1}$*
Incidence			
LSS (1958-1988) [U12], based on [P52]			
Sex	Males	0.26 (0.14, 0.42)	2.45 (0.92, 4.49)
	Females	0.51 (0.33, 0.72)	4.36 (2.78, 6.15)
Age at exposure	<20 years	0.56 (0.32, 0.85)	2.74 (1.52, 4.19)
	20–40 years	0.39 (0.22, 0.59)	6.18 (3.42, 9.32)
	>40 years	0.23 (0.07, 0.41)	7.99 (2.25, 14.59)
All		0.37 (0.26, 0.49)	3.61 (2.42, 4.96)

Study		*Average ERR [a] at 1 Sv*	*Average EAR [a] (10^4 PY Sv)$^{-1}$*
LSS (1958-1998) [P52]			
Age at exposure	10 [c] years	0.44 (0.20, 0.83)	9.9 (4.5, 18)
	30 years	0.34 (0.22, 0.47)	9.5 (6.1, 14)
	50 years	0.25 (0.12, 0.44)	9.2 (4.2, 16)
	0–9 [d] years	0.63 (0.23, 1.4)	
	10–19 years	0.38 (0.19, 0.68)	
	20–39 years	0.38 (0.22, 0.56)	
	≥40 years	0.23 (0.06, 0.42) [b]	
Mortality			
LSS [P50]			
Sex	Males	0.11 (<0, 0.30)	0.32 (<0, 1.33)
	Females	0.50 (0.27, 0.75)	1.46 (0.55, 2.56)
Age at exposure	<20 years	0.72 (0.29, 1.27)	0.51 (<0, 1.27)
	20–40 years	0.42 (0.18, 0.71)	2.78 (1.06, 4.82)
	>40 years	0.12 (<0, 0.31)	3.46 (<0, 8.03)
All		0.28 (0.14, 0.42)	0.94 (0.31, 1.71)
LSS [O25]			
Age at exposure	10 years [c]	0.46	2.8
	30 years	0.33 (95% CI: 0.17, 0.52)	4.1 (95% CI: 2.1, 6.7)
	50 years	0.22	5.7

[a] *90% CI in parentheses derived from fitting models for the LSS detailed in [P52], and from published data for the other studies, unless otherwise stated.*

[b] *Estimates based on UNSCEAR 2000 Report (annex I) [U10].*

[c] *Sex-averaged risk at attained age 70, smoothed assuming the ERR Gy^{-1} varies as a log-linear function of age at exposure.*

[d] *Sex-averaged risk at attained age 70, assuming that within each age-at-exposure group the ERR Gy^{-1} varies as a power of attained age, but with no smoothing across age-at-exposure groups.*

VII. SKIN CANCER

B147. An excellent review of radiation effects on the skin has been produced by the ICRP [I12] and the reader is referred to this for a more detailed discussion. Although skin cancers were the first malignant tumours reported to be induced by radiation (in 1902), and 50 cases were described by 1911, to date still few data are available on the frequency and the risks of these tumours.

B148. The most common cell type is basal cell carcinoma. Squamous cell carcinomas are about $^1/_3$ to $^1/_6$ as common. Skin cancer is not usually included in radiation mortality risk estimates because of the very low mortality associated with basal cell and squamous cell skin cancers. The statistics of the incidence of skin carcinomas are somewhat difficult to evaluate because often melanomas are included

with basal cell carcinoma and squamous cell carcinoma. However, it should be noted that there is no clear evidence of excess cutaneous malignant melanomas following ionizing radiation exposure.

A. Modifying factors

B149. Epidemiological studies suggest that the effects of ultraviolet irradiation and ionizing radiation are probably additive. One study suggested that ultraviolet and ionizing radiation exposure effects may be multiplicative [S62, S70], but a study on the atomic bombings did not confirm that finding [K35]. The latent period for induction of skin tumours is extremely wide, with the risk continuing for over four decades to the maximum lengths of follow-up thus far. Patients with ataxia telangiectasia have cells that are sensitive to ionizing radiation cell-killing effects, but there is no evidence of increased skin cancer after ionizing radiation exposure. The frequency of A-T in Jewish children of Morroccan ancestry is about five times higher than in most populations, and how much of a role this may play in the findings reported in Israeli children (discussed below) is unknown. A study has examined genetic susceptibility factors for radiation-associated non-melanoma skin cancer risk. Among atomic bombing survivors, certain alterations in the *p53* and *PTCH* genes were found in a greater proportion of the exposed group cancers than in low/unexposed group cancers [M43].

B. External exposure

1. Fallout and atomic bombing survivors

B150. Originally, there was no excess of skin cancer identified in the atomic bombing survivors. This may be because the studies were primarily mortality studies, and mortality from skin cancer is so low. At the end of the last decade, reports began to appear of an increased incidence of skin cancer at Nagasaki [S3, S1, S2, S4]. The incidence study from Hiroshima and Nagasaki [T24] of the 41,000 persons who received 0.01 Sv or more and an average dose of 0.23 Sv showed that there were 98 non-melanoma skin cancers observed versus 76 expected (excess of 22) in the 863,000 person years of observation. The data can fit a linear dose-response model, but there was no effect of sex, age at exposure, time since exposure, or attained age.

B151. A more detailed analysis of skin cancer data among atomic bombing survivors for the years 1958–1987 was based on 80 basal cell and 69 squamous cell skin cancers [R45]. They found that neither a linear-quadratic, nor a spline model with a change-point at 1 Gy improved the fit significantly, although the latter was marginal ($p = 0.09$). The ERR was strongly modified by age at exposure, decreasing by 11% (90% CI: 6, 16) per year of age at exposure.

B152. The published data for 1958–1998 [P52] were based on 330 non-melanoma skin cancers, including 166 basal cell and 131 squamous cell cancers. Because of possible Adult Health Study clinical surveillance effects, all analyses were adjusted for membership in the study. Radiation risk was confined to basal cell cancers (ERR Gy^{-1} of 0.57; 90% CI: 0.18, 1.38; squamous cell ERR Gy^{-1} of 0.17, not significant). For all non-melanoma skin cancer a linear model gave a ERR estimate of 0.58 Gy^{-1}. However, a spline model with a change-point at 1 Gy provided a significantly ($p = 0.005$) better fit and yielded an ERR estimate of 0.17 below 1 Gy and 1.2 above 1 Gy. The sex-averaged EAR was 0.35

$(10^4$ PY Sv$)^{-1}$. There was a strong age-at-exposure effect ($p < 0.001$), such that radiation risk decreased with increasing age at exposure. The age-at-exposure effect for the ERR was −73% (90% CI: −85, −55) per decade age at exposure, and for the EAR was −61% (−75, −42).

2. Radiation therapy

B153. Two studies have been conducted on children given radiotherapy to the scalp to treat tinea capitis (ringworm of the scalp). The study results are of special interest because they represent ethnic groups with different susceptibilities to ultraviolet-induced skin cancers. A study was conducted in Israel on 10,834 children (ages <1 to 15 years) given scalp irradiation plus 16,226 non-irradiated controls, including 5,392 non-irradiated sibling controls. The patients were followed up for up to 30 years [G19, M44, R40]. They estimated the mean scalp dose as 6.8 Gy (range 5.5 to 24.4 Gy). They identified medical records for 42 non-melanoma skin cancers (41 were basal cell) in the irradiated group and 15 in the larger group of controls. They found a significant dose response ($p < 0.001$) and an ERR Gy^{-1} of 0.7. The EAR $(10^4$ PY Sv$)^{-1}$ was 0.31. The relative risks for those given radiation treatment at ages 1–4, 5–9 and 10–15 were 19.0 (95% CI: 14, 28), 5.9 (CI: 3.3, 11) and 2.0 (CI: 1.3, 4.0), respectively. They reported that the patients who developed cancers reported more radiodermatitis and epilation, suggesting that they may have received higher doses than originally recorded [M46, R40]. There was also some indication that they were more frequent sunbathers, suggesting that there is a potentiating effect of ultraviolet light. The relative risk decreased significantly with increasing age at exposure. Specifically, a five-year increase in age at exposure led to an 80% decrease in the relative risk.

B154. The New York study was based on tinea capitis patients—2,224 children with and 1,380 without X-ray treatment. In both groups 24–25% were blacks and the remainder whites, and the groups were followed up for up to 50 years [S70]. The mean dose to the scalp and 2 cm around the scalp (where a number of basal cell carcinomas occurred) was estimated as 4.3 Gy. They identified 128 cases of non-melanoma skin cancer of the head and neck in the irradiated group and 21 in the non-irradiated controls. Seven irradiated cases had a squamous cell carcinoma, of which six also had one or more basal cell cancers. In the black subgroup, only three cases occurred among the irradiated and none among controls; the EAR was 10.0 (95% CI: 3.2, 31) times as great among whites as blacks. Among whites, the ERR Gy^{-1} was 0.6 (95% CI: 0.3, 1.1) and the EAR $(10^4$ PY Sv$)^{-1}$ was 1.9 (CI: 0.5, 3.3). An analysis of susceptibility factors showed that northern European ancestry, sunburn susceptibility and light skin colour were statistically significant joint predictors along with radiation of basal cell cancer risk, but no factors showed interaction (effect modification) with radiation. Age at irradiation was a significant co-factor ($p = 0.002$). Ionizing radiation exposure at a younger age conferred more skin cancer risk than exposure at an older age. The risk declined by 12% per year of age at irradiation.

B155. Four other groups were treated with radiation therapy for other reasons and, again, the results are diverse. Hempelmann et al. [H38] found nine of 2,872 persons irradiated for thymic enlargement to have skin cancer versus three among a group of 5,055 controls. Skin doses ranged from about 0.4 to 15 Gy, with a mean of 3.3 Gy. The absolute risk was not substantially different between those who received less than 4 Gy and those who received more than 4 Gy. The risk estimates did differ, depending on the number of fractions given in the dose regimen. There may be a slightly increased subsequent risk of skin cancer in children who have been treated with radiotherapy for retinoblastoma [M23]. Whether this is the result of radiation exposure or of a genetic susceptibility is not clear.

B156. A case-control study of non-melanoma skin cancer and history of radiotherapy found that only radiotherapy before age 20 conferred a significant risk for basal cell skin cancer (OR = 3.4; 95% CI:

1.5, 7.5) and squamous cell skin cancer (OR = 2.8, 95% CI: 1.1, 7.3) [L24]. The study was subsequently enlarged to include 1,121 basal cell carcinomas and 854 squamous cell carcinomas [K10]. For basal cell carcinomas within the radiotherapy field, the odds ratios before and after age 20 were 4.1 (95% CI: 1.8, 9.4) and 1.8 (0.9, 3.5), respectively. For squamous cell carcinomas, the corresponding odds ratios were 1.7 (0.6, 4.7) and 1.9 (1.0, 3.8), respectively.

B157. The CCSS reported 213 non-melanoma skin cancers as second cancers [P25]. They found that 90% of the skin cancers were among those who had received radiotherapy and that 90% of those were within the radiation field. Radiotherapy was associated with a RR of 6.3 (95% CI: 3.5, 11.3).

C. Summary

B158. A number of studies indicate an association between non-melanoma skin cancer and radiation. The positive studies include both Asians and Caucasians while the limited data available suggest there may be relatively little risk for blacks. The issue of interaction between exposure to solar UV radiation and ionizing radiation remains unclear though there are several suggestions that it may be the case. A few genetic conditions confer particular susceptibility. The induced tumours are predominantly basal cell and, to a much lesser extent, squamous cell carcinomas. The UNSCEAR 2006 Report [U12] has summarized radiation risk estimates for non-melanoma skin cancer that can be derived from the epidemiological literature (table B10) and concluded that there is strong evidence that non-melanoma skin cancer and, specifically, basal cell carcinoma is inducible by ionizing radiation with relative risk strongly decreasing with increasing age at exposure. Recent data have also supported that conclusion.

Table B10. Age differences in risk estimates for non-melanoma skin cancer incidence in the LSS and risks from studies of childhood radiation exposure

Based on the UNSCEAR 2006 Report (annex A, table 32) [U12].Studies listed are those for which quantitative estimates of risk could be made

Study		*Average ERR[a] at 1 Sv*	*Average EAR[a] (10^4 PY Sv)$^{-1}$*
LSS [P52]			
Age at exposure	10 years	2.3	2.3
	20 years	0.63	0.90
	30 years[b]	0.17	0.35
Israel tinea capitis [L27, R40] [c]		0.70 (0.35, 1.32)	1.31 (0.94, 1.77) [d]
New York tinea capitis (whites) [S70] [c]		0.6 (0.3, 1.1) [e]	1.9 (0.5, 3.3) [e]
Rochester thymic irradiation [H47, L27]		1.05 (0.50, 1.84)	15.9 (7.5, 27.9) [d]
Tonsil irradiation [L27, S32]		0.11 (0.04, 0.19)	10.2 (3.3, 18.3) [d]

[a] *90% CI in parentheses derived from fitting models for the LSS detailed in [P52], and from published data for the other studies, unless otherwise stated.*

[b] *Sex-averaged risk at attained age 70, smoothed assuming the ERR Gy^{-1} varies as a log-linear function of age at exposure.*

[c] *All estimates are for basal cell carcinoma.*

[d] *Risks normalized to 3,000 cm^2 of UVR-exposed skin as presented by Little et al. [L27].*

[e] *95% CI in parentheses.*

VIII.COLON CANCER

B159. Colon cancer is most common in industrialized countries. Although non-hereditary factors appear to play a major role in the aetiology, because migrants to an area soon have rates approaching that of the local population, a genetic factor also exists, at least for some cancer-prone families. There are a large number of studies relating colorectal cancer to diet. Positive associations have been reported for intake of red meat and diets low in fibre and high in dietary fat. Tumours of the rectum and colon appear to be aetiologically different because colon cancer is more frequent in females, and rectal tumours are more common in males [H45, I5, P39].

A. External exposure

1. Atomic bombing survivors

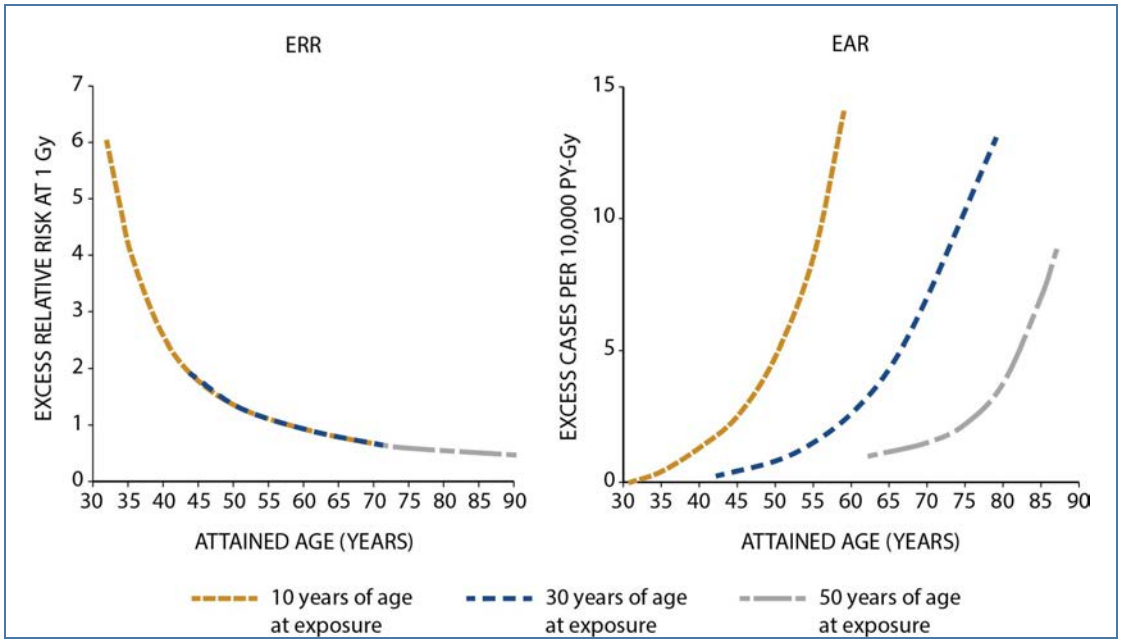
B160. In an early study of the incidence of colorectal cancer in the LSS sample of survivors of the atomic bombings reported by Nakatsuka et al. [N7], during 1950–1980 there was an excess risk of colon cancer, the ERR at 1 Sv being 0.8 (90% CI: 0.37, 1.36) but no excess rectal cancer risk. There was no difference in colon cancer risk by sex, but the ERR decreased with age at exposure (ERR Sv^{-1} of 3.7, 0.96 and 0.31 for ages <20, 20–39 and >=40, respectively). Later follow-up by Thompson et al. [T23] also indicated a statistically significant increase in cancer of the colon. In the period 1958–1987, 223 cases were observed compared to 194 expected (an excess of 29 cases) in the 788,600 person-years of observation for the 41,000 persons who received a dose of 0.01 Sv or more and a mean dose of 0.23 Sv. They estimated an ERR at 1 Sv of 0.72 (95% CI: 0.29, 1.28) and an EAR of 1.8 $(10^4 \text{ PY Sv})^{-1}$. There was no significant male–female difference in risk, nor was there an effect of age at exposure.

B161. In the latest cancer incidence report, there were 1,516 colon cancer cases based on follow-up through 1998 [P52], reporting no ERR change (+1% per decade), but a -56% per decade change in the EAR. However, the model they used (standardized for exposure at age 30 and risk assessed at age 70) may not fully account for the data. In particular, from the left-hand side of figure B-X, it can be see that the ERR is much higher at early ages for those exposed at age 10.

B162. Preston et al. [P50] reported on mortality among the survivors of the atomic bombings during the period 1950–1997. There was a statistically significant excess of colon cancer at dose levels of 1 Sv with an ERR of 0.54 (90% CI: 0.13, 1.2) in males and an ERR of 0.49 (90% CI: 0.11, 1.1) in females. There was an ERR change of -25% per decade of age at exposure, and an EAR change of -50% (but the statistical significance of those changes was not reported). The latest mortality report, through 2003, identified 621 deaths due to colon cancer [O25]. An analysis of the change in the ERR by age at exposure did not show a significant effect (a −3% change per 10 years of age, 95% CI: −51, 63); however, the change in the EAR $(10^4 \text{ PY Sv})^{-1}$ by age at exposure was nearly statistically significant: −30% per decade (95% CI: −58, 2).

Figure B-X. ERR and EAR models of colon cancer risk by age at exposure and attained age, averaged across sex

Adapted from [P52]



2. Background radiation

B163. Zou et al. [Z5] reported that the RR was less than 1.0 for colon cancer in the study of those in a relatively high-background area of China, where annual whole-body exposures were 2.1 to 4.7 mSv. No specific information was available regarding ages at exposure since all are exposed at this level of radiation throughout their lifetimes. No other data are available regarding colon cancer risk in relatively high-background areas.

3. Fallout and populations near nuclear plants

B164. A study of the cancer risk in the vicinity of the Three Mile Island nuclear power plant before and after the accident in March 1979 showed a nominal gradient of elevated risk close to the plant during the period from April 1979 to 1985 compared to the period from 1975 to March 1979 [H29]. However, evidence that there might have been an effect due to increased surveillance and the implausible time period for an excess suggest the pattern was likely an artefact according to the authors. Age at exposure was not examined in the study.

4. Medical irradiation for benign conditions

B165. Lundell and Holm [L41] studied 14,351 subjects who had received radiotherapy for skin haemangiomas at 0–17 months of age. The mean dose to the intestine was estimated to be about 0.09 Sv, with a range from <0.05 to 5.9 Sv [L39]. They were followed up until age 39 on average. The

authors observed 12 cases of colon cancer but found no significant dose-related increase in risk, with a reported ERR of 0.37 Sv^{-1} and an EAR of 0.11 $(10^4$ PY $Sv)^{-1}$.

B166. Several studies have been conducted of women who received X-ray treatment or radium implants for benign gynaecological disorders, often with colon doses of a sievert or more [I38], but essentially all were adults when exposed, so childhood risk cannot be documented from those studies [D8, I38, R66, W4]. Although studies of patients given radiotherapy for ankylosing spondylitis [W17] or for peptic ulcer [C6] had colon doses of one to several sieverts, essentially all the patients were adults when treated so no data on childhood exposure are available from the studies.

5. Radiotherapy for malignant disease

B167. There are several reports of children treated with radiotherapy for cancer. Hawkins et al. [H31] reported that the survivors of childhood cancer had an increased risk of second primary tumours in the digestive tract, with a relative risk of 10 (95% CI: 5, 20). Most of this risk was from five cases of colon cancer observed in over 10,000 patients studied. Tukenova et al. [T51] reported on cancers of the colon or rectum occurring after childhood cancer radiotherapy in the British and French parts of the European Childhood Cancer Survivor Study consortium. They found an SIR of 7.2 (95% CI: 4.4, 10.9; O/E 19/2.62), but did not present a further breakdown into colon and rectum.

B168. Travis et al. [T36] reported on the long-term survival and incidence of second cancers in over 40,000 testicular cancer patients almost all of whom received a dose from infradiaphragmatic radiotherapy of about 30 Gy. The relative risk for colon cancer was significantly increased among those given radiotherapy alone, with a relative risk of 1.9 (95% CI: 1.5, 2.5). They reported a strong age-at-exposure trend (p <0.001) for all solid cancers such that those youngest at the time of treatment had the highest subsequent cancer risk, and indicated that the trend was consistent across tumour sites.

B169. In a follow-up study of 1,507 Hodgkin's lymphoma patients, Tucker et al. [T48] observed four cases of colon cancer compared to 1.2 expected, giving an observed over expected ratio of 3.5 (95% CI: 0.9, 8.8). Castellino et al. [C8] found an elevated risk of colorectal/small intestine cancer among 2,633 five-year survivors of Hodgkin's lymphoma in the CCSS. About 94% of the study members had received radiotherapy and about 60% had received chemotherapy as well. The SIR was 6.6 (95% CI: 3.7, 12; n = 11 cancers). Another study reported 13 cases of gastrointestinal cancers among a cohort of 930 patients who had been treated for Hodgkin's lymphoma in childhood followed up for an average of 16.8 years (range of <1 to 39 years) [C48]. A total of 91% had received radiotherapy, including 48% with additional chemotherapy. The SIR for gastrointestinal cancer was 27.2 (95% CI: 15.1, 45.3).

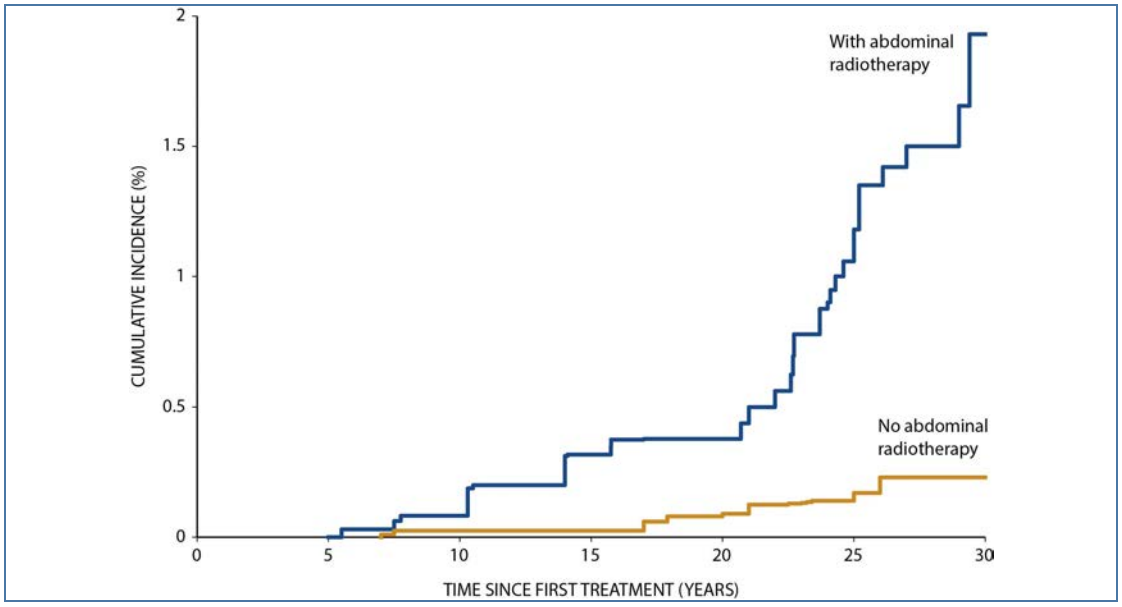
B170. A large pooled study of 32,591 patients who had been treated for Hodgkin's lymphoma examined second-cancer risks by age at exposure and time since exposure [D43]. In the subgroup of 5,925 diagnosed with Hodgkin's lymphoma at ages 0–20 years, they found four cases of colon cancers. The SIR of 4.7 (95% CI: 1.3, 12) was higher than for older age groups. The SIR was 3.5 for those treated at ages 21–30 years, and was about 1.4 (95% CI: 1.2, 1.7) for those treated at ages >30 years. Another pooled study of 18,862 five-year survivors of Hodgkin's lymphoma reported that modelled risk estimates for those treated at age 20 with Hodgkin's lymphoma were higher than for those treated at ages 30 or 40 [H52].

B171. Among 14,358 five-year survivors of all children cancers in the CCSS, the risk of gastrointestinal malignancies as a subsequent malignant neoplasm (GI SMN) was almost fivefold higher than the risk of such malignancies in the general population, with an SIR of 4.6 (95% CI: 3.5, 6.1). The SIR for colorectal cancer was 4.2 (95% CI: 2.8, 6.3). The highest risk for GI SMN was

associated with abdominal radiation exposure, with an SIR of 11.2 (95% CI: 7.6, 16.4). However, survivors who had not been exposed to radiation had a modest but significantly increased risk, with an SIR of 2.4 (95% CI: -1.4, 3.9). The 30-year post-cancer cumulative incidence of GI SMN was 0.64% (95% CI: 0.43, 0.86) for all patients, and almost 2% in those treated with abdominal radiation (cumulative incidence of 1.97% (95% CI: 1.15, 2.80) (figure B-XI). The most frequent GI SMN sites were the colon (38%) and rectum/anus (18%). In addition to abdominal radiation, with a relative risk of 5.4 (95% CI: 2.6, 11.2), high dose procarbazine and platinum drugs independently increased the GI SMN risk [H40].

Figure B-XI. Cumulative incidence of subsequent gastrointestinal malignancies in survivors of childhood malignancy treated with or without abdominal radiotherapy

Adapted from [H40]



B. Internal exposure

B172. The literature generally does not reveal a significant increase in the frequency of colon cancer after internal administration of radioiodine. However, the populations studied were essentially all adults when exposed [H5, H53, H59, H58, R45, R63].

B173. Thorotrast studies are a potential source of information on high-LET radiation exposure and colon cancer. The mortality experience of over 2,300 German thorotrast-exposed patients has been documented for up to 70 years since exposure [B11]. Only about 280 were under age 20 at the time of thorotrast administration. No excess of colon cancer mortality was seen in the cohort as a whole (SMR <1).

B174. A pooled analysis of cohorts given cerebral angiography with thorotrast was based on 1,650 exposed patients, of whom 220 were under age 20 at the time of thorotrast administration [T34]. The study showed a non-significant risk for colon cancer, with a relative risk of 1.5 (95% CI: 0.7, 3.0; n = 16) compared to patients diagnosed using a non-radioactive contrast agent; no analysis by age at exposure was conducted.

C. Summary

B175. The lifetime fatal risk estimate for a population of all ages exposed to low doses of radiation given by the ICRP in 1990 [I11] was 8.5×10^{-4} Sv^{-1}, and for workers 6.8×10^{-4} Sv^{-1}. In 2007, the ICRP [I25] gave an ERR for colon cancer mortality of 0.25 Gy^{-1} (for age 70 after exposure at age 30) with a change in the risk coefficient of -31% per decade of age at exposure.

B176. The BEIR V Committee [N38] pointed out that the data from the survivors of the atomic bombings did not show an increase in risk for at least 15 years after exposure, following which the ERR for fatal colon cancer was then 0.85 Gy^{-1} or 0.8 $(10^4$ PY $Gy)^{-1}$. The BEIR VII Committee [N43] estimated the ERR to be 0.65 for males and 0.79 for females, with a 19% decrease in risk per decade of age at exposure, up to age 30.

B177. The UNSCEAR 1988 Report [U7] risk estimate for radiogenic cancer of the colon, using a multiplicative risk model, was 7.9 (90% CI: 3.6, 13.4) excess lifetime fatal cancers for 1,000 persons exposed to a dose of 1 Gy of low-LET radiation at a high dose rate.

B178. The UNSCEAR 2000 Report [U9] indicates that the data on the Japanese survivors of the atomic bombings are consistent with a linear dose response. The report indicated that effects of sex, age at exposure and time since exposure on the ERR per sievert are not clear, although the EAR does increase with increasing time since exposure in the LSS. Changes over time in baseline rates in Japan make it difficult to decide how to transfer risks across populations. Also the lack of precision in low dose studies of external low-LET radiation exposure and of internal low-LET and high-LET radiation exposure do not allow conclusions to be drawn.

B179. Additional studies on radiation and colon cancer have been summarized by the UNSCEAR 2006 Report [U12] (table B11), and it was concluded that there is evidence that colon cancer can be induced by ionizing radiation, compatible with a linear dose-response pattern. The evidence for approximate linearity comes almost entirely from the Japanese LSS mortality data. The Committee cited ERR estimates from LSS for the period 1958–1997 of 0.54 (90% CI: 0.13, 1.2) for males and 0.49 (0.11, 1.1) for females, with a 25% decrease per decade of age at exposure.

B180. To summarize the present review of colon cancer risk in relation to childhood radiation exposure:

- Among the survivors of atomic bombings in the LSS, both the cancer mortality and cancer incidence data indicate that the EARs are greater after childhood radiation exposure than after adult exposure, with estimated declines of 30% and 56% per decade of age at exposure, respectively. No differences were reported in the ERRs by age at exposure in the most recent data, although that may be partly a function of the choice of model used to assess the ERR. Both mortality and incidence data agree that there is an age-at-exposure effect for the EAR model (i.e. a greater risk from exposure at younger ages), but it is inconclusive for the ERR model.

- No data are available regarding colon cancer risk after childhood exposures to fallout from the testing of nuclear weapons, from discharges or accidental releases from nuclear installations or in high-background areas. Occupational radiation studies also do not contain any information on colon cancer after childhood exposures.

- Several studies of irradiation for benign medical conditions had too few patients exposed before age 20 to provide useful information on childhood exposures. A study of infant

treatments for skin haemangiomas did not show a significant colon cancer risk, but the mean dose to the intestine was low (<0.1 Sv).

– An excess of colon cancer was reported among those given radiotherapy for childhood cancer. Studies of patients treated for Hodgkin's lymphoma before adulthood also reported colon cancer excesses. However, information on excesses per unit radiation dose was not available.

– Studies of internal exposures, either to low-LET radiation from ^{131}I or high-LET radiation from thorotrast, have not reported excesses of colon cancer, but nearly all the patients were adults at the time of exposure.

Table B11. Risk estimates for colon cancer incidence and mortality from studies of childhood radiation exposure

Updated and adapted from UNSCEAR 2006 Report (annex A, table 23) [U12, U13]. Studies listed are those for which quantitative estimates of risk could be made

Study		*Average ERR[a] at 1 Sv*	*Average EAR[a] (10^4 PY Sv)$^{-1}$*
Incidence			
LSS [P52]			
Sex	Males	0.85 (0.52, 1.26)	1.41 (0.10, 3.07)
	Females	0.42 (0.14, 0.76)	1.46 (0.69, 2.45)
Age at exposure	<20 years	0.81 (0.46, 1.24)	0.99 (0.31, 1.92)
	20–40 years	0.44 (0.14, 0.82)	1.78 (0.56, 3.46)
	>40 years	0.45 (<0, 1.13)	3.11 (0.22, 6.54)
Mortality			
LSS [P50]			
Sex	Males	0.53 (0.04, 1.20)	<0 (<0, 707.28)
	Females	0.50 (0.06, 1.09)	<0 (<0, 623.23)
Age at exposure	<20 years	1.13 (0.32, 2.34)	<0 (<0, 210.88)
	20–40 years	0.23 (<0, 0.84)	<0 (<0, 966.47)
	>40 years	0.38 (<0, 1.12)	<0 (<0, 1 440.1)
LSS [O25]			
Age at exposure	10 years[b]	0.36	2.7
	30 years	0.34 (95% CI: 0.05, 0.74)	1.6 (95% CI: 0.5, 3.0)
	50 years	0.32	0.8

[a] *90% CI in parentheses derived from fitting models for the LSS detailed in [P52], and from published data for the other studies, unless otherwise stated.*

[b] *Sex-averaged risk at attained age 70, smoothed assuming the ERR Gy^{-1} varies as a log-linear function of age at exposure.*

IX. LIVER CANCER

B181. The LSS of atomic bombing survivors has reported an excess risk for liver cancer incidence, with an ERR Gy^{-1} of 0.30 (90% CI: 0.11, 0.55, n = 1,494) and an EAR $(10^4$ PY $Sv)^{-1}$ of 4.3 (0.2, 7.2) [P52]. The analysis did not show any statistically significant changes in risk by age at exposure—an ERR estimate of 3% (CI: −37, 69) and EAR of −21% (−57, 378) change per decade of age at exposure. The most recent mortality data also show a significant dose-response relationship for liver cancer, with an ERR Gy^{-1} of 0.38 (95% CI: 0.11, 0.62) but a non-significant age-at-exposure effect for the ERR model: −8% (−62, 42) per decade [O25]. However, the LSS data on liver cancer risk by age at exposure are especially difficult to interpret because Japanese birth cohorts differed markedly in the frequency of infection by hepatitis C virus which is a major risk factor for hepatocellular carcinoma and may be an effect modifier of the radiation risk [S53].

B182. It should be noted that a number of other studies of liver cancer risk in relation to external low-LET exposures do not show statistically significant risks for liver cancer incidence or mortality [U12]. Most of the studies have shown a high risk for liver cancer after thorotrast injection: German study, RR = 152 (95% CI: 48, 594; n = 454) [V5]; Danish-Swedish study, RR = 109 (95% CI: 91, 129; n = 136) [T34]; Portuguese study, RR = 42 (95% CI: 14, 210, n = 67) [D45]; Japanese study, RR = 31 (95% CI: 19, 50; n = 143) [M49]. However, none of the studies had an analysis by age at exposure.

X. LUNG CANCER

B183. Lung cancer was one of the earliest cancers identified as possibly being related to radiation exposure. The relationship was initially suggested in a study of Bohemian miners. To date, several other major population groups have been studied, including those exposed to natural background, fallout, and occupational radiation, atomic bombing survivors, patients exposed to radiation therapy, and those exposed to radon daughter products in homes and underground mines. These sources of information used for risk estimates are rather discordant for several reasons: uncertainties in dosimetry in most of the studies, problems of comparison of external radiation exposure with internal exposure from radon daughter products, and confounding of the data by other associated carcinogenic agents (such as cigarette smoking).

B184. Estimates of the risk of radiation induction of lung cancer depend upon the age of the subjects at the time of exposure. Relative risk appears to differ in expression between the atomic bombing survivors and the uranium miners. In the uranium miners, the ERR declines over time—following cessation of exposure—while among the atomic bombing survivors, if this trend exists at all, it is much less marked [L1]. The risk from radiation-induced lung cancer at later ages rises steeply, as it does from normally occurring lung cancers.

B185. The interaction between smoking and radiation continues to be a subject of intense interest with reports based on miner radon studies [N41, S36, U14] residential radon studies [D5, K53] and the atomic bombing survivors [F28, U14]. However, it is notable that in all the studies, a radiation risk is seen for non-smokers as well as for smokers.

A. External exposure

1. Atomic bombing survivors

B186. The 1958 to 1987 incidence study of atomic bombing survivors [T24] yielded incidence risk estimates of an ERR of 1.0 at 1 Sv and an EAR of 4.4 (10^4 PY Sv)$^{-1}$. The mortality data from the same period yielded comparative risk estimates of 0.6 and 1.9, respectively. The mortality data up to 1985 published by Shimizu et al. [S55] found 638 lung cancer deaths and indicated a relative risk at 1 Gy of 1.46 (90% CI: 1.25, 1.72) and an EAR per 10,000 PYGy of 1.25 (90% CI: 0.70, 1.89). The attributable risk was estimated to be 11.4% (90% CI: 6.4, 17.1), given the dose distribution of the atomic bombing survivors. The paper also has data on ERR by dose level and age at exposure for lung cancer and indicates a significant ERR for lung cancer at <0.5 Gy. A later mortality study up to 1990 published by Pierce et al. [P33] in 1996 indicated an ERR/Sv in males of 0.33 (95% CI: 0.03, 0.69), an ERR in females of 0.75 (95% CI: 0.30, 1.33) and for both sexes an ERR of 0.42 Gy (95% CI: 0.24, 0.63).

B187. In an update through 1998 of tumour incidence in the LSS, there were 1,759 lung cancer cases [P52]. The analysis showed no variation by age at exposure. Using their analysis, which was standardized to exposure at age 30 and risk at age 70 years, the effect for the ERR model was a positive 20% (90% CI: −7, 54) per decade of age at exposure and that for the EAR model was 2% (90% CI: −20, 28). Estimated risks for representative age at exposure are shown in table B12.

B188. A recent update of lung cancer mortality through 2003 reported a sex-averaged ERR Gy^{-1} of 0.74 (95% CI: 0.51, 1.03) with a significant sex effect: female/male ratio of 2.7 (1.3, 6.8) [O25]. The age-at-exposure effect of −7% (95% CI: −35, 29) per decade of age at exposure was not significant.

Table B12. Risk estimates for lung cancer incidence and mortality from studies of childhood radiation exposure

Updated and adapted from UNSCEAR 2006 Report (annex A, table 27) [U12]. Studies listed are those for which quantitative estimates of risk could be made

Study		*Average ERR[a] at 1 Sv*	*Average EAR[a] (10^4 PY Sv)$^{-1}$*
Incidence			
LSS [P52][b]			
Both sexes		0.81 (0.56, 1.1)	7.5 (5.1, 10)
Age at exposure	10years	0.56 (0.26, 1.1)	7.3 (3.4, 14)
	30 years	0.81 (0.56, 1.1)	7.5 (5.1, 10)
	50 years	1.15 (0.69, 1.8)	7.8 (4.6, 12)
LSS [P52][c]			
Age at exposure	0-9 years	0.66 (-0.02, 2.0)	n.a.
	10–19 years	0.57 (0.23, 1.1)	n.a.
	20–39 years	0.79 (0.48, 1.2)	n.a.
	≥40 years	1.2 (0.71, 1.7)	n.a.

Study		Average ERR[a] at 1 Sv	Average EAR[a] (10^4 PY Sv)$^{-1}$
LSS [P52]			
Sex	Males	0.32 (0.13, 0.55)	0.57 (0.04, 1.54)
	Females	1.48 (1.04, 1.99)	2.38 (1.37, 3.53)
Age at exposure	<20 years	0.68 (0.28, 1.20)	0.64 (0.10, 1.38)
	20–40 years	0.65 (0.35, 1.00)	2.65 (1.04, 4.60)
	>40 years	0.71 (0.40, 1.09)	9.47 (5.75, 13.78)
All		0.69 (0.49, 0.92)	1.55 (0.84, 2.37)
Hodgkin's disease - international [G12, T33, V8] (5-year lagged dose >0)		0.15 (0.06, 0.39)	n.a.
Mortality			
LSS [P50]			
Sex	Males	0.57 (0.30, 0.89)	0.19 (<0, 0.85)
	Females	1.28 (0.84, 1.80)	<0 (<0, 1269.1)
Age at exposure	<20 years	0.94 (0.42, 1.63)	0.11 (<0, 0.56)
	20–40 years	0.78 (0.43, 1.19)	0.51 (<0, 1.83)
	>40 years	0.76 (0.38, 1.23)	<0 (<0, 4062.9)
All		0.84 (0.59, 1.11)	0.37 (0.02, 0.87)
LSS [O25]			
Age at exposure	10 years [b]	0.86	8.7
	30 years	0.75 (95% CI: 0.51, 1.03)	6.5 (95% CI: 4.3, 9.0)
	50 years	0.65	4.6

[a] *90% CI in parentheses derived from fitting models for the LSS detailed in [P52], and from published data for the other studies, unless otherwise stated.*

[b] *Sex-averaged risk at attained age 70, smoothed using the assumption that the ERR Gy^{-1} varies as a log-linear function of age at exposure.*

[c] *Sex-averaged risk at attained age 70, assuming that within each age-at-exposure group the ERR Gy^{-1} varies as a power of attained age, but with no smoothing across age-at-exposure groups.*

2. Radiation therapy

B189. A number of studies have examined the risk of second tumours after treatment for childhood cancers. In a study by van Leeuwen et al. [V6], 14 lung cancers were identified in 744 patients treated for Hodgkin's disease. Nine cases were seen in the patients treated with radiotherapy alone (RR = 5.4), and none were found in patients treated by chemotherapy alone. Kaldor et al. [K6] examined cases of lung cancer occurring in Hodgkin's disease survivors and found that lung cancer was twice as common in those treated with chemotherapy as compared to those treated with radiotherapy. They concluded that Hodgkin's disease itself may be associated with an increase in lung cancer. This was supported by the fact that 3/4th of the cases occurred within 10 years of the treatment.

B190. In an international study of second malignant neoplasms among 32,000 Hodgkin's lymphoma patients, Dores et al. [D43] observed 377 lung cancers and found a statistically significant trend for a

higher risk after treatment at young ages than at older ages. However, specific results were not provided by age at exposure for those who received radiotherapy.

B191. In a 2003 report by Gilbert et al. [G12] on 227 patients who developed lung cancer among 19,000 who had been treated for Hodgkin's disease, the ERR for lung cancer was elevated at 0.15 (95% CI: 0.06, 0.39). There was no evidence of a departure from linearity even though lung doses exceeded 30 Gy. Also the relationship of radiation to smoking was more consistent with a multiplicative than an additive relationship. Curtis et al. [C55] reported on solid cancer incidence in 19,229 patients following bone marrow transplantation. Treatment regimens often included total-body (usually about 10–12 Gy) or nodal irradiation and cyclophosphamide. Lung cancer was not found to be increased and the O/E ratio was 0.7. The study is limited by the small number of lung cancer cases.

B192. As reviewed by Goodman et al. [G20], a number of cohort studies of patients who received radiotherapy for Hodgkin's lymphoma, non-Hodgkin's lymphoma, breast cancer and a variety of other cancers have shown excess risks for pleural and other mesotheliomas, though the risks per sievert or breakdowns by age at exposure were generally not available.

B193. In summary, several studies have shown an increase in the risk of lung cancer following low-LET external radiation exposure. However, there are also a number of studies involving nuclear workers, populations exposed to fallout, and populations living in areas of high natural background radiation or around nuclear plants that do not show an increase in lung cancer. Many of the positive and negative studies are complicated by the lack of adjustment for factors such as cigarette smoking, other pollutants and the "healthy worker" effect.

B194. The data from the positive studies are compatible with a linear dose-response relationship. The minimum latent period for lung cancers appears to be at least 10 years. The atomic bombing survivor mortality study indicates that age at exposure has no consistent effect and there does not appear to be significantly decreasing relative risk with increasing time since exposure. The effect of fractionation is not clear, but the data suggest that the risk decreases with fractionation of low-LET radiation but not with high-LET radiation. The interactive effect of smoking is probably between additive and multiplicative. At low doses, the interaction of smoking and radiation has not been confirmed because of the overwhelming carcinogenicity of smoking which obscures any possible radiation effect.

B195. Risk estimates summarized by UNSCEAR 2006 Report [U12] from the various low-LET radiation epidemiological studies are shown in table B12.

B. Internal exposure

B196. The main body of scientific literature on the relationship between lung cancer and internal irradiation concerns radon exposure. The literature has been summarized by a number of scientific groups including the ICRP 1990 Recommendations [I11], NCRP reports [N16], the UNSCEAR 2006 Report [U12], and the BEIR Report on radon [N37].

1. Underground miner studies

B197. Although most miner studies have dealt exclusively with adult exposures to radon, in a Chinese tin miner cohort, 37% were first exposed before age 13 [L34, X1]. Of 2,585 lung cancer deaths

in a pooled analysis of 11 miner studies, only the Chinese tin miner study had miners first exposed under age 15 (522 cases, 20%) and various studies had 629 lung cancer deaths among miners first exposed at ages 15–24 years [L35]. The study found non-significant modification of the ERR per working level month by age at first exposure. There was a slight indication that those exposed at earlier ages had a higher lung cancer risk, but this needs to be tempered by the possibility that exposure to arsenic and other contaminants may have confounded the risk estimates.

XI. BRAIN AND CENTRAL NERVOUS SYSTEM TUMOURS

B198. The reported radiation-induced tumour types are often mesenchymal (sarcomas, meningiomas) but have also included malignant glioma, astrocytoma, haemangioblastoma, and acoustic neuroma [P41]. It is often difficult to separate brain tumours into either strictly malignant or non-malignant categories because many (particularly astrocytomas) may be very slow growing. Additionally, very few brain tumours metastasize in the way that other malignancies do and, for this reason, many of the published reports give a total brain tumour induction rate rather than indicating a separate malignant brain tumour rate.

A. Modifying factors

B199. Little et al. [L28] examined the interaction of radiation and various genetic syndromes with brain tumour risk among 4,000 brain tumour cases. They found a weak effect modification by neurofibromatosis (44 cases), but none by various other familial syndromes of which only two syndromes had appreciable cases (31 with Li-Fraumeni syndrome, 80 with bilateral retinoblastoma).

B200. Sadetzki et al. [F10, S6] examined candidate polymorphisms in 12 genes in the DNA-repair, cell-cycle control, or meningioma pathogenesis pathways in relation to radiation risk of meningioma. They found suggestive effect modification of radiation risk by polymorphisms in the *Cyclin D1* gene (p = 0.005) and the *p16* gene (p = 0.06). Another study of a variety of DNA repair genes found radiation risk for gliomas to be modified by variations in the *MGMT* and *PARP1* genes [L32]. However, these studies require confirmation by studies in other irradiated groups.

B. External exposure

1. Atomic bombing survivors

B201. Data from the survivors of the atomic bombings for 1958–1995 revealed an excess of brain tumours; however, the confidence intervals of relative risk usually encompassed unity for individual tumour types owing to the relatively small numbers. Preston et al. [P49] reported a dose-dependent ERR for nervous system tumours, with an ERR of 1.2 Gy^{-1} (95% CI: 0.6, 2.1) in the LSS. The EAR was 0.51 (95% CI: 0.17, 0.95) $(10^4$ PY $Gy)^{-1}$. For schwannomas, the ERR was 4.5 (95% CI: 1.9, 9.2,

n = 55), and for all other types, the ERR was 0.6 (95% CI: 0.1, 1.3, *n* = 173). For other specific types of interest, owing in part to the small numbers, the ERRs were positive but not statistically significant: for meningioma, the ERR was 0.6 (*n* = 88); for glioma, the ERR was 0.6 (*n* = 43); and for pituitary tumour, the ERR was 1.0 (*n* = 35) [P49]. Further details on subtypes are given in [Y6]. For those exposed before age 20, the ERR per unit dose for all nervous system tumours except schwannomas was 1.2 (95% CI: 0.3, 2.9) Sv^{-1}; that for those exposed at ages 20 or more was 0.2 (95% CI: <−0.2, 1.0) Sv^{-1}. A model of age at exposure for nervous system tumours other than schwannoma showed a relative change in ERR of −62% (95% CI: −95, 4) per decade of exposure age, which was nearly statistically significant (*p* = 0.06) [P49].

2. Fallout from nuclear weapon testing

B202. Darby et al. [D7] reported on 22,000 men who had participated in the United Kingdom's atmospheric nuclear weapon tests or related programmes compared to 22,000 others who had not participated. A non-significant SMR of 1.3 (95% CI: 0.8, 2.2) was found for tumours of the CNS among participants. The radiation doses were uncertain. Another study among United States military nuclear weapon test participants likewise reported no significant elevation in brain tumour risk, with an SIR of 1.4 (95% CI: 0.5, 3.2; *n* = 5) [C1]. However, in neither study would any subjects have been below the age of 16.

3. Diagnostic radiology

B203. Several population-based case–control studies of brain tumours and medical diagnostic radiation exposures have been conducted. Howe et al. [H66] found an odds ratio of 6.7 (95% CI: 1.7, 27) for the association of childhood brain tumours with a history of medical X-irradiation of the skull. Preston-Martin et al. [P43, P42] reported, in a study of meningiomas, an odds ratio of 4.0 (95% CI: 2.1, −7.5) for those receiving full-mouth dental radiological examinations before age 20. They also indicated an odds ratio of 2.1 (95% CI: 1.2, 3.6) for those receiving such examinations before 1945, when dental X-ray doses were sometimes as high as 100–150 mGy (10–15 R) per film and the beam diameters were excessive [J15, P46]. The association was evident for tentorial/subtentorial meningiomas, but not for supratentorial tumours, which accords with the likely topographical distribution of the dental X-ray dose to the brain [P42].

B204. However, other case–control studies have produced negative findings. A more recent study of gliomas and meningiomas by Preston-Martin et al. did not show a significant association with dental radiological examinations before age 25 [P45]. Ryan et al. [R65] reported no association between frequency of dental radiological examinations and either gliomas or meningiomas. Nor was there an association when dental X-rays before age 25 were examined, or when panoramic or full-mouth X-rays were specifically examined. The study by Burch et al. [B70] also produced negative findings with regard to dental radiological examinations and brain tumours. As part of the large European Interphone study of brain tumours, medical radiation exposure and brain tumours were examined in Germany [B29]. For 366 glioma and 381 meningioma cases, no positive associations were found with reported medical radiation exposure. The results of retrospective case–control studies should be treated cautiously because of the potential for differential recall between diseased cases and controls, which can produce biases of unknown direction and magnitude.

B205. Brain tumour incidence was recently reported for 176,000 patients who received one or more CT scans before the age of 22, including 135 who developed brain tumours five or more years after the

initial CT [P22]. Compared to children who received <5 mGy to the brain, those who received 50-74 mGy (mean of 60.4 mGy) had a RR of 2.82 (95% CI: 1.33, 6.03), and all those with >=50 mGy (mean of 104.2 mGy) had a RR of 3.32 (95% CI: 1.84, 6.42). They further reported a significant increase in the RR with increasing age at exposure. However, there are concerns about the risk estimates because of lack of information about indications for the CT scans and the consequent potential for "reverse causation" (i.e. cancers may have been caused by the medical conditions prompting the CT scans rather than by the CT dose) and lack of individual dosimetry.

B206. Brain tumour incidence among 860,000 persons following paediatric CT examinations was recently reported in comparison with 10 million persons without a report of a CT examination [M9]. For brain cancers diagnosed one or more years after the initial CT examination, they reported a relative risk of 2.44 (95% CI: 2.12, 2.81; n = 210) for those who received CT examinations of the brain, and a brain cancer relative risk of 1.51 (95% CI: 1.19, 1.91; n = 73) after CT scans of other body locations. The 50% elevated risk for brain cancer after receiving CT examinations at non-brain sites suggests the potential for bias in the study. When they further examined the radiation dose response for brain cancer risk with different lag periods after brain CT examinations, they found ERR Gy^{-1} estimates of 29 (95% CI: 23, 37), 21 (14, 29) and 15 (7, 26) for lag times of 1, 5 and 10 years, respectively. The implausibly early risk that declined with time suggests the possibility of "reverse causation".

4. Radiotherapy for benign conditions

B207. The effects of radiation therapy for childhood tinea capitis in New York patients has been reported by Shore et al. [S60] and in Israeli patients by Ron et al. [R37]. The mean dose to the brain in both studies was between 1.4 and 1.5 Gy. The Israeli tinea capitis studies by Ron et al. [M44, R38] include 10,834 exposed persons and 16,226 controls. The children were seven years old on average (range of 0 to 15 years) at the time of treatment. In the most recent report of the Israeli series, with a median follow-up of 40 years since exposure, an excess incidence of brain cancers was found, based on 67 meningiomas and 44 malignant brain tumours in the irradiated group [S5]. Seventy-five per cent of the malignant tumours were of neuroepithelial tissue origin. There was some statistical evidence for a linear-quadratic model for meningiomas, but a linear fit was adequate for malignant brain tumours. Since the linear models provided a good fit up to a dose of 2.7 Gy (the range that contained 95% of the data points) for both tumour types, the risks were estimated using a linear model. For benign meningiomas, the ERR was 4.63 (95% CI: 2.43, 9.12) Gy^{-1} and the EAR was 0.48 (95% CI: 0.28, 0.73) $(10^4 \text{ PY Sv})^{-1}$. For malignant brain tumours, the ERR was 1.98 (0.73., 4.69) Gy^{-1} and the EAR was 0.31 (95% CI: 0.12, 0.53) $(10^4 \text{ PY Sv})^{-1}$. For malignant brain tumours, but not benign meningiomas, the risk was higher during the first 20 years after irradiation than subsequently.

B208. Sadetzki et al. [S5] did not see any age-at-irradiation effect for benign meningiomas, but there was a significant (p = 0.03) decrease in the ERR with irradiation age for malignant brain tumours; the ERRs were 3.6 (95% CI: 1.0, 9.9), 2.2 (0.8, 5.5) and 0.5 (<0, n.a.) Gy^{-1} for ages 0–4, 5–9 and 10–15 years, respectively. In the New York study [S60, S71] of 2,224 irradiated and 1,380 non-irradiated tinea capitis patients, seven malignant brain tumours (six gliomas/astrocytomas, one haemangioblastoma) and nine benign intracranial tumours (four meningiomas, five acoustic neuromas) were found in the irradiated group versus only one benign tumour in the controls. By comparison with the general population, the SIR for malignant brain tumours was 3.0 (95% CI: 1.3, 5.9) which, with a mean brain dose of about 1.4 Gy, gives an ERR of 1.4 (95% CI: 0.2, 3.5) Gy^{-1}.

B209. Colman et al. [C38] reported on nervous system tumours found in about 3,100 children who had received X-ray treatment for tonsillar enlargement or other head/neck/chest disorders in Chicago at

a mean age of 3.5 years and were followed up for 30 years, on average. The mean dose was about 0.8 Gy at the midbrain [N38] and 4.6 Gy at the cerebellopontine angle. They found 14 intracranial tumours when about 1.6 would have been expected; the SIR was 8.8 (95% CI: 4.4, 12.7) [N37]. Six of the tumours were malignant. A more recent report showed 15 meningiomas of the brain and 27 cranial nerve schwannomas, but no expected numbers were provided [S119].

B210. Another series of 2,580 patients received radiotherapy for various head-and-neck benign conditions at young ages were followed up for subsequent tumours. A total of 66 neural tumours was reported [S32, S59], of which about half were intracranial tumours. No analysis by age at exposure was reported.

B211. Furst et al. [F25] followed up a cohort of 14,647 children who were treated with ^{226}Ra for skin haemangiomas in Sweden between 1920 and 1959, as compared to 2,694 patients not treated with radiotherapy. In this study, there was no elevation in the relative risk of brain cancer in the irradiated group. However, the estimated mean brain dose was only 0.1 Gy, so a null result is not surprising [F27].

B212. Karlsson et al. [K11] reported on a cohort of 11,805 infants treated with ^{224}Ra for skin haemangioma in Sweden and followed up for about 34 years. They reported an SIR compared to general population rates of 1.8 (95% CI: 1.3, 2.4; n = 46) for all intracranial tumours; an SIR of 1.9 (95% CI: 1.2, 2.8; n = 23) for gliomas; and an SIR of 2.4 (95% CI: 1.1, 4.8; n = 8) for meningiomas. The mean dose to the brain was only about 70 mGy, so the excesses are unexpected; furthermore, there was no significant dose response.

B213. Karlsson et al. [K12] then pooled the two Swedish cohorts of infants treated with radiation for skin haemangiomas, making a total of 26,949 irradiated infants and 1,859 who did not receive radiotherapy. For almost all irradiated infants the treatment consisted of ^{226}Ra applicators on the skin. Again the mean brain dose was low, about 70 mGy, but the range was substantial (from 0 to 11.5 Gy). They found intracranial tumours (including 35 gliomas and 20 meningiomas) in 83 irradiated and three non-irradiated infants, giving an SIR of 1.4 (95% CI: 1.1, 1.8). They found a statistically significant dose response (p = 0.02). The ERR Gy^{-1} was 2.7 (95% CI: 1.0, 5.6) and the EAR was 2.1 (95% CI: 0.3, 4.4) (10^4 PY Sv)$^{-1}$. The slope of the dose response was significantly modified by age at first irradiation, such that it was higher at younger ages (p = 0.02). Specifically, the ERR was 4.5 Gy^{-1}, if treatment occurred before five months of age; 1.5 Gy^{-1}, if given at five–seven months; and 0.4 Gy^{-1}, if given at over seven months.

B214. An excess of brain neoplasms has been reported in subjects who had received radiation exposure in childhood for the prevention of deafness. In those circumstances, a radium applicator was applied to the nasopharynx to reduce the size of the adenoid tissue. The dose at a distance of 1 cm from the applicator was estimated to be 7.2 Gy, dropping to 0.78 Gy at 3 cm. The series included 904 irradiated subjects and 2,021 controls, who were treated surgically. Three brain tumours were identified in the irradiated population compared to none in the controls in the earliest report [S20]. Continued follow-up of the study subjects found three malignant and four benign brain tumours in the irradiated group and none in the unexposed comparison group [Y5]. A Dutch study of over 4,000 patients with nasopharyngeal irradiation found five malignant brain tumours, which was not statistically significant; the SIR was 1.3 (95% CI: 0.4, 3.1) [R48].

B215. An excess of benign nervous system tumours (mostly non-intracranial) was found in a thymus infant irradiation study; the odds ratio was 6.0 (95% CI: 2.0, 19; n = 13), but there was no excess of malignant tumours [H47].

5. Radiotherapy for cancer

B216. A number or studies [E9, F11, S11] link gliomas to previous cranial radiation for childhood leukaemia (usually acute lymphocytic leukaemia). A number of authors [H31, K33] have indicated the possibility of genetic predisposition, IT methotrexate, and radiation as possible causes. In one study of 981 children in Nordic countries [N45], the incidence of brain tumours was 27 times greater than expected. No increase was seen after chemotherapy alone. There are several isolated case reports of meningioma occurring after cranial radiotherapy [D41, S107].

B217. Neglia et al. [N21] followed up 9,720 children who had been treated for ALL at the average age of 4.7 years and who were enrolled in one of 23 clinical (mostly randomized) trials conducted by the United States Children's Cancer Study Group. The doses of cranial radiation were 18–24 Gy. Seventy-two per cent were followed up for five or more years and 10% for over ten years. A total of 24 neoplasms of the CNS were diagnosed as second primaries compared to 1.06 expected, which represents an SIR of 23 (95% CI: 15, 33). All of the CNS tumours occurred among those who had received cranial irradiation. However, the numbers with and without irradiation were not reported, and no indication was given as to what percentage of the study population and cases also had had chemotherapy.

B218. In a 2006 report on 14,000 persons in the CCSS who were treated for childhood cancers, Neglia et al. [N22] reported that radiation was associated with an increased risk of subsequent glioma; the odds ratio was 6.78 (95% CI: 1.54, 29.7), and meningioma; the odds ratio was 9.94 (95% CI: 2.17, 45.6). The dose response for ERR was approximately linear—for glioma, the slope was 0.33 (95% CI: 0.07, 1.71) Gy^{-1} and for meningioma, the slope was 1.06 (95% CI: 0.21, 8.15) Gy^{-1}. For glioma, the ERR per unit dose was highest among children exposed at less than five years of age. After adjustment for radiation dose, neither the original cancer nor chemotherapy was associated with the increased risk. The distribution of subsequent gliomas and meningiomas differed strikingly over time. The radiation-related increase in glioma became apparent five–ten years after exposure but largely disappeared after 15–20 years. By the time the survivors of childhood cancer had reached their mid-20s, the risk of glioma had dropped to nearly background levels. The ERR per unit dose for subsequent glioma was significantly greater than zero only for ages at irradiation of less than five years, which suggests that susceptibility to radiation-related brain cancer decreases as brain development nears completion. In contrast to gliomas, meningiomas took longer to appear and showed no signs of subsiding in the latest follow-up intervals.

B219. Subsequent brain and CNS tumours have been ascertained among 18,000 children treated for cancers in the British Childhood Cancer Survivor Study [T11]. They observed 247 second primary tumours of the CNS, including 73 gliomas and 137 meningiomas. For gliomas, there was not a linear radiation dose response although the risk was statistically significantly elevated at the highest dose levels (40 Gy or greater). However, for mengiomas there was a strong, approximately linear dose response, with relative risks ranging from 1.8 at <10 Gy up to 479 at >=40 Gy (analyses adjusted for concomitant intrathecal methotrexate exposure).

B220. Albo et al. [A14] reported on brain tumours that developed among 8% of the children involved in a clinical trial for the treatment of ALL. The protocol involved radiation exposures of 24 Gy (2,400 R) and several types of chemotherapy. Nine brain tumours occurred when 0.04 were expected. The brain tumours developed 16–54 months after the irradiation. This study is difficult to interpret because of the concomitant chemotherapy. In a study of second malignancies after treatment for childhood cancer, Smith et al. [S90] observed 12 CNS second malignancies, but none was associated with radiotherapy alone and only four with radiation plus an alkylating agent. Among 4,400 persons treated for childhood cancer, subsequent brain tumour incidence was determined [L28]. A statistically

significant ($p = 0.003$, $n = 10$) radiation dose response was reported for benign brain tumours, but not for malignant ones ($n = 12$).

B221. Curtis et al. [C55] studied 19,229 bone marrow transplant patients who averaged 25 years of age at transplant. A conditioning regimen of total-body irradiation was given to 73% and another 3% received limited-field irradiation; 65% also received cyclophosphamide and 8% other drugs. Doses to the brain were not reported. An excess of brain/CNS cancers was observed; the SIR was 7.6 (95% CI: 3.8, 13.5; $n = 11$). Of particular interest was the fact that 9 of the 11 cases occurred among the 18% who were under age 10 at the time of transplantation, for whom the SIR was 41 (95% CI: 20, 75), but there was no excess at older ages, for whom the SIR was l.6 (95% CI: 0.3, 5.4).

B222. There is a substantial mortality among childhood cancer survivors with secondary neoplasms of the CNS. A study by Vasudevan et al. [V13] based on the Surveillance, Epidemiology, and End Results (SEER) database, reported a 10-year survival rate of 13.6% among those with secondary CNS tumours after a primary diagnosis of paediatric solid tumour. A report from the British CCSS [T10] reported 62 patient deaths among 73 survivors with secondary gliomas, but only 42 patient deaths among 137 survivors with secondary meningiomas.

C. Internal exposure

B223. In a study by Hall et al. [H5] of patients treated with ^{131}I for thyroid cancer, the irradiated group showed a suggestive, but not statistically significant, excess of nervous system malignancies when compared to the general population (the SIR was 2.4) or to an non-irradiated thyroid cancer group (the relative risk was 1.5). Other studies of patients treated for thyroid cancer have similarly shown no excess of brain/CNS cancers. However, the numbers of patients in the series were relatively small [B62, D27, D46, G13]. Holm et al. [H59] reported a modest excess of brain cancer in patients who had been treated with ^{131}I for hyperthyroidism; the SIR was 1.3 (95% CI: 1.0, 1.7; $n = 48$). None of the studies showed brain tumour results for those young at exposure.

B224. Andersson and Storm [A18] found a large excess of malignant brain/CNS tumours (the SIR was 28, $n = 71$) among 999 Danish patients who had received thorotrast for cerebral arteriography. However, many of those tumours were diagnosed by or shortly after the cerebral arteriography and should be discounted. For the period of 10 or more years after the thorotrast injection, the SlR was 5.6 (95% CI: 3.0, 9.8; $n = 11$). For the period of more than 20 years after thorotrast injection, the relative risk was found to be approaching unity and increased risk was no longer statistically significant [A19]. Doses to the brain were not reported. Van Kaick et al. [V4] also reported a small excess of brain tumours in patients with administered thorotrast—the SMR was 1.32 (95% CI: 0.8, 2.1; $n = 18$)—but again, doses to the brain were not reported and there may have been subjects with pre-existing brain tumours.

D. Summary

B225. Ionizing radiation can induce tumours of the CNS, with a moderate degree of association (relative risk) in the LSS, although it does not account for a large number of excess cancers because CNS tumours are relatively rare. There appear to be strong age-at-exposure effects. The risk for glioma

is greatest at ages of irradiation of five years or less and there is little risk for irradiation after age 20, suggesting that susceptibility decreases as brain development nears completion. The UNSCEAR 2006 Report [U12] points out that malignant tumours of the CNS are seen mostly after high doses from radiotherapy and the risk is predominantly after exposure in childhood (table B13).

Table B13. Age differences in risk estimates for brain and CNS cancer incidence and mortality from studies of radiation exposure

Updated and adapted from UNSCEAR 2006 Report (annex A, table 39) [U12]. Studies listed are those for which quantitative estimates of risk could be made

Study		*Average ERR[a] at 1 Sv*	*Average EAR[a] (10^4 PY Sv)$^{-1}$*
Incidence			
LSS [P52] [c]			
Age at exposure	<20 years	0.88 (0.28, 1.78)	0.68 (0.24, 1.28)
	20–40 years	0.64 (<0, 1.82)	0.48 (<0, 1.43)
	>40 years	<0 (<0, 0.51)	<0 (<0, 0.28)
All		0.55 (0.16, 1.07)	0.57 (0.23, 1.01)
LSS–incidence (excluding schwannomas) [P49] [b]			
Age at exposure	<20 years	1.2 (0.3, 2.9)	
	≥20 years	0.2 (<-0.2, 1.0)	
All		0.6 (0.1, 1.3)	
Israeli tinea capitis [S5] – Malignant brain tumours			
Age at exposure	0–4 years	3.6 (1.0, 9.9)	
	5–9 years	2.2 (0.8, 5.5)	
	10–15 years	0.5 (<0, n.a.)	
All		1.98 (0.73, 4.69)	0.31 (0.12, 0.53)
All benign meningiomas		4.63 (2.43, 9.12)	0.48 (0.28, 0.73)
New York tinea capitis [S71]			
Brain cancer		1.4 (0.2, 3.5)	n.a.
Swedish pooled skin haemangioma [K12] [b]			
Age at exposure	0–4 months	4.5	
	5–7 months	1.5	
	>7 months	0.4	
All		2.7 (1.0, 5.6)	2.1 (0.3, 4.4)
Childhood cancer survivors [L28] [b]			
All brain tumours		0.19 (0.03, 0.85)	n.a.
Malignant tumours		0.07 (<0, 0.62)	n.a.
Benign tumours		n.a.	n.a.

Study		*Average ERR[a] at 1 Sv*	*Average EAR[a] (10^4 PY Sv)$^{-1}$*
Incidence			
Childhood cancer survivors [N22]			
Gliomas			
Age at exposure	<5 years	0.64 (0.12, 5.66)	
	5–9 years	0.10 (-0.20, 0.39)	
	10–20 years	0.15 (-0.23, 0.52)	
Meningioma			
Age at exposure	<5 years	0.75 (00.11, 6.59)	
	5–9 years	1.99 (0.28, 21.1)	
	10–20 years	1.36 (0.10, 30.7)	
Mortality			
LSS [P50][c]			
Age at exposure	<20 years	5.72 (1.56, 17.04)	<0 (<0, <0)
	>20 years	0.77 (<0, 4.88)	<0 (<0, 35.70)
All		2.86 (0.83, 6.76)	<0 (<0, 35.75)

[a] *90% CI in parentheses derived from fitting models for the LSS detailed in [P52], and from published data for the other studies, unless otherwise stated.*

[b] *95% CI in parentheses.*

[c] *Data are for all brain and nervous system tumours combined.*

XII. KIDNEY CANCER

B226. The incidence of primary renal-cell carcinoma has increased slowly over the last decade. Primary renal-cell carcinoma accounts for about 85% of primary malignant tumours of the kidney. Other malignant tumours include Wilms' tumour, transitional cell carcinoma and lymphoma.

A. External exposure

B227. There are no data available regarding age-at-exposure effects for induction of radiation-related kidney cancer from epidemiological studies of populations exposed to relatively high levels of natural background radiation, populations living near nuclear facilities or patients who have undergone medical diagnostic exposure.

B228. The incidence study of the survivors of the atomic bombings through 1987 [T24] yielded an ERR for kidney cancer of 0.71 (90% CI: -0.11, 2.2) Sv^{-1} and an EAR of 0.29 (90% CI: −0.50, 0.79) (10^4 PY Sv)$^{-1}$. The attributable risk was 15.2% (90% CI: -2.6, 41.3). In a report on mortality through 2000 [P50] for kidney cancer in males, there was a non-significantly reduced relationship with radiation dose. The male ERR at 1 Sv was −0.2 (90% CI: <−0.3, 1.1) and the EAR was −0.01 (90% CI: −0.1, 0.28) (10^4 PY Sv)$^{-1}$ and the attributable risk was –0.4% based on 36 deaths. For kidney cancer in females, there was a non-significantly reduced relationship with radiation dose. The ERR at 1 Sv was

0.97 (90% CI: <−0.3, 3.8), the EAR was 0.14 (90% CI: <−0.1, 0.42) (10^4 PY Sv)$^{-1}$ and the attributable risk was 14% based on 31 deaths. No age-at-exposure effect was identified (see table B14).

Table B14. Risk estimates for kidney cancer incidence and mortality from studies of childhood radiation exposure

Adapted from UNSCEAR 2006 Report (annex A, table 38) [U12]. Studies listed are those for which quantitative estimates of risk could be made

Study		*Average ERR[a] at 1 Sv*	*Average EAR[a] (10^4 PY Sv)$^{-1}$*
Incidence			
LSS [P52]			
Sex	Males	<0 (<0, 0.42)	0.18 (0.02, 0.61)
	Females	1.04 (0.02, 2.83)	<0 (<0, 244.95)
Age at exposure	<20 years	0.75 (<0, 2.19)	0.31 (0.08, 0.74)
	20–40 years	0.23 (<0, 1.94)	<0 (<0, 304.44)
	>40 years	<0 (<0, <0)	<0 (<0, <0)
All		0.16 (<0, 0.78)	0.28 (0.09, 0.58)
Mortality			
LSS [P50]			
Sex	Males	<0 (<0, >10 000)	<0 (<0, 114.09)
	Females	1.17 (<0, 4.28)	<0 (<0, 71.62)
Age at exposure	<20 years	<0 (<0, >10 000)	<0 (<0, 39.84)
	20–40 years	0.86 (<0, 4.13)	<0 (<0, 106.20)
	>40 years	<0 (<0, <0)	<0 (<0, 198.97)
All		0.35 (<0, 1.51)	<0 (<0, 88.31)

[a] *90% CI in parentheses derived from fitting models for the LSS detailed in [P52], and from published data for the other studies, unless otherwise stated.*

B229. In the LSS incidence study for 1958–1998 of renal cell cancer [P52] the estimated ERR at 1 Sv was 0.13 (90% CI: −0.25, 0.75). An analysis of effect modification suggested that the ERR decreased with either age at exposure (p = 0.005) or attained age (p < 0.001), but both could not be modelled simultaneously because the excess number of cancers was too small. The EAR at 1 Sv was statistically significant (EAR = 0.25; 90% CI: 0.07, 0.53 (10^4 PY Sv)$^{-1}$).

B230. Radiotherapy can give quite high doses to specific organs. Radiotherapy patients have been followed up after treatment for benign as well as those treated for malignant conditions. Hawkins et al. [H31] reported a slight increase in genitourinary second primary tumours in survivors of childhood cancer. The ratios of observed over expected numbers of tumours was 1.9 (95% CI: 0.5, 4.8). Friedman et al. have followed up 14,359 five-year survivors in the CCSS [F17] and reported an increase in kidney cancer (ratio of observed over expected numbers was 20/3) with an SIR of 7.4 (95% CI: 4.6, 11.6) with a median time to occurrence of 19.6 years (range of 6.3 to 28.4 years). These results should be treated with caution as they include patients treated with chemotherapy, radiotherapy or a combination of both. Wilson et al. [W26] updated the kidney cancer data in the CCSS study and observed 26 kidney cancers. For renal-directed radiotherapy of 5 Gy or greater, they observed a relative risk of 3.8 (95% CI: 1.6,

9.3). Dores et al. [D43] reported in a pooled follow-up study of 32,000 patients an SIR of 1.5 (95% CI: 1.1, 2.1, *n* = 42) for subsequent kidney cancer, but did not report results by age at treatment.

B. Summary

B231. The BEIR VII report [N43] does not provide any risk factor for kidney cancer. The UNSCEAR 2006 Report [U12] has summarized those epidemiological studies that can be used to derive risk estimates for kidney cancer following childhood exposure. These are shown in table B14. The UNSCEAR 2006 Report also indicates that there is only weak evidence linking kidney cancer with radiation exposure and it comes primarily from those studies where the dose to the kidney is high (in the radiotherapy range). There does not appear to be any significant age-at-exposure effect.

XIII.BLADDER CANCER

B232. Bladder cancer represents about 3 to 4% of all cancers in the world. Rates are high in industrialized countries, particularly in Europe and North America. Low rates occur in India and Japan. A wide variety of causes of bladder cancer have been identified. The most common causes in adults are tobacco smoking, occupational exposure to aromatic amines and parasitic infection.

A. External exposure

1. Atomic bombing survivors

B233. The incidence study of atomic bombing survivors through 1987 and published by Thompson et al. [T24] yielded an ERR for bladder cancer of 1.0 (95% CI: 0.27, 2.1) Sv^{-1} and an EAR of 1.2 $(10^4$ PY $Sv)^{-1}$. The ERR risk was 0.35 for males and 1.80 at 1 Sv for females. The absolute risk for males was 0.84 $(10^4$ PY $Sv)^{-1}$. The attributable risk was 16.3%. In the report on mortality through 2000 by Preston et al. [P50], there was a statistically significant relationship between radiation dose and cancer of the bladder. For males, the ERR at 1 Sv was 1.1 (90% CI: 0.2, 2.5) and the EAR was 0.7 (90% CI: 0.1, 1.4) $(10^4$ PY $Sv)^{-1}$ and the attributable risk (17%) was based on 83 deaths. For females, the ERR at 1 Sv was 1.2 (90% CI: 0.1, 3.1) and the EAR was 0.33 (90% CI: 0.02, 0.74) $(10^4$ PY $Sv)^{-1}$ and the attributable risk (16%) was based on 67 deaths.

B234. The incidence data were updated through 1998 by Preston et al. [P52]. The ERR for bladder cancer was among the highest of the tumour sites, with a sex-averaged ERR Gy^{-1} of 1.23 (90% CI: 0.59, 2.1). However, since bladder cancer is relatively uncommon, the EAR $(10^4$ PY $Sv)^{-1}$ was moderate: 3.2 (90% CI: 1.1, 5.4). The ERR was much higher for females than males: 1.9 (0.8, 3.4) versus 0.6 (0.1, 1.2), respectively, though the EAR estimate was nominally lower for females 2.6 (90% CI: 1.1, 4.4) than for males 3.8 (90% CI: 0.2, 8.0). There was no age-at-exposure trend per decade of

age at exposure for either the ERR model −3% (90% CI: −42, 56), or the EAR model −19% (90% CI: −54, 41).

B235. The updated mortality data likewise indicate no age-at-exposure effect; the effect on the ERR model was −2% (95% CI: −62, 92) per decade of age at exposure [O25]. A detailed study of urothelial cancer incidence by Grant et al. [G26] (of which >90% were bladder cancers) found very similar results to the Preston et al. study [P52] regarding risk estimates, and additionally found that smoking and other lifestyle or occupational factors had almost no impact on the radiation risk estimates, indicating that secular or birth cohort trends in smoking did not appear to confound the age-at-exposure risk estimates for bladder/urothelial cancer.

2. Radiation therapy

B236. Radiation therapy can give quite high doses to specific organs, and patients have been followed up after therapy for benign, as well as for malignant, conditions. Travis et al. [T36] have reported on long-term survival and second cancers in over 40,000 testicular cancer patients almost all of whom received infradiaphragmatic radiotherapy. The relative risk for bladder cancer was significantly increased (RR = 2.7; 95% CI: 2.2, 3.1). Hawkins [H31] reported a slight increase in genitourinary second primary tumour GU SPT as a group (ICD-8: 180–189) (O/E = 1.9; 95% CI: 0.5, 4.8).

B. Summary

B237. The bladder appears to be sensitive to radiogenic tumour induction. In spite of this, the most common cause of bladder cancer is cigarette smoking, and a number of other causative factors are known as well. All of these need to be considered in evaluation of any specific case, as was recently done in the LSS study of atomic bombing survivors. Most occupational radiation studies are negative, and the positive correlations come primarily from the atomic bombing survivors and patients who received very high bladder doses from radiotherapy.

B238. The 1990 ICRP report [I11] estimates the probability of fatal bladder cancer after exposure of the general population to be 0.30×10^{-2} Sv^{-1}. The 1990 BEIR V report [N38] concluded that radiation can cause cancer of the bladder and, to a lesser extent, cancer of the kidney and suggested use of the atomic bombing survivor risk estimates. The BEIR VII report [N43] provides a lifetime risk estimate for bladder cancer of 25 excess deaths for a population of 100,000 persons exposed to 0.1 Gy and a lifetime bladder cancer estimate of 0.90 Sv^{-1} (95% CI: 0.30, 2.90).

B239. The UNSCEAR 2006 Report [U12] has summarized those epidemiological studies that can be used to derive risk estimates for bladder cancer. These are shown in table B15. It is clear that there is a positive association between radiation and bladder cancer in the atomic bombing survivors and after high dose radiotherapy. However, most low dose studies of nuclear workers and medical applications do not show increased risk of bladder cancer (perhaps due to limited statistical power). The atomic bombing data do not show any special radiation sensitivity among those irradiated in childhood.

Table B15. Risk estimates for urinary bladder cancer incidence and mortality from studies of childhood radiation exposure

Updated and adapted from UNSCEAR 2006 Report (annex A, table 37) [U12]. Studies listed are those for which quantitative estimates of risk could be made

Study		*Average ERR [a] at 1 Sv*	*Average EAR [a] (10^4 PY Sv)$^{-1}$*
Incidence			
LSS [P52]			
Sex	Males	0.63 (0.17, 1.25)	0.47 (<0, 1.60)
	Females	1.74 (0.71, 3.22)	0.52 (0.12, 1.13)
Age at exposure	<20 years	1.00 (0.16, 2.32)	<0 (<0, 0.46)
	20–40 years	0.95 (0.23, 2.01)	0.69 (<0, 1.89)
	>40 years	0.78 (0.14, 1.70)	2.28 (0.21, 5.01)
All		0.92 (0.46, 1.50)	0.51 (0.14, 1.02)
LSS [P52] [c]			
Age at exposure	0–9 [b] years	–0.09 (<–0.1, 5.1)	
	10–19 years	1.3 (0.16, 3.9)	
	20–39 years	1.1 (0.33, 2.2)	
	≥40 years	1.4 (0.47, 2.8)	
Mortality			
LSS [P50]			
Sex	Males	1.03 (0.07, 2.53)	<0 (<0, 313.73)
	Females	1.37 (0.15, 3.40)	<0 (<0, 170.04)
Age at exposure	<20 years	<0 (<0, 2.28)	<0 (<0, 43.45)
	20–40 years	1.52 (<0, 4.72)	<0 (<0, 176.04)
	>40 years	1.36 (0.34, 2.89)	<0 (<0, 848.46)
All		1.17 (0.36, 2.30)	<0 (<0, 226.53)
LSS [O25]			
Age at exposure	10 years [b]	1.24	1.22
	30 years	1.19 (95% CI: 0.27, 2.7)	1.2 (95% CI: 0.3, 2.4)
	50 years	1.15	1.18

[a] *90% CI in parentheses derived from fitting models for the LSS detailed in [P52], and from published data for the other studies, unless otherwise stated.*

[b] *Sex-averaged risk at attained age 70, smoothed using the assumption that the ERR Gy^{-1} varies as a log-linear function of age at exposure.*

[c] *Sex-averaged risk at attained age 70, assuming that within each age-at-exposure group the ERR Gy^{-1} varies as a power of attained age, but with no smoothing across age-at-exposure groups.*

XIV. OVARIAN CANCER

B240. Cancer of the ovary is more common in industrialized countries. Most tumours are serous or pseudomucinous cystadenocarcinomas, and most have a relatively poor prognosis. Studies of changes in incidence among migrant populations suggest environmental influences may be present [H45]. Early and frequent parity may be associated with an over 50% reduction in risk. Breast cancer is also associated with ovarian cancer. Oral contraceptives may reduce the risk of ovarian cancer. There are some unusual genetic associations, including the Peutz-Jeghers syndrome, basal cell nevus syndrome, and gonadal dysgenesis.

A. External exposure

1. Atomic bombing survivors

B241. Incidence and mortality studies [R42, S55, T24] of the atomic bombing survivors report risks of ovarian cancer. The 1958–1987 incidence study yielded an ERR estimate for ovarian cancer of 1.0 (95% CI: 0.12, 2.34) Sv^{-1} and an EAR of 1.1 (10^4 PY $Sv)^{-1}$. There was a statistically significant linear relationship between dose and risk. No effect of age at exposure, time since exposure, or of attained age was found. In the update of mortality of atomic bombing survivors during the period 1950–1997, Preston et al. [P50] found a statistically significant excess of ovarian cancer with an ERR of 0.94 (90% CI: 0.07, 2.0) Sv^{-1}. There was no significant difference in risk between those <20 years at exposure compared with those >40 years of age at exposure.

B242. In the latest incidence report for 1958–1998 [P52], the ovarian cancer ERR Gy^{-1} was 0.61 (90% CI: 0.00, 1.5) and the EAR was 0.56 (90% CI: 0.02, 1.3) (10^4 PY $Gy)^{-1}$. There were too few excess cases, however, to examine age at exposure meaningfully. The mortality report for 1950–2003 [O25] indicated an ERR Gy^{-1} of 0.79 (95% CI: 0.07, 1.86). Age at exposure was examined, but the CIs were very wide, and the modelled age-at-exposure effect was −22% per 10 years of age (95% CI: −96, 218).

2. Radiation therapy

B243. Few studies have examined radiation therapy for benign diseases and the subsequent risk of ovarian cancer. Many patients were treated with radiotherapy for ankylosing spondylitis. Darby et al. [D6] have extended the follow-up of this group, and cancer of the ovary was not elevated, with a reported O/E ratio of 0.93. Most studies of radiotherapy for benign gynaecological disease have not reported on ovarian cancer risk [D8, I38], although one study reported no excess based on small numbers [S91].

B. Internal exposure

B244. The studies examining ovarian cancer after administration of radioiodine have yielded negative results although essentially all the patients were exposed as adults [E8, H5, H53, H59, H58, R45].

C. Summary

B245. With the exception of the atomic bombing survivor data, not much epidemiological evidence of radiation induction of ovarian cancer exists either in those exposed as adults or children. The UNSCEAR 2006 Report [U12] has summarized risk factors that can be obtained from epidemiological studies (table B16) and concluded that although the body of evidence is not strong, the Japanese LSS provides evidence that ovarian cancer is inducible by ionizing radiation.

Table B16. Risk estimates for ovarian cancer incidence and mortality from studies of childhood radiation exposure

Adapted from UNSCEAR 2006 Report (annex A, table 35) [U12]. Studies listed are those for which quantitative estimates of risk could be made

Study		*Average ERR[a] at 1 Sv*	*Average EAR[a] (10^4 PY Sv)$^{-1}$*
EXTERNAL LOW-LET EXPOSURES			
Incidence			
LSS [P52]			
Age at exposure	<20 years	1.16 (0.15, 2.86)	0.71 (0.09, 1.72)
	20–40 years	<0 (<0, 0.71)	<0 (<0, 0.71)
	>40 years	1.73 (0.20, 4.45)	3.24 (0.45, 7.21)
All		0.61 (0.08, 1.35)	0.59 (0.07, 1.34)
Stockholm skin haemangioma [L41]		0.62	0.33
Mortality			
LSS [P50]			
Age at exposure	<20 years	1.53 (0.19, 4.06)	<0 (<0, 185.15)
	20–40 years	0.92 (<0, 2.65)	<0 (<0, 386.99)
	>40 years	1.33 (<0, 4.25)	<0 (<0, 717.59)
All		1.18 (0.39, 2.31)	<0 (<0, 348.40)

[a] *90% CI in parentheses derived from fitting models for the LSS detailed in [P52], and from published data for the other studies, unless otherwise stated.*

XV. UTERINE CERVIX AND CORPUS CANCER

B246. Worldwide, cervical cancer is the second most common cancer in women but, in developing countries, it is the most frequent cancer [I5]. Endometrial cancer is $^1/_3$ as frequent as cervical cancer. Cancer of the endometrium is more common in nulliparous women. Obese women have a two- to fivefold increase in risk. Menopause may have a protective influence. Exogenous oestrogens are a major risk factor, with increases in cancer associated with use of oral conjugated oestrogens administered for replacement therapy and use of sequential oral unopposed oestrogen contraceptives. The risk of cervical cancer is higher with earlier age at first intercourse and rises with the number of sexual partners throughout life. Thus, there is very likely a sexually transmitted factor (human papilloma virus). In most studies there is also an increased risk of cervical cancer with smoking, and smokers have a relative risk of about two compared with non-smokers.

A. External exposure

1. Atomic bombing survivors

B247. Neither the 1958–1987 incidence [T24] nor the 1958–1987 mortality study [R42] of the atomic bombing survivors showed any increase in cancer of the uterus. The ERR at 1 Sv derived from the incidence study was negative, at –0.2, and the EAR was –1.1 $(10^4 \text{ PY Sv})^{-1}$. In the mortality study through 1987, the corresponding values were 0.1 and 0.3 $(10^4 \text{ PY Sv})^{-1}$. In the 2003 mortality update for 1950–1997 [P50], the survivors had a non-significant excess of uterine cancer with a corresponding ERR Gy^{-1} of 0.17 (90% CI: −0.10, 0.52). No age-at-exposure effect was identified.

B248. The most recent study of uterine cancer incidence for 1958–1998 [P52] reported no association of radiation with cervical cancer (ERR at 1 Sv, 0.06; 90% CI: −0.14, 0.41) and no overall association with uterine corpus cancer (ERR, 0.3; CI: −0.14, 0.95). However, among those exposed before age 20, the ERR at 1 Gy was 1.00 (CI: 0.14, 2.4) for uterine corpus cancer and the risk was significantly greater ($p = 0.04$) among those exposed before age 20 compared with after age 20.

2. Radiation therapy

B249. No specific data relevant to childhood exposure is available. Although various studies of radiotherapy for benign [I38, S91] or malignant [B37] gynaecological disease have reported on subsequent uterine cancer, they have had few or no patients irradiated before age 20. A study of second cancers among Hodgkin's disease patients treated in childhood or adolescence reported a statistically significant excess of cervical cancer but no excess for uterine corpus cancer [M32]. Another larger pooled study that included those and other subjects found, however, that cervical cancer risk was elevated with or without radiotherapy [D43].

B. Summary

B250. The epidemiological literature in general does not support radiation induction of uterine neoplasms. While there are a few anecdotal case reports in the literature, these should not be taken to prove a causal relationship, and the recent suggestive finding of an excess of uterine corpus cancers among those exposed to the atomic bombings when young requires confirmation with longer follow-up and other studies. The UNSCEAR 2006 Report [U12] has summarized those epidemiological studies that provide risk factors for uterine cancer following radiation exposure (table B17). The UNSCEAR 2006 Report [U12], concluding that there is no strong radiation dose response for uterine cancer and that the absence of an association between cervical cancer and radiation is a consistent finding even after very high radiation doses. It also concludes that for cancer of the uterine corpus (endometrial cancer), the evidence is largely negative and that if there is an association with radiation it is confined to very high doses.

Table B17. Risk estimates for uterine cancer incidence and mortality from studies of radiation exposure

Adapted from UNSCEAR 2006 Report (annex A, table 34) [U12]. Studies listed are those for which quantitative estimates of risk could be made

Study		*Average ERR*[a] *at 1 Sv*	*Average EAR*[a] *(10^4 PY Sv)$^{-1}$*
Incidence			
LSS [P52]			
Age at exposure	<20 years	0.38 (<0, 0.90)	0.75 (<0, 2.59)
	20–40 years	<0 (<0, 0.33)	0.20 (<0, 2.85)
	>40 years	<0 (<0, 0.41)	0.09 (<0, 4.88)
All		0.10 (<0, 0.32)	0.09 (<0, 1.48)
Mortality			
LSS [P50]			
Age at exposure	<20 years	0.42 (<0, 1.68)	<0 (<0, 333.82)
	20–40 years	0.17 (<0, 0.77)	<0 (<0, 1.61)
	>40 years	<0 (<0, 0.51)	<0 (<0, 3.53)
All		0.09 (<0, 0.44)	<0 (<0, 0.33)

[a] *90% CI in parentheses derived from fitting models for the LSS detailed in [P52], and from published data for the other studies, unless otherwise stated.*

XVI. BONE AND CONNECTIVE TISSUE TUMOURS

B251. Tumours of bone and cartilage account for about 0.5% of all malignant neoplasms. Malignant bone tumours are divided into several types, with osteosarcoma accounting for 38%; chondroblastic sarcoma, 17%; Ewing's sarcoma, 15%; and all other histological forms, 30%. There is a male–female sex ratio of 1:3; five-year survival is approximately 30% for radiation-induced tumours of bone. An overall fatality rate of 75–80% is usually seen. The various types of tumours are quite age dependent. Osteosarcomas tend to occur in teenagers and in adults who have predisposing Paget's disease. Ewing's

sarcoma occurs in childhood and early adult life. Fibrosarcomas mostly occur in middle-aged adults and chondrosarcomas in older adults. There is a relative lack of variation in incidence rates, which argues against a common environmental aetiology. There may be some evidence of a familial tendency for osteogenic sarcoma in families with multiple tumours. An increase in bone tumours occurs after use of alkylating agents in treatment of childhood cancer. The attributable risk due to radiation is estimated to be less than 10% [H45, I5]. The frequency of soft tissue sarcomas is greater than for bone sarcomas, but the former has been studied less in relation to radiation.

A. Modifying factors

B252. The absolute radiation risk estimates are somewhat clouded by the fact that many of the population groups exposed to external irradiation received irradiation in body areas where the spontaneous incidence of osteosarcomas is low. For example, the most common site of osteosarcoma is the distal femur (i.e. peripheral skeleton). The patients exposed either for treatment of tinea capitis or for ankylosing spondylitis received the radiation predominantly to the axial skeleton. People who received internal exposures from radium are somewhat difficult to evaluate because the different radioisotopes of radium decay with substantially different rates; thus, the dose is delivered by alpha radiation to different portions of the bone on the basis of the position of the radionuclide in the metabolic cycle of bone. With a physical half-life of 3.62 days, ^{224}Ra yields a relatively high endosteal dose, whereas longer-lived ^{226}Ra decays mainly within the bone volume. An additional problem in deriving risk estimates is the appropriate RBE to be used for alpha particles. In general, the ICRP quality or radiation weighting factor of 20 has been used by most authors. Fractionation is a major modifying factor that has been rather clearly demonstrated in the case of ^{224}Ra. Contrary to most other types of irradiation, for radium the effectiveness of a given dose increases as the time of irradiation is protracted. Thus, the absolute risk factors rise if ^{224}Ra is administered over weeks and years rather than in a single injection. The risk factors appear to be relatively similar for children and adults, and also for males and females [S101, S102].

B. External exposure

1. Atomic bombing survivors

B253. The older incidence and mortality studies of the atomic bombing survivors do report case numbers, but they did not show significantly increased risks for bone and connective tissue cancers. The incidence study during the period 1958–1987 [T24] observed 16 cases of bone and connective tissue cancer versus 12 expected in 41,000 persons who received 0.01 Sv or more. In the comparable mortality study [S55], there were 24 deaths versus 19 expected. A recent report suggested a dose threshold up to a dose of about 0.85 Gy with an approximately linear, statistically significant slope above that level. Those younger at exposure had a shorter interval between atomic bombing exposure and bone cancer diagnosis than did those who were older when exposed, but the groups did not differ in overall risk [S12]. For connective tissue malignancies (104 soft-tissue sarcomas), a recent report showed an approximately linear dose response and an ERR risk estimate of 1.0 (95% CI: 0.13, 2.5) Gy^{-1}

and an EAR of 0.4 (95% CI: 0.1, 0.9) (10^4 PY Sv)$^{-1}$ [S13]. The effects did not vary by age at exposure for either model.

2. Radiation therapy

B254. In treatment of tinea capitis, bone tumours have been reported in at least two studies. The UNSCEAR 1977 Report [U6] reviewed these latter studies and, assuming that the skull forms about 25% of total bone mass in children, derived an absolute lifetime risk factor of three–five cases/million persons for each 10 mGy. Most studies involving external irradiation yield risk estimates that may vary with the skeletal site involved. The BEIR III report [N37] indicated that different portions of the skeleton may have different radiosensitivity.

B255. In a study by Evans et al. [E14] of about 700 patients treated for Wilms' tumours with radiotherapy, subsequent bone cancer was not observed, even though there were 19 patients with benign exostoses or osteochondromas. Osteosarcomas have been reported after radiation therapy for Ewing's tumour, although the series are too small to develop risk estimates [S89].

B256. In a study by Hawkins et al. [H31] of 10,106 childhood cancer survivors, there was a significant increase (20-fold) in the number of sarcomas. Risk was particularly high (400-fold) in patients with familial retinoblastomas. In fact, in patients with this entity, the risk was 200-fold times the normal even without radiotherapy or chemotherapy. Sagerman et al. [S9] have reported that approximately 1.5% of children treated for retinoblastoma will develop radiation-induced malignancies with about half of these being osteosarcomas. However, that children with heritable retinoblastomas are at increased risk for other tumour types even outside the radiation therapy field [S29]. The CCSS reported an SIR for osteosarcoma of 30 (95% CI: 21, 42; $n = 35$) after treatment for childhood cancer [F17]. A more detailed study of sarcomas after childhood cancer in the CCSS reported that the risk function was essentially linear with an excess odds ratio (EOR) of 1.32 (95% CI: 0.44, 4.22) Gy^{-1} based on 105 sarcomas and adjusted for chemotherapy [H41]. Within the childhood age range there was no significant age-at-exposure effect, nor was there modification by sex or attained age.

B257. In a study of patients treated for Hodgkin’s disease, Tucker et al. [T48] reported an O/E ratio of 31 (95% CI: 3.5, 111.8) based upon two cases versus one expected. Most patients received both radiotherapy and chemotherapy [T46]. Woodard et al. [W41] have reported on 16 cases of malignant bone tumours that arose 4–31 years after irradiation for Hodgkin’s disease. The median absorbed dose was 40 Gy, and it was estimated that up to 25% of the skeleton was exposed in the primary beam. The same authors also reported on the survival of 59 patients with post-irradiation osteosarcomas and 20 with malignant fibrous histiocytomas. The five-year, disease-free survival rate for osteosarcomas was 17% compared with a three-year disease-free survival rate for malignant fibrous histiocytoma of 58% [H77]. A similar pattern of subsequent tumours was also reported by Laskin et al. [L8] and in children by Newton et al. [N30]. A post-radiation case of multicentric osteosarcoma has been reported by Tillotson et al. [T26] and there are case reports of chondrosarcomas [V12].

B258. Radiation-induced osteochondromas have been reported in 6% of long-term surviving children who received radiation therapy. It has been postulated that this represents a growth disturbance in the epiphyseal plate rather than a true neoplasm [J8]. These benign “tumours” have been noted in the spine, pelvis, scapula and ribs [N28].

C. Summary

B259. The epidemiological data show convincing excesses of bone and connective tissue tumours after childhood radiation therapy and a small risk among atomic bombing survivors. Most authoritative reports give risk estimates for bone cancer although usually not at low doses. The UNSCEAR 2006 Report [U12] has summarized radiation risk factors regarding bone and connective tissue cancer from epidemiological studies (table B18) and concluded that there is an increased risk of bone sarcomas following low-LET radiation in the range of tens of grays and that risk factors cannot be derived at doses below a few grays.

Table B18. Risk estimates for cancer incidence and mortality from studies of childhood radiation exposure on malignancies in bone and connective tissue

Adapted from UNSCEAR 2006 Report (annex A, table 30) [U12]. Studies listed are those for which quantitative estimates of risk could be made

Study		*Average ERR[a] at 1 Sv*	*Average EAR[a] (10^4 PY Sv)$^{-1}$*
Incidence			
LSS [P52]			
Sex	Males	3.34 (0.90, 9.69)	<0 (<0, <0)
	Females	<0 (<0, <0)	<0 (<0, 9.75)
Age at exposure	<20 years	4.33 (0.90, 16.11)	<0 (<0, <0)
	20–40 years	3.16 (<0, 24.05)	<0 (<0, 12.66)
	>40 years	<0 (<0, <0)	<0 (<0, <0)
Retinoblastoma patients [W39][b] (bone and soft-tissue sarcoma)		0.19 (0.14, 0.32)	n.a.
Childhood radiotherapy, international [T46][c]		0.06 (0.01–0.2)	n.a.
Childhood cancer, United Kingdom (bone) [H34][b]		0.16 (0.07, 0.37)	n.a.
Mortality			
LSS [P50]			
Sex	Males	1.24 (0.03, 4.47)	<0 (<0, 24.40)
	Females	<0 (<0, 3.15)	<0 (<0, 25.43)
Age at exposure	<20 years	2.11 (<0, 11.62)	<0 (<0, 7.21)
	20–40 years	8.26 (0.70, 50.09)	<0 (<0, <0)
	>40 years	<0 (<0, 0.01)	<0 (<0, 35.48)

[a] *90% CI in parentheses derived from fitting models for the LSS detailed in [P52], and from published data for the other studies, unless otherwise stated.*

[b] *95% CI in parentheses.*

[c] *Estimates based on UNSCEAR 2000 Report (annex I) [U10].*

XVII. PROSTATE CANCER

B260. Prostate cancer is the most common cancer in elderly males, and the highest rates in the world are observed in African Americans. The causes of the tumour remain generally obscure. At various times, sexual activity, vasectomy, intake of dietary fat, hormonal factors and cirrhosis have been implicated as causes but have yet to be confirmed. Radiation does not appear to be a cause of prostate cancer [H45, I5].

A. External exposure

B261. There are no data on radiation-induced prostate cancer by age at exposure in areas of relatively high natural background radiation, populations living near nuclear facilities or patients following medical exposure.

B262. The only age-at-exposure data are from the survivors of the atomic bombings. The incidence data [T24] for prostate cancer in the survivors show that there was no excess except for one data point at 2.5 Sv. The ERR at 1 Gy for cancer of the prostate was non-significantly elevated at 0.29 (95% CI: -0.21, 1.16) and the EAR was 0.6 $(10^4 \text{ PY Sv})^{-1}$. In the LSS mortality study of the survivors of the atomic bombings from 1958 to 1987, the calculated ERR at 1 Sv was 0.3 (95% CI: -0.3, 1.6), and the EAR was 0.2 (95% CI: –0.2, 0.9) $(10^4 \text{ PY Sv})^{-1}$. In the update studies of mortality of the survivors of the atomic bombings from 1950 to 1997, Preston et al. [P50] found that there was a non-significant excess of prostate cancer at doses of 1 Sv amounting to a non-significant ERR of 0.21 (90% CI: <−0.3, 0.96). In the most recent update of prostate cancer incidence (1958–1998), Preston et al. [P52] found no evidence ($p > 0.5$) of an association with radiation dose. The ERR at 1 Sv was 0.11 (90% CI: −0.10, 0.54) and the EAR was 0.34 (CI: −0.64, 1.60). No childhood exposure data were reported.

B263. Most radiotherapy studies have likewise not seen elevations in prostate cancer rates. An international study of Hodgkin's lymphoma patients found an SIR of 1.0 (95% CI: 0.8, 1.2, $n = 98$) for subsequent prostate cancer in about 19,000 male patients [D43].

B. Summary

B264. A number of epidemiological studies have looked for an increased risk of prostate cancer after radiation exposure. At present, there is no clear evidence that prostate cancer is induced by radiation as a result of either childhood or adulthood exposure. In the UNSCEAR 2006 Report [U12], the Committee summarized the risk estimates for prostate cancer from various epidemiological studies (table B19) and concluded that there was little indication of radiation effects on prostate cancer risks. A committee of the National Research Council [N42] was more definite and concluded that there was no convincing epidemiological evidence that prostate cancer was induced by radiation.

Table B19. Risk estimates for prostate cancer incidence and mortality from studies of childhood radiation exposure

Adapted from UNSCEAR 2006 Report (annex A, table 36) [U12]. Studies listed are those for which quantitative estimates of risk could be made

Study		*Average ERR [a] at 1 Sv*	*Average EAR [a] (10^4 PY Sv)$^{-1}$*
Incidence			
LSS [P52]			
Age at exposure	<20 years	0.12 (<0, 1.38)	<0 (<0, 0.42)
	20–40 years	0.03 (<0, 0.70)	<0 (<0, 1.84)
	>40 years	0.11 (<0, 0.70)	<0 (<0, 2.96)
All		0.12 (<0, 0.51)	<0 (<0, 0.38)
Mortality			
LSS [P50]			
Age at exposure	<20 years	<0 (<0, >10 000)	<0 (<0, 45.63)
	20–40 years	<0 (<0, 1.10)	<0 (<0, 473.90)
	>40 years	1.01 (0.01, 2.78)	<0 (<0, 910.84)
All		0.40 (<0, 1.31)	<0 (<0, 298.22)

[a] *90% CI in parentheses derived from fitting models for the LSS detailed in [P52], and from published data for the other studies, unless otherwise stated.*

XVIII. PANCREATIC CANCER

B265. The most recent report on pancreatic cancer incidence in the LSS of atomic bombing survivors did not find a statistically significant dose-related increase in pancreatic cancer [P52]. Neither the ERR, which was estimated to be 0.26 Gy^{-1} (90% CI: −0.07, 0.68), nor the EAR was statistically significant. There was no examination of age at exposure as a co-factor. Similarly, the pancreatic cancer mortality data were not significant: ERR Gy^{-1} of 0.08 (95% CI: −0.18, 0.44) [O25].

B266. A study of 1,859 patients given X-ray treatment for peptic ulcer and 1,860 without irradiation was conducted with an average follow-up of 22.5 years for the irradiated group [C6]. Those who received <13 Gy to the stomach had an excess of pancreatic cancer, but cell-killing apparently reduced the risk at higher doses. The study reported a marginal trend ($p = 0.13$) by age at radiation exposure. The RRs, adjusted for sex and smoking, were 2.99 (95% CI: 1.15, 7.8), 1.69 (0.74, 3.9) and 1.19 (0.32, 4.4) for ages <35, 35–54 and ≥55, respectively. However, few if any study subjects would have been exposed before age 20.

B267. A study of 40,000 men treated for testicular cancer showed an excess of pancreatic cancers (RR = 3.8; 95% CI: 2.7, 5.0) among those who received radiotherapy for testicular cancer with pancreas doses in the range of about 13–28 Gy [T36]. No data were reported for age at exposure. A report on pancreatic cancer after radiotherapy for ovarian cancer also showed a modest excess of pancreatic cancer (SIR = 2.1; 95% CI: 1.1, 3.6), but age at exposure was not considered [T32]. An international

study of patients treated for Hodgkin's lymphoma reported a small elevation in risk (SIR of 1.5, 95% CI: 1.1, 2.0, $n = 40$), but no information on an age-at-exposure effect was available [D43].

B268. In a cohort of patients who received thorotrast for cerebral angiography in Denmark and Sweden, an excess of pancreatic cancer was seen (RR = 3.8; 95% CI: 1.3, 12.3; $n = 11$), but no comparison was made by age at exposure [T34]. A German thorotrast cohort study also found an excess of pancreatic cancer (RR = 2.4; 95% CI: 1.0, 6.0; $n = 18$) but age at exposure was not examined [V5].

XIX. MULTIPLE MYELOMA

B269. Until about 1990, the risk of multiple myeloma was thought to be increased by radiation exposure [N38]. However, as more evidence has accumulated, this seems unlikely to be the case. There is little or no evidence of the induction of myeloma by radiation as a result of childhood exposure in the areas of relatively high natural background radiation, among populations living near a nuclear facility or among those having received medical radiation exposure [M35].

B270. The LSS mortality study data as of 1985 indicated statistically significant increases in mortality from multiple myeloma due to radiation exposure [S55]. However, a more recent LSS incidence study by Preston et al. [P47] did not find an increase in the incidence of multiple myeloma among the survivors of the atomic bombings in Japan. For the 41,000 persons who received a dose of 0.01 Sv or more and a mean dose of 0.23 Sv, there were 30 observed cases of the disease whereas 29 were expected in over one million person-years of study. This study has included a large number of new cancer cases. Several of the incident cases used in the earlier reports were excluded from the new analysis as a result of dose-range restrictions or as a consequence of a review of the clinical pathology of presumed cases. In a recent analysis, the estimated risk using a linear dose-response model was not statistically significant (ERR Gy^{-1} of 0.38, 95% CI: −0.23, 1.36, $p = 0.21$) [H70]. The addition of a quadratic term was not significant ($p = 0.44$). There was no indication of a trend by age at exposure ($p > 0.5$) for the ERR model. For the linear EAR model, the estimated risk was 0.07 $(10^4 \text{ PY Sv})^{-1}$ (95% CI: <−0.05, 0.29, $p = 0.25$) and there was no variation by age at exposure ($p > 0.5$).

B271. In summary, radiation risk estimates for multiple myeloma that can be derived from childhood exposure epidemiological studies were summarized by the Committee in the UNSCEAR 2006 Report [U12] and are shown in table B20. The UNSCEAR 2006 Report concluded that there was only weak evidence linking myeloma to radiation exposure and that the better quality of diagnostic information from incidence data would suggest that there was little evidence of an association with low-LET radiation exposure. While there was some evidence of an association with high-LET radiation exposure, it was based on only a few studies and very few cases. There was no evidence of an age-at-exposure effect.

Table B20. Risk estimates for cancer incidence and mortality from studies of childhood radiation exposure on multiple myeloma

Adapted from UNSCEAR 2006 Report (annex A, table 43) [U12]. Studies listed are those for which quantitative estimates of risk could be made

Study	*Average ERR[a] at 1 Sv*	*Average EAR[a] (10^4 PY Sv)$^{-1}$*
Incidence		
LSS [P47][b]		
Sex Males	0.17	0.26
Females	0.28	0.08
Age at exposure <20 years	1.07	0.07
>20 years	0.09	0.04
All	0.20 (<0, 21.7)	0.05 (<−0.05, 0.4)
Mortality		
LSS [P33][b]		
Sex Males	1.13 (<0, 6.41)	0.15 (<0, 0.51)
Females	1.16 (0.01, 3.9)	0.19 (0.001, 0.5)
All	1.15 (0.12, 3.27)	0.17 (0.02, 0.4)

[a] *90% CI in parentheses derived from published data for the LSS and using exact Piosson methods for other studies.*

[b] *Estimates based on UNSCEAR 2000 Report (annex I) [U10].*

XX. HODGKIN'S LYMPHOMA

B272. Hodgkin's disease typically afflicts teenagers and young adults and is thought to be associated with viral infections such as the Epstein-Barr virus and with immunosuppression in HIV, AIDS and bone marrow transplant patients. There also appears to be a significant genetic component with an elevated shared risk between identical compared to fraternal twins.

B273. A recent update of the atomic bombing data did not show a statistically significant association between radiation and Hodgkin's disease (ERR of 0.20 (95% CI: -1.0, 2.6) Gy^{-1}), nor was there effect modification by age [H70]. A review of the available epidemiological data indicates that there is no demonstrable risk for Hodgkin's disease from radiation exposure and no age-at-exposure effect. Friedman et al. have followed up 14,359 five-year survivors in the CCSS [F17] and reported no increase in Hodgkin's disease (ratio of observed over expected of 9/9) with an SIR of 1.0 (95% CI: 0.5, 1.9). Evaluation for the induction of secondary Hodgkin's disease post-therapy would be complicated by the need to distinguish secondary from the more likely recurrent disease.

B274. In summary, with the exception of what are thought to be statistical chance associations [G10, M18], radiation has not been found to be associated with the development of Hodgkin's disease following either childhood or adult radiation exposure. The wide confidence limits on the risk estimates are due to the very small number of cases in most studies. The UNSCEAR 2000 Report [U10] concluded that the available data did not indicate an association between Hodgkin's disease and

external or internal radiation exposure, but that the data were limited. The UNSCEAR 2006 Report [U12] summarized the radiation risk factors for Hodgkin's disease and concluded that there was no clear indication of an excess of Hodgkin's disease associated with radiation exposure but that the data remained sparse and lacked a dose-response analysis. A committee of the National Research Council [N42] concluded that epidemiological studies failed to show any significant association between Hodgkin's disease and radiation exposure.

XXI. NON-HODGKIN'S LYMPHOMA

B275. An earlier analysis by Preston et al. of non-Hodgkin's lymphoma incidence in the LSS found no excess for females, but an estimated EAR for males of 0.56 $(10^4$ PY $Sv)^{-1}$ (95% CI: 0.08, 1.39) [P47]. No age-at-exposure effect was found ($p > 0.5$). A recent analysis by Hsu et al. suggested the possibility of risk among men, with an ERR Gy^{-1} of 0.46 (95% CI: -0.08, 1.3) and an EAR $(10^4$ PY $Sv)^{-1}$ of 0.54 (95% CI: 0.09, 1.32), but both the ERR and EAR were essentially zero among women [H70]. The male EAR did not vary with age at exposure ($p = 0.15$).

B276. A study of tuberculosis patients who received multiple fluoroscopic examinations in monitoring pneumothorax treatments found a non-significant excess of non-Hodgkin's lymphoma (RR = 1.3, 95% CI: 0.5, 3.5) and did not examine age at exposure [D15].

B277. A follow-up of Hodgkin's disease patients in the CCSS found an excess of non-Hodgkin's lymphoma (SIR = 8.1; 95% CI: 4.6, 14.3), but the excess was not analysed specifically for radiotherapy [C8]. Similarly, an examination of secondary cancer incidence in the entire CCSS cohort found an excess of non-Hodgkin's lymphoma (SIR = 2.5; 95% CI: 1.6, 4.0) but it was not broken down by whether the first primary cancer treatment had included radiotherapy [F17].

XXII. SALIVARY GLAND TUMOURS

B278. Salivary gland tumours are uncommon, with incidence rates below 0.1 per 100,000. Much higher rates have been seen in Eskimos. About 80% of the malignant salivary tumours involve the parotid glands.

A. External exposure

1. Atomic bombing survivors

B279. Benign and malignant tumours of the salivary, and particularly parotid, glands have been reported to follow external exposure in the atomic bombing survivors and in children who have received radiation therapy. These are easily detected because spontaneous salivary gland tumours are rare. The risk rates are usually reported in numbers of cases rather than mortality. Presently, data are

insufficient for assessing the effect of age at irradiation or the possible difference in induction rates between males and females.

B280. An analysis of radiation and salivary gland tumours among atomic bombing survivors [L4] reported a dose response based ERR of 3.5 (90% CI: 1.5, 7.5) at 1 Sv for malignant tumours and 0.7 (90% CI: 0.1, 1.7; $n = 41$) for benign tumours. EARs were 3.73 (90% CI: 2.02, 6.04; $n = 94$) $(10^4 \text{ PY Sv})^{-1}$ for malignant tumours and 1.89 (90% CI: 0.27, 4.21) for benign tumours. They reported ERRs of 8.3 (90% CI: 2.5, 29.6) for mucoepidermoid cancers and 3.1 (90% CI: 0.6, 10.3) for benign Warthins' tumours. The risk estimates for malignant tumours were non-significantly higher for exposures before age 20, compared to those older at exposure. In a pathological review of the atomic bombing survivor data, Saku et al. [S10] reported on 120 histologically confirmed salivary gland tumours. Mucoepidermoid tumours were more highly represented ($p = 0.04$) among the 41 malignant tumours than were other types. Benign Warthins tumours were most strongly related to radiation exposure ($p = 0.06$).

2. Medical radiation uses

B281. Studies involving children who received radiotherapy for benign diseases have been performed by Saenger et al. [S8], Pifer et al. [P35], Janower and Miettinen [J13], Shore et al. [S60] and Modan et al. [M45]. The series yield absolute risk factors in the range of 5–16 excess salivary gland tumours in one million exposed children for each 0.01 Gy over a follow-up of approximately 20 years. Annual risk estimates are in the range of 0.06 to 0.25 cases of malignant and benign tumours in one million persons annually for 0.01 Gy. If there were a longer follow-up period, the absolute risk factor might be somewhat greater. Although the data concerning adults and children are limited and from fairly different exposure circumstances and populations, it appears that exposure may involve a higher risk in children than in adults.

B282. A paper by Schneider et al. [S32] reported an increase in salivary gland tumours after head and neck therapy following childhood irradiation. A more detailed analysis [S59] reported 40 benign and 14 malignant salivary gland tumours among 2,311 irradiated study subjects after childhood radiotherapy (85% <10 years old) for enlarged tonsils and adenoids. Although a formal dose-response analysis was not conducted, there appeared to be a radiation dose effect. Within the restricted age range there was no age-at-exposure effect. Colman et al. [C38] reported a dose-related excess of salivary gland tumours (10 malignant and 27 benign) following X-ray treatment for benign conditions in childhood. The mean neck dose for tumour cases was 8.1 Gy.

B283. A study was conducted of about 11,000 patients given radiotherapy for Hodgkin's disease, for which the salivary gland doses were thought to range from 20 to 35 Gy, depending on the treatment regimen [B52]. It revealed 21 salivary gland cancers (SIR = 16.9; 95% CI: 10.4, 25.8). The risk was higher among those under the age of 20 at the time of radiotherapy (SIR = 45.5; 95% CI: 12.4, 117). In the CCSS, salivary gland cancer incidence was determined among 14,100 childhood cancer survivors [B53]. The SIR for second-primary salivary gland cancers was 39.4 (95% CI: 25, 58) based on 23 tumours. Individualized radiation doses to the salivary glands were estimated, and the ERR Gy^{-1} was 0.36 (95% CI: 0.06, 2.5).

B. Internal exposure

B284. Holm et al. [H59] reported no excess of salivary gland cancer among 10,500 patients treated with ^{131}I for hyperthyroidism. Similarly, a report of 1,771 patients treated with ^{131}I for thyroid cancer showed no excess of subsequent salivary gland cancers [D27]. Dottorini et al. [D46] found 3 salivary cancers (SIR = 60; 95% CI: 12, 175) in a cohort of 627 patients treated for thyroid cancer with ^{131}I, as did Hall et al. [H5] among 834 thyroid cancer patients, SIR = 15.0 (95% CI: 3.1, 44). All of the studies contained few or no exposed children.

C. Summary

B285. The UNSCEAR 2006 Report [U12] has summarized radiation risk factors for salivary gland cancer from the epidemiological studies where they could be derived (table B21) and concluded that the salivary gland is susceptible to the induction of cancer by ionizing radiation. The evidence for this comes almost exclusively from studies of external low-LET exposure. There appears to be little modifying effect of sex, age at exposure or time since exposure [U12].

Table B21. Age differences in risk estimates for salivary gland cancer incidence from studies of childhood radiation exposure

Adapted from UNSCEAR 2006 Report (annex A, table 20) [U12]. Studies listed are those for which quantitative estimates of risk could be made

Study		*Average ERR [a] at 1 Sv*	*Average EAR [a] (10^4 PY Sv)$^{-1}$*
Incidence			
LSS [P52] [b]			
Age at exposure	<20 years	11.12 (3.40, 43.32)	<0 (<0, 64.40)
	20–40 years	<0 (<0, 0.46)	<0 (<0, 0.05)
	>40 years	1.39 (<0, 8.30)	<0 (<0, 63.69)
All		2.55 (0.87, 5.72)	<0 (<0, 73.21)
Childhood benign head and neck tumour cohort [S34] [c]			
Benign tumours		19.6 (0.16, ∞)	n.a.
Malignant tumours		–0.06 (–∞, 4.0)	n.a.
All tumours		0.82 (0.04, ∞)	n.a.

[a] *90% CI in parentheses derived from fitting models for the LSS detailed in [P52], and from published data for the other studies, unless otherwise stated.*

[b] *Calculated using brain dose.*

[c] *95% CI in parentheses.*

XXIII. RECTAL CANCER

B286. The incidence of rectal cancer is lower than that of cancer of the colon. The geographical incidence is broadly similar. In contrast, however, rates in immigrants to an area tend to remain similar to those in the country of origin [I5]. While many reports group colon and rectal cancers together, the two organ sites seem to have different susceptibilities relative to radiation carcinogenesis. In the Japanese atomic bombing survivor incidence data, there is a fairly strong, approximately linear dose–response relationship for colon cancer, but no relationship between radiation dose and rectal cancer.

A. External exposure

1. Atomic bombing survivors

B287. In a study of colorectal cancer incidence in the atomic bombing survivor LSS sample reported by Nakatsuka et al. [N7], there was no excess risk of rectal cancer. Later follow-up by Thompson et al. [T24] did not indicate a significant ERR; at 1 Sv, the ERR was estimated to be 0.21 (95% CI: 0.17, 0.75). The LSS mortality study data as of 1985 also demonstrated a statistically significant increase in colon cancer but, again, cancer of the rectum was not increased. In the 2003 update studies of mortality of atomic bombing survivors during the period 1950–1997, Preston et al. [P50] analysed a cohort of 86,572 persons with an average external dose of 0.23 Sv. In males there was a statistically non-significant decrease of rectal cancer at dose levels of 1 Sv with an ERR of −0.25 (90% CI: <−0.3, 0.15). In females there was a statistically significant excess at dose levels of 1 Sv with an ERR of 0.75 (90% CI: 0.16, 1.6). In the most recent cancer incidence report, the radiation risk for rectal cancer was not statistically significant (ERR Gy^{-1} of 0.19; 90% CI: −0.04, 0.47), nor was there significant variation in risk by sex ($p = 0.3$), age at exposure ($p = 0.4$) or attained age ($p > 0.5$) [P52].

B288. The most recent mortality study reported an ERR Gy^{-1} of 0.17 (95% CI: -0.17, 0.64) based on 427 rectal cancer deaths [O25]. The age-at-exposure effect was not reported. In neither the incidence nor the mortality studies is there an effect of age at exposure.

2. Radiation therapy

B289. Reulen et al. [R19] have reported an increase in digestive cancers in the British CCSS, with an SIR of 4.6 (95% CI: 3.8, 5.6; $n = 105$). Friedman et al. [F17] reported an elevated risk for small intestine and colorectal cancer in the CCSS cohort (SIR of 4.6 (95% CI: 3.2, 6.8; $n = 27$). Among 5,400 Hodgkin's disease patients, the risk of rectal cancer was elevated for 10 or more years after radiotherapy. Based on 15 cases, the SIR = 2.5 (95% CI: 1.4, 4.0) [D43]. Five of the rectal cancer cases had been diagnosed with Hodgkin's disease before age 21 (SIR = 12.4; 95% CI: 4.0, 29), but it was not reported whether they had received radiotherapy.

B. Summary

B290. The epidemiological data indicate that, compared with the colon, the rectum has a low sensitivity to radiation-induced cancer. A statistically significant risk is evident only after extremely high radiation therapy doses. The UNSCEAR 2006 Committee [U12] reviewed risk estimates from epidemiological studies. These are shown in table B22, where it can be seen that most studies did not show a statistically significant relationship between rectal cancer and radiation exposure (especially at doses less than 1 Gy) but there is an excess evident at high rectal doses (tens of Gy).

Table B22. Risk estimates for rectal cancer incidence and mortality from studies of childhood radiation exposure

Adapted from UNSCEAR 2006 Report (annex A, table 24) [U12] Studies listed are those for which quantitative estimates of risk could be made

Study		*Average ERR [a] at 1 Sv*	*Average EAR [a] (10^4 PY Sv)$^{-1}$*
Incidence			
LSS [P52, U12]			
Sex	Males	<0 (<0, 0.28)	<0 (<0, 0.35)
	Females	0.46 (0.08, 0.97)	0.40 (0.03, 1.11)
Age at exposure	<20 years	0.16 (<0, 0.60)	0.10 (<0, 0.58)
	20–40 years	0.12 (<0, 0.58)	<0 (<0, 1.70)
	>40 years	0.24 (<0, 0.97)	0.64 (<0, 3.44)
All		0.18 (<0, 0.46)	0.19 (<0, 0.64)
Mortality			
LSS [P50]			
Sex	Males	<0 (<0, 0.33)	<0 (<0, 601.18)
	Females	0.95 (0.28, 1.86)	<0 (<0, 488.26)
Age at exposure	<20 years	0.48 (<0, 1.82)	<0 (<0, 167.70)
	20–40 years	0.20 (<0, 1.08)	<0 (<0, 590.50)
	>40 years	0.49 (<0, 1.37)	1.11 (<0, 3.23)
All		0.36 (<0, 0.88)	<0 (<0, 532.76)

[a] *90% CI in parentheses derived from fitting models for the LSS detailed in [P52], and from published data for the other studies, unless otherwise stated.*

APPENDIX C. DETERMINISTIC EFFECTS

I. INTRODUCTION

C1. The ICRP—in its publication 118—groups adverse health effects from radiation exposure into: *(a)* stochastic or probabilistic (e.g. the mutagenic and carcinogenic effects), which are assumed to increase in frequency as non-threshold functions of the dose; and *(b)* deterministic, which occur only above certain dose thresholds, and are also sometimes referred to as "harmful tissue reactions". Cell death (including mitotic arrest and apoptosis) and cell malfunction are central to all deterministic effects [I29]. The UNSCEAR 1993 Report (annex I) [U8] contained information on late deterministic effects in children.

C2. The depletion of renewing parenchymal cell populations, modified by interactions with other tissues, is the pathogenesis of early tissue reactions (or acute effects). After depletion of a certain proportion of the cells, a level is reached (threshold) at which there is clinical manifestation of injury. Above the threshold, deterministic effects increase in both frequency and severity with further increase in the dose.

C3. The deterministic effects observed in a person depend on the dose received, volume of tissue irradiated, quality or type of radiation, time over which the dose is received and age. The magnitude and type of deterministic effects that may be evident also depend critically on the time of observation after irradiation. Comprehensive reviews of deterministic effects in children may be found in the publications of Rubin and Casarett [R57], Schwartz et al. [S44] and Friedman and Constine [F16]. Further publications dealing with both acute and late deterministic effects include textbooks on radiation pathology by Fajardo [F5], Scherer et al. [S28] and UNSCEAR Reports [U8, U10, U12]. Finally, this is an ongoing area of investigation with comprehensive studies continually appearing, such as the one by Hudson et al. at St. Jude Children's Research Hospital [H74].

C4. Deterministic radiation effects were initially classified into a temporal scheme by Rubin and Casarett [R57]. In their scheme, acute effects were those occurring within the first six months of exposure, subacute effects within the second six months, chronic effects in the second through fifth years, and late effects after the fifth year. Fajardo [F5] divided pathological effects into immediate, acute effects occurring within days to weeks, and delayed effects occurring within months to years. The ICRP [I25] refers to early effects as those occurring in hours to a few weeks. Obviously, the effects observed are a spectrum of cellular responses occurring over various times, and often these cannot be strictly related to temporal categorizations.

C5. Deterministic effects of radiation exposure can be augmented or suppressed by various modifying agents and conditions that include chemical and physical factors, and genetic predisposition causing increased radiation damage. Acute deterministic effects usually result from sterilization of the rapidly proliferative-stem and progenitor-cell lines (particularly those of the intestine, bone marrow, germinal cells, and embryonal tissues) resulting in a transitory or permanent lack of mature cells

depending on the level of the radiation dose. Early changes may be accompanied by transient vascular dilatation, histamine release and permeability changes at the capillary level [M35].

C6. Delayed lesions are usually progressive stromal lesions whose full clinical impact is manifest long after progressive fibrosis can be demonstrated pathologically. Fibrosis is the result of oedema followed by fibrinous exudate, fibrin deposition, and collagen formation. Late effects can also be the result of dysfunction of intercellular signalling pathways. The most characteristic delayed radiation lesion is eccentric myointimal proliferation of the small arteries and arterioles. The dose–survival relationship for late effects differs from that of acute effects and injury to slowly responding tissues is more dependent on fraction size. In radiotherapy, fewer fractions with larger doses lead to an increase in late complications. It was dogma for decades that the most critically radiation-sensitive cell type within a tissue was its parenchymal-cell population, and that dysfunction of this population and the microcirculation was responsible for the manifestation of late effects. It is now recognized that the interaction of multiple cell systems is affected by complex intra- and extra-cellular signalling, the immune system and genetic factors [C44].

C7. Paulino et al. [P19] have pointed out that there are significant differences in chronic adverse tissue effects based upon the age of the individual. Sensitivity to radiation injury is a function of the developmental dynamics and status of the organ, its regenerative potential, and ultimately the extent to which it has begun to senesce. Pathogenetically, cell death, cell malfunction, perturbation of both intracellular and intercellular signalling, and fibrosis are central to all deterministic effects. Increased mitotic activity in developing tissues may relatively increase radiation sensitivity in these tissues during periods of rapid growth. However, cellular damage from radiation can sometimes also occur during intervals when the cellular activity is relatively quiescent, but the injury is not expressed until development of that tissue accelerates. The role of stem cells in response to radiation exposure at various ages is unclear. Stem cells can be depleted by radiation, with injury expressed as the patient ages. However, a greater abundance of stem cells in some tissues at a younger age may decrease radiation sensitivity because of compensatory mechanisms. Conversely, limitations in cellular repair capacities at an older age can sometimes actually increase the sensitivity of some normal tissues in developed or senescing tissues. Consequently, the ultimate expression of deterministic effects results from a complex array of issues related to cellular proliferation, developmental stage of the tissue, regenerative potential and cell attrition. For instance, organizational maturational processes in children can be impaired or even disabled by radiation therapy leading to a spectrum of effects that differ from those in adults in which the capacity and means for tissues to repair damage are the predominant predictor for chronic injury. Radiation-induced impairment of growth and maturation is unique to children, whereas organ damage, with tissue-specific dysfunction in repair processes is common to both children and adults. Susceptibility to late effects in the elderly seems to involve not only a decline in their ability to repair damage but also cell attrition combined with co-morbid illness. These issues are central to contrasting deterministic effects in children with those of adults.

C8. Few tissues show clinically significant deterministic effects at doses of less than a few grays. The exceptions are gonads, lens of the eye and bone marrow. Deterministic effects in humans have since been seen in radiation accidents and, clinically, in radiation therapy. Since it is rarely possible to sterilize a cancer without having an adverse effect on the normal surrounding tissue, radiotherapists have developed the concept of a tolerance dose. The tolerance dose depends upon the level of risk of deterministic effects in normal tissue that the physician is willing to accept in order to sterilize a tumour. The TD5/5 refers to a dose that is documented to cause a 5% incidence of serious complications or side effects within five years. It is important to realize that the “tolerance dose” can hardly be termed a dose that is tolerable to healthy people but rather refers to the dose that is tolerable or acceptable to patients in order to cure them of cancer. Moreover, it must be understood that this is a probabilistic figure and not specific to an individual patient. The significance of the tolerance dose for

this text is that the practice of radiotherapy using the tolerance dose has provided a relatively large body of literature on the incidence and dose levels required to produce deterministic effects in normal tissue, their time course, and their dependence upon quality and temporal distribution of the irradiation [N14].

C9. Radiation oncologists have devised a scoring system for toxicity in an attempt to have uniform reporting of deterministic effects [R61]. The late effects normal tissue (LENT) system considers subjective, objective, management and analytical (SOMA) factors. *Subjective* refers to what is generally reported as symptoms by the patient, *objective* to findings of a skilled clinician, *management* to measures taken to alleviate or reduce toxicity and *analytical* to laboratory and procedural findings. These measures can be combined into a summary score. The system uses grades 1–4 for the degree of toxicity. Grade 0 is not used as it would indicate no toxicity, and Grade 5 is not used as it indicates a fatal outcome.

II. BRAIN

C10. The developing human brain is especially sensitive to ionizing radiation exposure. The response of the normal brain to radiation exposure depends on the total dose, individual fraction size, the time interval over which radiation is delivered, the volume of the exposed tissue and the age of the exposed subject. The outcome of iatrogenic radiation damage to the normal brain depends on the magnitude of the damage and the brain's limited capacity for cellular repopulation (neurogenesis). Although partial recovery takes place between fractionated exposures, the brain has very little repair capacity. After birth, the period of greatest radiosensitivity of the human brain is during the first two years of life, because of the relative immaturity of myelination and synaptogenesis [P4]. Normal maturation of the brain has been discussed earlier in this annex. High dose radiation involving the whole brain is more likely to have an adverse effect compared with comparable doses of focal irradiation [U8].

C11. Radiation changes in the brain are of several general types: acute reactions; early delayed reactions; and late delayed reactions. There are several target cell types and pathways by which radiation injury of the CNS may occur. Historically, late changes were thought to be secondary to vascular changes, but it now appears that the two main target cells are both oligodendrocytes and endothelial cells: however, other glial cells, and also neuronal cells can be primary or secondary targets. In addition, the vascular changes appear to be preferentially venous (rather than arterial) damage [S37].

A. Radiotherapy for malignant lesions

C12. Primary brain damage is usually the result of an insult to the glial cells and vascular system although occasionally an acute demyelinating process is observed [R22]. Subacute changes appear to be the result of deterministic effects on proliferating oligodendrocytes and temporary changes in the blood–brain barrier. Abrupt deterioration has been reported in radiotherapy when large fractional doses (i.e. 7.5–10 Gy) have been used. Excessive (by current therapeutic standards) doses or relatively few fractions of large doses (i.e. greater than 10 Gy) have caused radiation-induced brain necrosis [K49].

C13. The tolerance dose to the brain with fractionated radiotherapy over a period of five–six weeks is thought to be 55 Gy, although small areas of the brain may tolerate doses up to 65–70 Gy. Post-

irradiation necrosis has rarely been reported at fractionated doses of less than 60 Gy. Overall, the white matter of the CNS is more susceptible to radionecrosis than the grey matter or the brain stem. The paraventricular and supraoptic nuclei of the hypothalamus appear to be more radiosensitive than the white matter.

C14. Early delayed reactions appear from a few weeks to a few months after radiotherapy. They are usually self-limiting and are easily mistaken for effects of the residual tumour or chemotherapy. In children treated for leukaemia with methotrexate and radiation, about 60–80% will exhibit anorexia, irritability, and a "somnolence syndrome" 2–6 months post-therapy, probably due to transient diffuse demyelination. The late delayed reaction has a number of forms, ranging from asymptomatic periventricular white matter changes to decreased mental status, endocrine changes, and even focal necrosis. The maximum tolerable dose in children up to the age of three is 33% less than that for adults, and Bloom [B34] has also estimated that for children 3–5 years of age, the adult dose has to be reduced by 20%.

C15. With the advent of magnetic resonance imaging (MRI), it has become clear that many patients will develop areas of diffusely increased signal in the white matter seen on T2-weighted images. Reports indicate that 50–100% of patients will show these findings after radiotherapy. The changes occur preferentially in the periventricular white matter and may extend to the grey–white junction. Patients with mild forms appear to have no clinical symptoms, while patients with extensive abnormalities on MRI are more likely to have more mental impairment such as personality change, confusion, seizure disorders, and learning difficulties [C54, T44]. Leukoencephalopathy refers to white-matter injury caused by demyelination following treatment with chemotherapeutic agents with or without associated radiotherapy. The most typical situation is after doses of 20 Gy, combined with the use of methotrexate [K20, P29, R64], although it has also been reported after whole-body doses of 10 Gy given in total body irradiation (TBI) conditioning regimens for bone marrow transplantation. On CT and MRI scans, this entity is indistinguishable from the white-matter radiation changes. Cortical grey matter and basal ganglia are not affected. Clinical findings are lethargy, poor school performance, ataxia, spasticity, progressive dementia, and even death.

C16. Another change sometimes seen in children treated for leukaemia with cranial irradiation and methotrexate is mineralizing microangiopathy [B30]. This is seen as calcification in the grey matter, basal ganglia, putamen, and sometimes in the cortex and even the brain stem [P53]. There is calcification in small blood vessels that are surrounded by necrotic mineralized brain tissue. It is not fatal and it is unknown if this produces any specific neurological signs, although it is often associated with leukoencephalopathy. The entity is seen in about 25% of patients who have received intrathecal methotrexate and cranial irradiation of 24 Gy and who survive for more than nine months. Another late change that may be seen in about 50% of patients after cranial radiotherapy is cortical atrophy. This is seen either on CT or MRI scans as enlarged cortical sulci and enlarged ventricles, usually detectable one to four years after radiotherapy. This is seen in about half of the patients who have received a dose of more than 30 Gy to the brain with fractionated radiotherapy, but can occur at lower doses [R14]. In addition to parenchymal changes of the brain due to radiation exposure, there are vascular changes that can be imaged. Koike et al. [K40] have shown that MRI can visualize radiation-induced telangiectasia in about 20% of children who have received cranial radiotherapy. All doses quoted in this report were 18–20 Gy and the abnormalities appeared as early as three years after exposure, although additional lesions still developed 10 years post-therapy. They were seen as small foci of very low-signal intensity on MRI images.

C17. The increased sensitivity of the nervous system in children requires radiotherapy treatment schedules to be adjusted according to the age of the patient. Arteriosclerosis may lower the tolerance of the brain since the occlusive changes due to radiation exposure may be additive with regard to pre-

existing arteriosclerotic changes. Sheline et al. [S54] and others [R64] have suggested that chemotherapy contributes (perhaps synergistically) to the occurrence of radionecrosis and possibly enhances the level of injury. Both depression and somnolence, probably as a result of a transient demyelination, have been reported six to eight weeks after cranial irradiation to dose levels of 24 Gy given in 10 to 15 fractions, but can occur at lower doses. Such findings have been seen in children and adults treated for ALL [F14, P59]. The somnolence is distinct from the more severe neurological abnormalities produced by intrathecal methotrexate.

1. Neurocognitive late effects

C18. Neurocognitive late effects most commonly follow treatment of CNS malignancies using cranial irradiation or intraventricular/intrathecal chemotherapy, and even high dose systemic chemotherapy such as methotrexate or cytosine arabinoside [P4].

C19. Children with CNS tumours, head and neck sarcomas, and ALL are most commonly affected. Reductions have been observed in the following [N11, R31]:

(a) General intelligence;

(b) Age-appropriate developmental progress;

(c) Academic achievement (especially in reading, language, and mathematics);

(d) Visual and perceptual motor skills;

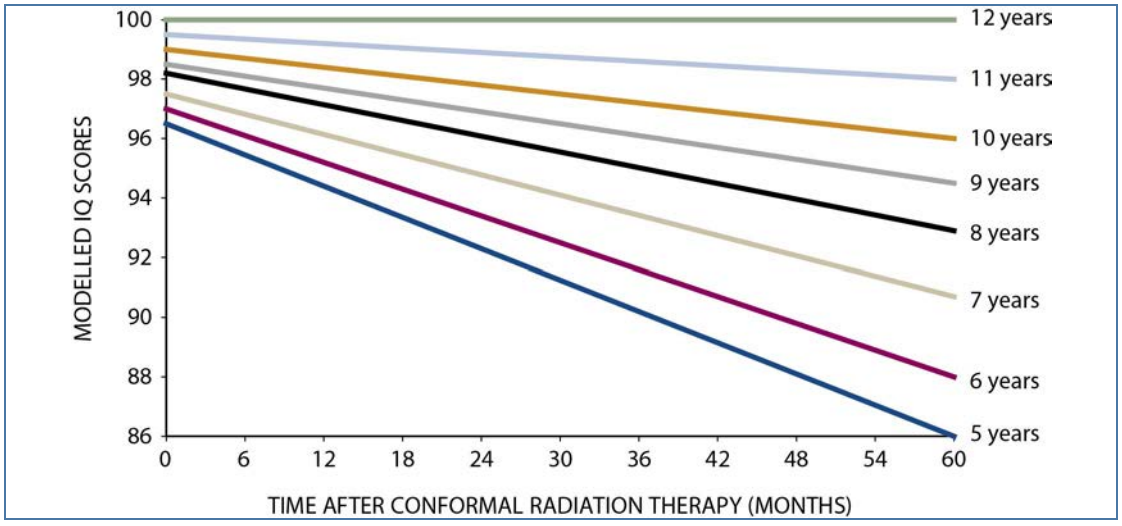
(e) Non-verbal and verbal memory;

(f) Receptive and expressive language and attention.

For both CNS tumours and ALL, a younger age at time of treatment is associated with an increased neurocognitive deficit (figure C-I).

Figure C-I. Interpolation of IQ scores after conformal radiation therapy by age for paediatric low-grade glioma

Adapted from [M29]



C20. Some studies of children treated with radiotherapy for CNS tumours have demonstrated a significant adverse neurocognitive effect of therapy [P2, R31]. Other studies using lower doses and more targeted volumes, however, have demonstrated less neurocognitive compromise [M57, P3, R23]. One study supports the hypothesis that medulloblastoma patients demonstrate a decline in IQ values indicated by an inability to acquire new skills and information, but not a loss of those previously acquired [P5].

C21. In a Danish study of children treated for brain tumours, younger age at diagnosis, tumour site in the cerebral hemisphere, hydrocephalus treatment with shunt, and radiotherapy were predictors of lower cognitive functions [R16]. Similar findings were obtained in a series of 182 five-year survivors of childhood low-grade gliomas in which 34% had an IQ below average, and this was associated with younger age at diagnosis, epilepsy and shunt placement [A26]. Merchant et al. [M29] have shown that decreases in IQ are very dependent on the age at irradiation for treatment of low-grade gliomas (figure C-I).

C22. In a large cohort of adult survivors of CNS malignancy (n = 802) reported from the CCSS, the risk of neurocognitive dysfunction was significantly associated with treatment involving cranial irradiation or placement of a ventriculoperitoneal shunt, and also a history of stroke, paralysis or auditory difficulties [E11]. In this study, CNS-malignancy survivors with neurocognitive impairment, when compared with non-CNS-malignancy and sibling-control groups, were found to have deficits in both the speed of information processing and in working memory Another study evaluated quantitative tissue volumes from MRI scans, correlating these results with neurocognitive assessments for 40 long-term survivors of paediatric brain tumours treated with radiotherapy with or without chemotherapy 2.6 to 15.3 years earlier (median, 5.7 years) at ages between 1.7 and 14.8 years (median, 6.5 years). The analyses revealed significant impairment in neurocognitive test performance by the patients on all measures. After statistically controlling for age at time of radiotherapy and time from radiotherapy, significant associations were found between normal-appearing white-matter volumes and both attentional abilities and IQ. MRI abnormalities were also correlated with deficiencies in academic skills such as reading, spelling, and solving mathematical problems [R13].

C23. For children with ALL, studies again show significant neurocognitive impairment [M24, S39] when cranial irradiation is combined with intrathecal chemotherapy. Reduction in the cranial radiation dose (e.g. from 24 Gy to 12–18 Gy) may result in less neurocognitive impairment [H30, K32, S78, W2, W1].

C24. The effects of radiation on the brain are difficult to define, especially when cranial irradiation is a part of multimodal therapy that may also include surgery, systemic chemotherapy, or intrathecal chemotherapy. Tumour-related deficits resulting from direct invasion of the brain, seizures and hydrocephalus are confounding factors that must also be considered [K30]. The CCSS reported that in adult survivors of childhood CNS malignancies, neurocognitive impairment was high and proportional to the radiation dose for specific tumour types. There was a dose-dependent association between radiotherapy to the frontal/temporal lobes and lower rates of employment and marriage [A24].

C25. Studies on CNS prophylaxis for ALL, comparing craniospinal radiotherapy with cranial radiotherapy combined with intrathecal methotrexate, showed that children who were younger than five years at time of treatment and had received radiotherapy and intrathecal chemotherapy had lower IQ scores than those who received craniospinal radiotherapy alone [B32]. Similarly, another study found a significant IQ deficit in children treated with a dose of 24 Gy to the cranium combined with intrathecal methotrexate, compared with children who had received no CNS-directed therapy, and the effect was greatest among those younger than five years [M24]. A similar effect on cognition with the addition of intrathecal methotrexate has been found in children treated for medulloblastoma [R26].

C26. Systemic methotrexate in high doses and combined with radiotherapy can lead to leukoencephalopathy with severe neurocognitive deficits [B31, C33, D48]. The deleterious effects of systemic methotrexate, especially at doses above 1 g/m^2, may be no different or even worse than those of a cranial radiation dose of 18 Gy [B67, O5]. At lower methotrexate doses, there does not appear to be a consistent pattern of neurocognitive deficits [B72].

C27. Neurocognitive abnormalities have been reported in other groups of cancer survivors besides patients with CNS tumours and ALL. In a study of adult survivors of childhood non-CNS cancers, 13-21% of the survivors had impairment in task efficiency, organization, memory or emotional regulation. This rate of impairment was approximately 50% higher than that in the sibling comparison. Factors such as diagnosis at an age younger than six, female sex, cranial radiotherapy, and hearing impairment were associated with neurocognitive compromise [K2].

C28. Cognitive consequences of stem cell transplantation in children have also been evaluated. In a report from the St. Jude Children's Research Hospital in which 268 patients were treated with stem cell transplant, minimal risk of late cognitive and academic sequelae was seen. Subgroups of patients were at relatively higher risk, including those undergoing unrelated donor transplantation, those receiving total-body irradiation, and those with graft-versus-host disease (GVHD). However, these differences were small relative to differences in premorbid functioning [P31]. The greatest decline in neurocognitive function occurred in patients who received cranial irradiation either as part of their initial therapy or as part of their haematopoietic stem cell transplant (HSCT) conditioning [S47]. Most neurocognitive late effects are thought to be related to white-matter damage in the brain [A17].

2. Other neurological sequelae

C29. In a report from the CCSS on 4,151 adult survivors of childhood ALL compared to their siblings, survivors were at an elevated risk for late onset coordination problems, motor problems, seizures and headaches. The overall cumulative incidence was 44% at 20 years after treatment. Serious headaches were most common, with a cumulative incidence of 25.8% at 20 years after treatment, followed by focal neurological dysfunction (21.2%) and seizures (7%). Children who were treated with regimens that included cranial irradiation (and also intrathecal methotrexate), and those who suffered relapse, were at an increased risk for late-onset neurological sequelae [R12].

C30. Many survivors of childhood cancer have an inferior quality of life or other adverse psychological outcomes compared with siblings or age-matched controls. In a study of adult survivors of childhood cancer, psychological screening was performed during a routine annual evaluation at the survivorship clinic at the Dana Farber Cancer Institute. On the Symptom Checklist 90 Revised, 32% of subjects had a positive screen (indicating psychological distress), and 14% reported at least one suicidal symptom. Risk factors for psychological distress included dissatisfaction with physical appearance, poor physical health, and treatment with cranial irradiation [B66]. Some authors have indicated a correlation between calcification and other abnormalities on CT scans and learning disabilities or seizures [C16], but these conclusions are not confirmed in other studies.

B. Radiotherapy for benign conditions

C31. There are several published reports evaluating possible changes in mental function after relatively low doses of radiation. Follow-up studies have been performed and include both Israeli [R34]

and American [S60] children who had received a dose of about 1–2 Gy during treatment for tinea capitis. In the Israeli study, males with multiple irradiations had a higher rate of admissions to mental hospitals (34.0 observed compared to 17.4 expected per 1,000), but this difference was not seen with females. Children irradiated at less than six years of age had a relative risk of mental hospital admissions of 1.7 (95% CI: 1.1, 2.8), but for older children, there was no increased risk.

C32. Information on high-school aptitude tests was available for about 1,800 irradiated children, 2,000 matched population controls and 1,000 matched sibling controls. Although the irradiated children scored lower on the aptitude test than the population controls, there was no difference compared with the sibling controls, suggesting that inter-family genetic or environmental factors unrelated to radiation exposure may have contributed to the difference with regard to the population controls [S60].

C33. An IQ test administered to military inductees (in a country with universal military service) showed that a smaller percentage of the irradiated children studied than either the population or sibling controls, and scored high enough to qualify as officer candidates; however, the average IQ scores of the groups did not differ significantly. From the Israeli mental-retardation registry, there was no clear evidence that diagnosed mental retardation was in excess in the irradiated group compared to the control group [R34]. An electroencephalogram (EEG) evaluation did not detect a significantly greater frequency of abnormalities among the irradiated group (31%) compared to the non-irradiated group (25%) [Y1].

C34. In the United States series, there was about a 40% excess of reported psychiatric disorders among the irradiated children; however, a systematic psychological study by Omran et al. [A12, O14] showed only a borderline difference between the irradiated and non-irradiated groups. There does not appear to be a good biological or pathological basis for such psychiatric effects at these dose levels, and these results are not supported by follow-up studies of children treated for tumours. As with most studies of this type, there is the possibility of recall bias and other potential confounders.

C35. Hall et al. [H9] reported that persons treated for cutaneous haemangioma with radiotherapy in infancy had some types of lower cognitive function. The male children were treated between 0 and 17 months of age (median, 6 months) and the mean dose to the brain was 52 mGy. They analysed records of school attendance and cognitive tests of learning ability and logical reasoning (but not IQ tests) at ages 18–19 years. The proportion of boys who attended high school decreased with increasing dose from 32% among those not exposed to about 17% in those who received a dose to the brain of >250 mGy. The cognitive tests performed comprised an index of learning ability that was intended to measure general verbal ability and be sensitive to education. A test of spatial recognition was the basis for a logical-reasoning score. Father's occupation was used as a surrogate to assess the impact of socioeconomic, social and educational influences upon cognitive performance. They reported a dose-related decrement in the score for verbal learning ability, but none for logical reasoning. That they found a nominal effect for verbal learning ability but not for logical reasoning suggests the possibility that there may have been residual confounders related to familial, socioeconomic and educational factors that could not be sufficiently adjusted for by father's occupation and that affected the verbal learning-ability results.

C36. Another possible explanation is that the radiation exposure may have affected thyroid function that secondarily impacted cognitive function, although other data do not generally indicate effects on thyroid function in the dose range of the study [I34]. They had hypothesized that the radiation dose to the frontal brain would have had a greater impact than that to the posterior part, but the high correlation ($r = 0.84$) between the two sets of dose estimates made it impossible to see separate effects. Finally, the magnitude of effects suggested here are considerably higher than that noted at doses to the brain over 100 times higher given for CNS prophylaxis of leukaemia. Those studies indicate that doses of 24 Gy

are associated with about a 10–15 point loss of IQ [O5, T3]. On the other hand, the effects they reported are quite similar to the reported IQ deficits seen among the survivors of the atomic bombings exposed in utero at 8–25 weeks post-conception [O23].

C. Accidental exposure

C37. An accident occurred with a radiotherapy unit in San Jose, Costa Rica [I3], in which an error was made in the replacement of the ^{60}Co source. The units on the timer were incorrectly interpreted as seconds instead of hundredths of a minute. As a result, the dose rate was underestimated by a factor of 1.66. As a result, 114 patients were exposed to higher doses than intended. Complications of the CNS occurred within 24 months in a child who received a dose to the cranium of 58 Gy in 20 fractions. Over the next nine months, the child lost all ability to speak and was confined to a wheelchair.

III. NEUROENDOCRINE SYSTEM

A. Radiotherapy for malignancies

C38. Survivors of childhood cancer who have been treated with radiotherapy are at risk for a spectrum of neuroendocrine abnormalities, primarily due to the effect of hypothalamic radiation exposure [N14].

C39. The damage to the hypothalamic–pituitary axis generally results from deterministic effects on the hypothalamus and to a lesser extent on the pituitary [C47, G39, S85]. There are six anterior pituitary hormones: growth hormone, prolactin, luteinizing hormone, follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and adrenocorticotropin. Clinical manifestations of damage to the hypothalamic–pituitary axis often include loss of weight, impaired or precocious development of secondary sexual characteristics and body hair; dry skin, slow pulse, genital atrophy, and low body temperature.

C40. Growth hormone deficiency is the most common neuroendocrinological deficit following cranial irradiation for brain tumours due to the low threshold dose for this injury. The risk increases with radiation dose and time after treatment. Growth hormone deficiency is also the earliest hormone deficiency to arise following exposure and can be observed even following exposure to relatively low radiation doses. Other hormone deficiencies are manifest only following higher doses and their onset time is generally longer than for growth hormone deficiency [D11].

C41. The prevalence in a pooled analysis of survivors of brain tumours in childhood was found to be approximately 35.6% [M56]. The potential for neuroendocrine damage is lower after current treatment approaches owing to the use of more focused radiotherapy that reduces hypothalamic exposure, and a decrease in the dose used for the treatment of some malignancies such as medulloblastoma. Follow-up studies of patients who received radium therapy applications to treat otitis

serosa, resulting in doses to the pituitary of about 11 Gy, did not demonstrate any significant hormonal deficiencies [R47, R49].

1. Growth hormone deficiency

C42. Approximately 60–80% of paediatric patients who were irradiated in the treatment of brain tumours and received doses greater than 30 Gy will have impaired serum growth hormone response to provocative stimulation, usually within five years of treatment. The dose–response relationship has a threshold of 18–20 Gy; the higher the radiation dose, the earlier that growth hormone deficiency will occur after treatment. A study of children who had been treated for tumours of the CNS using conformal radiotherapy indicates that growth hormone deficiency can usually be demonstrated within 12 months following treatment, depending on hypothalamic dose–volume exposure [M26]. On the basis of data from 118 patients with localized brain tumours that were treated with radiation therapy, peak growth hormone was modelled as an exponential function of time after conformal radiotherapy and mean radiation dose to the hypothalamus. The average patient was predicted to develop growth hormone deficiency within 12 months after a dose of more than 60 Gy; 36 months after 25–30 Gy; and 60 months after 15–20 Gy. A cumulative dose of 16.1 Gy to the hypothalamus would be considered the mean radiation dose required to achieve a 50% risk of growth hormone deficiency at five years (TD50/5) [M30].

C43. Children treated with CNS irradiation for leukaemia are also at increased risk of growth hormone deficiency. One study evaluated 127 children or adolescents with acute lymphocytic leukaemia treated with 24 Gy, 18 Gy, or no cranial irradiation. The subsequent change in the height of the patients, compared with population norms and expressed as the standard deviation score, was significant for all three groups with a dose response of -0.49 ± 0.14 for the group that did not receive radiotherapy, -0.65 ± 0.15 for the group that received a dose of 18 Gy, and -1.38 ± 0.16 for the group that received a dose of 24 Gy [S82]. Another study found similar results in 118 survivors of acute lymphocytic leukaemia treated with a dose to the cranium of 24 Gy; 74% had a standard deviation score of −1 or greater and the remainder had a score of −2 or greater [S35].

C44. Survivors of acute lymphocytic leukaemia in childhood who are treated with chemotherapy alone are, however, also at increased risk of diminished growth, though the risk is highest for those treated with cranial and craniospinal irradiation at a young age [C23]. In this cross-sectional study, attained adult height was determined for 2,434 survivors of acute lymphocytic leukaemia participating in the CCSS. All survivor groups (those who had been treated with chemotherapy alone and those who had been treated with both chemotherapy and cranial or craniospinal irradiation) had decreased adult height (standard deviation score <−2) compared with siblings (p <0.001). The risk of short stature in adulthood for the survivors treated with chemotherapy alone was elevated, with an odds ratio of 3.4 (95% CI: 1.9, 6.0). Significant risk factors for short stature included treatment of acute lymphocytic leukaemia before puberty, magnitude of the dose to the cranium (doses of ≥20 Gy resulted in a higher risk than doses of <20 Gy), any radiotherapy to the spine, and sex (females had a higher risk than males). Growth hormone deficiency has been reported in 14% of survivors of nasopharyngeal carcinoma in childhood resulting from high dose radiation exposure to the hypothalamic/pituitary axis [C17]. This incidence is likely to be an underestimate since screening was selective.

C45. Children who undergo HSCT with whole-body irradiation have a significant risk of both growth hormone deficiency and impaired bone growth because of the direct effects of radiation on skeletal development. The risk is increased if: *(a)* the dose is given in a single fraction rather than in multiple fractions; *(b)* pre-transplant cranial irradiation has been given; *(c)* the patient is female; and *(d)*

post-treatment complications such as GVHD develop [O12, W23, W27]. Regimens containing busulfan and cyclophosphamide appear to increase the risk in some studies [B15, W27] but not others [C13]. Hyperfractionation of the dose markedly reduces the risk in patients who have not undergone pre-transplant cranial irradiation for prophylaxis or therapy for CNS leukaemia [H75].

C46. The late effects that occur after HSCT have been studied and reviewed by the Late Effect Working Party of the European Group for Blood and Marrow Transplantation. For 181 patients with aplastic anaemia, leukaemia, and lymphomas who underwent HSCT before puberty, an overall decrease in their final height was found compared to what would have been predicted from their parents' heights. The mean loss of height is estimated to be approximately one standard deviation score (i.e. 6 cm). The type of transplantation, graft versus host disease, growth hormone deficiency, or steroid treatment did not influence the final height. The major factors affecting long-term loss of height were the use of single dose TBI rather than its administration in multiple smaller fractions, sex of the person (males were more affected than females), and the age at transplant (the effect was greater at younger ages). Most patients (140 of 181) reached adult height within the normal range of the general population [C31, S94].

2. Gonadal abnormalities

C47. Pubertal development can be adversely affected by cranial irradiation. Doses greater than 30-40 Gy can result in gonadotropin deficiency, while doses greater than 18 Gy can result in precocious puberty [N8]. Precocious puberty has been reported in some children, mostly girls, who had received doses from cranial irradiation of 24 Gy or higher. Earlier puberty and earlier peak height velocity, however, have been observed in girls treated with doses from cranial irradiation of 18 Gy [D38, S50].

C48. Another study showed that the age of pubertal onset is positively correlated with age at the time of cranial irradiation. The impact of early puberty in a child with radiation-associated growth hormone deficiency is significant, and timing of growth hormone therapy is especially important for growth hormone deficient females also at risk of precocious puberty [C25]. With higher doses of cranial irradiation (>35 Gy), deficiencies in the gonadotropins can be seen, with a cumulative incidence of 10% to 20% at five–ten years post-treatment [A25].

3. Central hypothyroidism

C49. Central hypothyroidism in survivors of childhood cancer can have profound clinical consequences and is often underappreciated. Symptoms of central hypothyroidism (e.g. asthaenia, oedema, drowsiness, and skin dryness) may have a gradual onset and go unrecognized until thyroid replacement therapy is initiated. In addition to delayed puberty and slow growth, hypothyroidism may cause fatigue, dry skin, constipation, increased sleep requirement and cold intolerance. A radiation dose to the hypothalamus in excess of 42 Gy is associated with an increase in the risk of developing TSH deficiency, 44% ± 19% (for a dose >42 Gy) and 11% ± 8% (for a dose <42 Gy) [L11]. It occurs in as many as 65% of the survivors of brain tumours in childhood, 43% of the survivors of nasopharyngeal tumours in childhood, 35% of bone marrow transplant recipients in childhood, and 10–15% of survivors of leukaemia in childhood [C17, R52].

C50. Mixed primary and central hypothyroidism can also occur and reflects separate injuries to the thyroid gland and the hypothalamus (e.g. radiation injury can occur in both structures, and sometimes concomitantly in children irradiated to the cranial-spinal axis). TSH values may be elevated and, in

addition, the secretory dynamics of the hormone are abnormal with a blunted or absent surge or a delayed peak response to thyrotropin-releasing hormone (TRH) [C47, R51]. In a study of 208 survivors of childhood cancer referred for evaluation of possible hypothyroidism or hypopituitarism, mixed hypothyroidism was present in 15 (7%) patients [R51]. Among the patients who had received whole-body irradiation (fractionated total doses of 12–14.4 Gy) or craniospinal irradiation (fractionated total doses to the cranium higher than 30 Gy), 15% had mixed hypothyroidism. In one study of 32 children treated for medulloblastoma, 56% were found to have developed hypothyroidism, including 38% with primary hypothyroidism, and 19% with central hypothyroidism [P17].

4. Adrenal-corticotropin deficiency

C51. Adrenocorticotropic hormone (ACTH) deficiency is less common than other neuroendocrine deficits but should be suspected in patients who have a history of brain tumour (regardless of therapy modality), cranial irradiation, growth hormone deficiency, or central hypothyroidism [C46, C47, D11, K22, L11, P13, R53]. Although uncommon, ACTH deficiency can occur in patients who have received doses of intracranial irradiation that did not exceed 24 Gy and it has been reported to occur rarely (in less than 3% of patients) after treatment with chemotherapy alone [R53]. Patients with partial ACTH deficiency may have only subtle symptoms unless they become ill when a stress response is necessary. Illness can disrupt the usual homeostasis in these patients and cause a more severe, prolonged, or complicated course than expected. As in patients with complete ACTH deficiency, partial or unrecognized ACTH deficiency can be life-threatening during concurrent illness.

5. Hyperprolactinaemia

C52. Hyperprolactinaemia has been described in patients who have received doses of radiation higher than 50 Gy to the hypothalamus or who have undergone surgery that disrupts the integrity of the pituitary stalk. Hyperprolactinaemia may result in delayed puberty. In adult women, hyperprolactinaemia may cause galactorrhea, menstrual irregularities, loss of libido, hot flushes, infertility and osteopaenia; in adult men, it may result in impotence and loss of libido. Primary hypothyroidism may lead to hyperprolactinaemia as a result of hyperplasia of thyrotrophs and lactotrophs, presumably owing to TRH hypersecretion. The prolactin response to the TRH is usually exaggerated in these patients [C46, C47, D11].

IV. VASCULAR DISEASE/CEREBROVASCULAR ACCIDENT

C53. A spectrum of vascular morbidities may occur after radiotherapy has been used to treat malignancies such as lymphomas, head and neck cancers, and brain tumours. Specifically, carotid artery and cerebrovascular injury occur after cervical and CNS irradiation. The relative risk for cerebrovascular accident (CVA), i.e. stroke, in the CCSS cohort was almost 10-fold higher than that in the sibling control [O9]; notably, the risks were highest among the adult survivors of acute lymphocytic leukaemia, brain tumours, and Hodgkin's lymphoma in childhood [B57, B56]. Survivors of leukaemia were six times more likely to suffer a CVA than their siblings, whereas survivors of brain tumours were 29 times more likely to suffer a CVA. Of the cohort of 1,411 patients who had had brain tumours and a history of radiotherapy, 69 reported a CVA (4.9%), with a cumulative incidence of 6.9% (95% CI: 4.47,

9.33) at 25 years. Survivors exposed to cranial irradiation greater than 30 Gy had an increased risk for CVA, with the highest risk being among those who had been treated with doses greater than 50 Gy [M55].

C54. French investigators observed a significant association with radiation dose to brain and long-term cerebrovascular mortality among 4,227 five-year childhood cancer survivors (median follow-up 29 years). Survivors who received more than 50 Gy to the prepontine cistern had a hazard ratio of 17.8 (95% CI: 4.4, 73) of death from cerebrovascular disease compared to those who had not received radiotherapy or who had received less than 0.1 Gy in the prepontine cistern region [H1]. In another recent study of children irradiated for brain tumours, the incidence of neurovascular events was 100-fold higher than in the general population [C2]. Adult survivors of Hodgkin's lymphoma in childhood who had been treated with radiotherapy to the thorax, including the mediastinum and neck, had a 5.6-fold higher risk for CVA than their siblings (median dose 40 Gy) [B56].

C55. In another study from the Netherlands of 2,201 five-year survivors of Hodgkin's lymphoma (of whom 547 were younger than 21 years at the time of treatment), and with median follow-up of 17.5 years, 96 developed cerebrovascular disease—55 with CVA, 31 with transient ischaemic attacks (TIA), and 10 both CVA and TIA. The median age at diagnosis was 52 years [D24]. Most ischaemic events were from large-artery atherosclerosis (36%) or cardioembolism (24%). The SIRs were 2.2 for CVA and 3.1 for TIA. The cumulative incidence of ischaemic CVA or TIA 30 years after treatment for Hodgkin's lymphoma was 7%. For patients younger than 21 years at the time of treatment, the SIRs were 3.8 for CVA and 7.6 for TIA. These SIRs were greater than those for patients older than 21 years at the time of treatment. Specifically, the SIRs for CVA were 3.1, 2.0, and 1.4 in the 21–30, 31–40, and 41–50 year-olds, respectively. Similarly, the SIRs for TIA were 4.2, 3.1, and 2.1 in the 21–30, 31–40, and 41–50 year-olds, respectively. Radiation exposure of the neck and mediastinum was an independent risk factor for ischaemic cerebrovascular disease, with a hazard ratio of 2.5 (95% CI: 1.1, 5.6) compared to those without radiotherapy. Treatment with chemotherapy was not associated with increased risk of CVA and TIA.

C56. There are few studies regarding the risk of stroke in populations exposed to lower doses than those used in radiotherapy. Tatsukawa et al. [T7] studied the risks associated with in utero exposure. Of interest, and for purposes of comparison, it should be noted that this study also included a cohort of children exposed at <10 years of age at the time of the bombings. No significant effects associated with radiation exposure were observed in the cohort exposed in utero. However, a positive association was found between radiation exposure and hypertension and cardiovascular disease in this cohort of children. Yet, there was no statistically significant difference in relative risks between the two cohorts; the relative risk for the cohort exposed in utero was 1.20 (95% CI: 0.61, 2.38) and for the childhood cohort was 1.15 (95% CI: 0.99, 1.34). The median dose in the childhood cohort was 0.13 Gy with a range of 0-3.53 Gy.

C57. In a more recent study, Shimizu et al. [S57] found an increased risk of circulatory disease in the survivors of the atomic bombings at doses in excess of 0.5 Gy. The degree of risk at lower doses was unclear. This study included data on stroke specifically. There was a non-significant indication ($p = 0.23$) that the risk of stroke associated with radiation may be highest after exposure at young ages: the ERRs per unit of dose were 36%, 9%, 15% and 5% Gy^{-1} for those exposed at ages <10, 10–19, 20-39 and >40 years, respectively.

V. ORBIT AND EYE

C58. Deterministic effects of radiation exposure of the eye were noted as early as 1897, and by 1908 corneal changes were clearly recognized as deterministic effects. In the 1950s, there was extensive investigation of radiation-induced eye damage, particularly cataract formation. The historical aspects are well reviewed by Rubin and Casarett [R57]. More recent reviews are also available [A10, A13, B58, G22, P12, S72].

C59. Most of the tissues around the eye have the same sensitivity to radiation exposure as skin; however, the lens is particularly radiosensitive. Radiation exposure can produce opacities within the lens and cataract formation. The excretory ducts, particularly in the meibomiam glands, are relatively sensitive to radiation-induced deterministic effects, as are the equatorial regions of the optic lens and the basal layer of the cornea. The neurons of the retina probably represent the most radioresistant cells in the eye. In addition to cataract formation, other late effects of radiation exposure in the eye can include retinopathy, optic neuropathy and lachrymal gland atrophy. These types of injuries rarely occur below a dose of 45 Gy, although subclinical indications of retinopathy have been observed at much lower doses [M41].

A. Radiotherapy for malignancies

C60. Orbital complications are common following radiotherapy treatment of children for retinoblastoma, childhood head and neck sarcomas, CNS tumours, and other conditions. For survivors of retinoblastoma, a small orbital volume may result from either enucleation or radiotherapy. The risk may be higher at ages younger than one year, but the information on this is not consistent across studies [K15, P30]. Survivors of orbital rhabdomyosarcoma are at risk of dry eye, cataract, orbital hypoplasia, ptosis, retinopathy, keratoconjunctivitis, optic neuropathy, lid epithelioma, and impairment of vision following radiotherapy doses of 30–65 Gy. The higher doses (>50 Gy) are associated with lid epitheliomas, keratoconjunctivitis, lachrymal duct atrophy, and severe dry eye. Retinitis and optic neuropathy may also result from doses of 50–65 Gy, and even at lower total doses if the individual fractional size of the dose is greater than 2 Gy [K37]. Cataracts are reported following lower therapeutic doses of 10–18 Gy [H44, O4, P12, P14, P15, R9, R8].

C61. Survivors of childhood cancer are at increased risk for ocular late effects, related to both glucocorticoid and radiation exposure. The CCSS reported that survivors of five or more years were at an increased risk for cataracts, glaucoma, legal blindness, double vision and dry eyes compared to siblings. The radiation dose was significantly associated with those risks in a dose-dependent manner. The risk of cataracts was associated with a radiation dose of 30 Gy or more to the posterior fossa and temporal lobe, and exposure to prednisone. In these situations, the eye is not directly in the radiation pathway but may still receive some marginal or scattered dose. The cumulative incidence of cataracts, double vision, dry eyes, and legal blindness continued to increase up to 20 years for those who received more than 5 Gy to the eye [W19].

C62. The dose absorbed by the lens when irradiating the cranium for acute leukaemia is associated with the induction of cataracts [K38]. The dose to the lens is approximately 15-30% of the midline dose, depending on the type of treatment fields. Nesbit et al. [N27] found one case of posterior subcapsular cataracts in 50 survivors of acute leukaemia in childhood. In contrast, Inati et al. [I35] observed a 50% incidence of cataract formation in 69 children with acute leukaemia who had been given a dose of 24 Gy to the cranium in 13 fractions over 2.5 weeks, intrathecal methotrexate and high

doses of steroids. All cataracts were small and did not impair vision. In another study of 34 long-term survivors of acute leukaemia, all 18 patients in the non-irradiated group had normal results on eye examination, while 4 of 16 of those who had received a dose of 24 Gy to the whole brain in 12 fractions over 2.5 weeks had ocular abnormalities [W16]. None of the ocular findings could, however, be definitely attributed to radiation, and all patients had normal visual acuity.

C63. Ocular complications such as cataracts and dry-eye syndrome are common after stem cell transplant in childhood. Patients who were treated with single-dose or fractionated whole-body dose compared to those treated with busulfan or other chemotherapy are at increased risk of cataracts. The risk ranges from approximately 10% to 60% at 10 years post-treatment, depending on the total dose and fractionation, with a shorter latency period and more severe cataracts noted after single fraction and higher dose or dose-rate TBI [F1, F7, G41, K4]. Patients receiving whole-body doses of less than 4 Gy have a less than 10% risk of developing severe cataracts [K4].

B. Radiotherapy for benign conditions

C64. Qvist and Zachau-Christiansen [Q1] estimated the minimum lenticular dose to produce cataracts in children to be 13.8 Gy from radium moulds based on a small study in which four cataracts were observed in 57 irradiated patients; the maximum non-cataract dose for infants was 9.9 Gy and for school-aged children, 11.4 Gy. The text did not describe the mode of examination (whether ophthalmoscope or slit-lamp microscope). Notter et al. [N36] conducted a slit-lamp examination and observed cataracts after considerably lower doses in 234 patients who had been irradiated with ^{226}Ra containing applicators for skin haemangioma between 1920 and the mid-1950s. An ophthalmological examination was conducted in 1961–1965. Of the 468 eyes examined, cataracts were observed in 51 (11%). No cataracts were observed in the 246 eyes which had received a dose to the lens of <2.5 Gy. The prevalence of cataracts was 8% (out of 100 eyes) after a lenticular dose of 2.5-3.5 Gy and 54% (out of 122 eyes) after higher doses.

C65. In another study [H8], the prevalence of lens opacities in 484 adults who had been treated as infants (at median age 4 months; range 0–16 months) with external X-ray (12%) or radium therapy (88%) for haemangiomas of the head, face or neck was compared to that in a control population of 89 unexposed, age-matched persons who presented with skin haemangiomas as infants. These people had been treated for the condition between 35 and 54 years prior to the study. The exposed subjects had received an average of two treatments with a cumulative mean dose of 0.4 Gy (median 0.2 Gy, maximum 8.4 Gy, 10% with >1 Gy). Lens opacities of any type were found in 37% of exposed eyes (357 opacities in 953 eyes) compared to 20% in controls. However, because of the low rate of study subject participation (39%) for controls and their younger age at examination, the dose–response analyses were based on only the irradiated group. A dose–response relationship was found which was independent of age at exposure. When corrected for age at examination, dose rate and steroid use, the authors reported an odds ratio at 1 Gy of 1.50 (95% CI: 1.15, 1.95) for cortical opacities and 1.49 (95% CI: 1.07, 2.08) for posterior subcapsular cataracts. In contrast, no dose response was noted for changes to the nuclear lens.

C66. A small study of 20 treated infants by Wilde and Sjostrand [W22] noted precataractous subcapsular lens changes in the eyes of subjects, who were 31–46 years old at the time of examination, on the untreated side of the face, where doses to the lens were estimated to average 0.1 Gy.

C67. In the first half of the twentieth century, before the development of modern antifungal medication, ringworm of the scalp (tinea capitis) was often treated by epilation using X-ray doses to the scalp ranging from an average 3.3 Gy, up to 6 Gy at the vertex and occasionally as high as 8.5 Gy. As many as two hundred thousand persons may have been irradiated worldwide [S60]. Despite the fact that the eyes of the patients were covered with lead foil, recreation of the original treatment procedures indicated that the lens had received doses ranging from 0.2 to 0.8 Gy [S41].

C68. From 1964 to 1965, approximately 15 years after treatment, an increased incidence of early posterior lens changes characteristic of ionizing radiation exposure was noted after slit-lamp examination of people given X-ray treatment at a mean age of eight years [S68]. While the overall severity of such changes was minor, the authors noted an increase in capsular opalescence or sheen and an accumulation of bright dots or micro-opacities, probably corresponding to Merriam-Focht stages 0.5–1.0. Thirteen cases of posterior subcortical opacities were noted in the exposed persons compared to two cases in the non-irradiated controls. An estimated odds ratio of 5.9 (95% CI: 1.4, 24) was calculated, adjusted for age at examination. A second follow-up from 1968 to 1973, based on a mail survey roughly 25 years after exposure, did not detect any difference in cataract incidence between the exposed persons and the controls. Unlike the previous detailed ocular examination, which detected early, radiation-associated lens changes unaccompanied by visual disability, the later survey asked respondents to self-report on any subsequent cataract diagnosis, surgery or associated visual disability. This could account for the differences in outcomes between the two studies.

C69. Patients who had received ^{224}Ra intravenously for treatment of ankylosing spondylitis and tuberculosis had an increased incidence of cataract formation [S103]. This was particularly apparent since many of the patients were young, and cataract formation was not expected. Stefani et al. [S111] reported on the development of cataracts in 899 patients who had received multiple injections of ^{224}Ra. Cataracts were found in 6% of the 218 juvenile patients and in 5% of the 681 adult patients. Those juveniles who were known have received an injected activity of ^{224}Ra of >1 MBq/kg of body weight, and had a cataract incidence of 14% (11 patients out of 80) compared to 0.8% (1 patient out of 131) among those who had received less than that amount. The cataract incidence increased significantly with the ^{224}Ra activity per unit body weight in both juveniles and adults.

C70. In a later report, 58 cataracts, including 42 cataract extractions, were found among 831 patients [C20, C19]. The authors reported that the induction of severe cataracts was proportional to the square of the ^{224}Ra activity per unit body weight and the square of the time since radiation exposure. The data were also compatible with a linear dose response above a threshold ^{224}Ra activity of 0.5 MBq/kg of body weight. In their analysis, no effect of age at exposure was found, but the analysis was primarily in terms of cataract acceleration (time from irradiation to cataract diagnosis) rather than magnitude of cataract induction. Taylor and Thorne [T13] estimated the dose to the anterior surface of the lens to be 0.035–0.22 Gy from an uptake of 1 MBq of ^{224}Ra after injected into the systemic circulation, and a large uncertainty in the dose from alpha particles to the germinative epithelium.

C. Atomic bombing survivors

C71. There have been several studies of lens opacities among the survivors of the atomic bombings in Japan in relation to radiation dose and risk modification by age at exposure. In a study conducted among subjects of the Adult Health Study (AHS) clinical examination programme in Hiroshima and Nagasaki in 1978–1980, a significant excess risk for posterior subcapsular changes was observed in residents of Hiroshima (but not of Nagasaki) of all ages in the group who had received a dose of >3 Sv

compared to those in the control group [C21]. The study was based on the 1965 dosimetry system and the examination was conducted on 2,385 persons, including those with doses of ≥1 Sv, and a matched unexposed group. Ophthalmological examinations were conducted largely without the use of mydriatics. The relative risk of cataracts for persons in Hiroshima exposed to a dose of >3 Sv was 4.8 in persons under age 15 years at the time of the bombings, 2.3 in persons aged 15–24 years at the time of the bombings and 1.4 in persons more than 25 years of age at the time of the bombings. The relative risk for posterior subcapsular changes in Hiroshima for persons under age 15 years at the time of the bombings was 2.8 in the group with doses of 1–1.9 Sv, 4.3 in the group with doses of 2–2.9 Sv and 5.3 in the group with doses of >3 Sv. A comparison of the relative risks in the different age groups suggested a stronger effect in Hiroshima for persons under age 15 years at the time of the bombings. These results support the hypothesis that younger are more sensitive than older people to radiation-induced cataracts.

C72. A reanalysis of the data from the study of Choshi et al. [C21] by [O21, O20], confirmed the previous findings of a higher sensitivity for radiation-induced cataracts in young persons. The magnitude of radiation-associated relative risks for cataracts in persons aged 40, 50, 60 and 70 years at the time of examination was 8.2, 6.4, 4.6 and 2.8-fold higher, respectively, than in persons aged 80 years at the time of examination. However, it is unclear how much the age-comparative ratios of risks are due to a younger age at exposure (which correlates with those who were younger at examination), or to a greater frequency of age-related cataracts among the elderly which could dilute the dose–response slope for radiation risk.

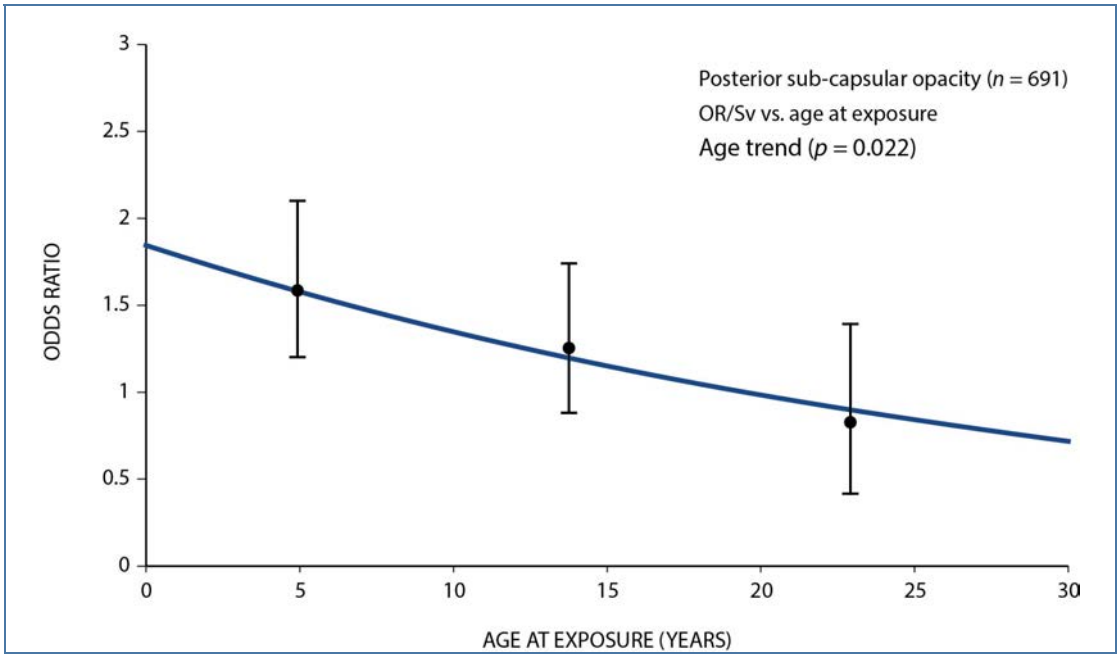
C73. Minamoto et al. [M41] reported an examination of 913 persons during 2000–2002, including mostly persons who were younger than 13 years at the time of the bombings. A variety of potential risk factors for opacity formation were examined, including ultraviolet exposure, smoking, white blood cell and neutrophil counts, serum markers for thyroid dysfunction, inflammation and oxidative stress; those that were potentially confounders were included in the analyses. A significant increase in cortical and posterior subcapsular cataracts was reported with increasing radiation dose adjusted for age, sex, history of diabetes, smoking and a composite index of inflammation–oxidative stress markers.

C74. A 2006 reanalysis of essentially the same cataract data by Nakashima et al. showed a clear increase in the dose–effect odds ratio for posterior subcapsular opacity with decreasing age at exposure (p <0.001) (figure C-II) [N6]. The odds ratios at 1 Gy for the age-at-exposure groups of 0–10, 10–20 and >20 years were 1.64 (95% CI: 1.26, 2.14), 1.32 (1.02, 1.72), and 0.87 (0.52, 1.46), respectively.

C75. The data on the survivors of the atomic bombings prior to 2000 had been based on ophthalmological screening, and so most of the opacities being analysed were small, subclinical opacities. A new study examined the prevalence of cataract surgery in 2000–2002 among the AHS cohort to evaluate the association of radiation with vision-impairing cataracts [N25]. Among 3,761 AHS subjects, 479 had had a cataract extraction. About 70% of those examined were under age of 20 at the time of irradiation, including 21% who were under 10. With adjustment for city, sex, age at exposure and diabetes, the odds ratio at 1 Sv was 1.39 (95% CI: 1.24, 1.55). The interaction of age at exposure and radiation dose was not evaluated.

C76. Further data on the incidence of cataract extractions in the AHS cohort have indicated an age-at-exposure effect [N26]. A total of 1,028 persons out of the cohort of 6,066 had a first cataract extraction during 1986–2005. The analysis found no confounding by any of 16 cataract risk factors. After adjustment for city, sex, diabetes and time since exposure it showed that fifty years after exposure, the relative risks at 1 Sv were 1.61, 1.32 and 1.15 for those exposed at ages 10, 20 and 30 years, respectively, and the age-at-exposure effect was statistically significant (p = 0.006).

Figure C-II. Odds ratio per Sv for posterior sub-capsular (PS) versus age at exposure
Adapted from [N6]



D. Accidental exposures

C77. Lens examinations of those exposed as a result of the Chernobyl accident have provided important epidemiological data for protracted, low-dose exposures of similar magnitudes to those received by the survivors of the atomic bombings [W42]. This is especially important given that considerable animal and human data indicate that dose fractionation of low-LET radiation results in a significant reduction in the prevalence of cataracts.

C78. A study of lens changes in a paediatric population exposed as a result of the Chernobyl accident has been published by Day et al. [D23]. Estimates of cumulative dose ranged from 29 to 86 mSv. A small but statistically significant increase in the incidence of subclinical posterior subcapsular opacities (2.8%) compared to the unexposed (1.0%), which was greatest among males 12-17 years old at the time of examination, was noted in ~1,000 exposed children, compared to a matched population of ~800 unexposed subjects. The odds ratio for posterior subcapsular opacities was 2.8 (95% CI: 1.3, 6.1). It should be noted, however, that the dose estimates contain large inherent uncertainties. The authors also noted that the ophthalmologists knew whether the children were exposed or unexposed, though they took precautions to have many of the children with lens changes examined by a second ophthalmologist to confirm the diagnosis. The presence of posterior subcapsular defects of a type characteristic of ionizing radiation exposure and not normally found in a paediatric population is suggestive of causal relationship.

C79. A study of nearly 30,000 residents living near the Techa River at the time of the relatively high radionuclide discharges from the Mayak nuclear plant has shown an exposure-related excess of diagnosed cataracts [M38]. However, effects of age at exposure were not reported.

C80. A study of a paediatric population accidentally exposed while living in ^{60}Co-contaminated apartments in Taiwan indicated an odds ratio of 1.18 at 1 Gy for subclinical lens changes [C14]. The mean dose to this population was 170 mGy, with a range of 1 to 1,200 mGy. Annual exposures of >5 mGy, in some cases for more than 10 years, were reported. A recent follow-up of some of the exposed children, with an estimated mean dose to the eye of 191 mSv received over an average of 7.4 years, indicated that radiation-induced lens changes, measured as subclinical focal lens defects, continued to increase in size and with the number years after relocation from the contaminated buildings and were significantly in excess compared to those in the unexposed control group [H69]. The progressive nature of such changes five years after the children had been removed from the contaminated environment, supports the earlier findings of radiation-associated lens changes and demonstrates that such changes may persist and progress with time.

E. Summary

C81. Survivors of various childhood malignancies who have had radiation treatment are at an increased risk of cataracts and other ocular pathologies, although the risks per unit dose cannot be unequivocally quantified because radiotherapy was often administered in conjunction with chemotherapy or other systemic agents (e.g. steroids). Infants who were treated with ^{224}Ra plaques for haemangiomas have an excess incidence of cataracts. Some older studies suggested that there was a dose threshold of ≥3 Sv for the induction of cataracts, but a more recent study has found that cataracts can be induced by lower doses. The results of studies of persons treated with ^{224}Ra in the second or later decades of life for ankylosing spondylitis or tuberculosis are unclear as to whether the risk of cataracts varied with age at exposure. A study of children treated with X-rays for scalp ringworm has suggested an excess of precataractous changes when the children were examined in their late teens and twenties. Several studies of cataract induction have been conducted over the years since the atomic bombings in Hiroshima and Nagasaki. The studies undertaken 30 or more years after the bombings have consistently shown dose-related excesses of cataracts, and the risk is greater for those exposed at younger ages. These studies have also suggested that children are about two times more sensitive than adults for the induction of preclinical posterior subcapsular and cortical opacities, and of vision-impairing cataracts. Studies of the effects of the protracted radiation exposures as a consequence of the Chernobyl accident and of the contamination of dwellings by ^{60}Co in Taiwan also indicate a substantial radiosensitivity for early opacities among children. Much evidence suggests that radiation-induced lens changes may be progressive after childhood exposure.

VI. EAR

C82. The external ear consists of the elastic connective tissue, epithelium, and fibroblasts. The middle ear has an epithelial lining in the tympanic cavity. The mucous membrane is squamous and epithelial in nature and is composed of reverting post-mitotic cells. The inner ear has many different cell types, but most of the cells are of the reverting post-mitotic type. The radiosensitivity of the external ear, therefore, is similar to that of the skin elsewhere, and the middle and inner ear are relatively radioresistant. Clinical effects that can be identified as a result of radiation exposure are primarily due to changes in the fine vasculature, which is moderately radiosensitive.

C83. Findings related to radiation effects on the ear may be identified soon after high-dose irradiation. They include hearing loss, tinnitus and earache [C49, D37, L17, M48]. Tinnitus may occur with localized radiotherapy at dose levels of 40 Gy. The situation resembles a serous otitis media and is due to hyperaemia of the capillaries, increased capillary permeability, and serous exudate.

C84. A conductive hearing loss also may be present. Fractionated doses of 40–60 Gy will cause acute radiation otitis media in 50% of patients. From six months to a few years after radiotherapy (subacute clinical period), there may be a sudden onset of Meniere's disease [G1]. The aetiology of these vestibulocerebellar signs is unknown. Usually, the patient recovers within several weeks. Sensorineural hearing loss is usually more pronounced at high frequencies [R1] and has a latent period of 12 months or more.

C85. There is some information concerning age as a modifying factor in late radiation effects from radiotherapy. Children treated for malignancies may be at a risk for early- or delayed-onset hearing loss that can affect learning, communication, school performance, social interaction, and overall quality of life. Hearing loss as a late effect of therapy can occur after exposure to platinum compounds (cisplatin and carboplatin) and cranial irradiation [G35, M19].

C86. Cranial irradiation, when used as a single modality, results in ototoxicity when the dose to the cochlea exceeds 32 Gy. Young patient age and the presence of a brain tumour/hydrocephalus can increase susceptibility to hearing loss. The onset of radiation-associated hearing loss may be gradual, manifesting itself months to years after exposure. When used concomitantly with cisplatin, radiotherapy can substantially exacerbate the hearing loss [C17, H71, M28, P20]. In a recent report from the CCSS, five-year survivors were at increased risk of impaired sound perception (RR = 2.3), tinnitus (RR = 1.7), hearing loss requiring an aid (RR = 4.4) and hearing loss in one or both ears not corrected by a hearing aid (RR = 5.2) when compared with unexposed siblings. These outcomes were associated with doses of >30 Gy to the temporal lobe and >50 Gy to the posterior fossa.

VII. ORAL CAVITY AND PHARYNX

C87. The epithelial lining of the mouth and pharynx are somewhat more radiosensitive than the skin because of the higher renewal rate of their cells. Methotrexate and 5-fluorouracil can produce severe mucositis and oesophagitis when used in combination with radiation. Because there is increased sensitivity of the mucosa compared to skin, radiation-induced mucositis will be noted before radiation-induced dermatitis. For these acute changes, the mechanisms of injury are quite similar but vary in time of expression. Most patients (more than 75%) receiving fractionated radiotherapy schemes totalling 60-70 Gy have impairment in taste for several years [K45].

C88. At the end of the second week of radiotherapy and doses of 20–24 Gy, dysphasia, soreness and pain, and dryness of the mouth occur, and taste deteriorates further. Definite erythema, and patchy mucositis of the palate may be noted. At doses of 30–36 Gy, the saliva becomes thick, and mucositis is identified in the region of the tonsils and the posterior pharynx. At doses of 50–60 Gy, mucositis develops into a pseudomembrane involving all tissues including the tongue. Clearing of these changes begins in approximately two weeks and is completed within two months. Rubin and Cassarett [R57] indicate that the same radiotherapy dose schedules are more easily tolerated by children than adults. The reactivity of children is greater but this is compensated by a more rapid recovery with the end effect seeming to be less.

C89. Delayed effects include progressive fibrosis of the submucosa, telangiectasia, and interstitial fibrosis of the mucous glands. Chronic ulcers may occur in the mucosa, in a fashion similar to that for the skin, as the result of arterial intimal fibrosis. They commonly occur along the lateral border of the tongue, floor of the mouth, and other areas where there is friction or microtrauma. High radiation doses administered at young ages can cause delayed pharyngeal hypoplasia.

VIII. TEETH

C90. Adverse long-term abnormalities of dentition can result directly from radiation and chemotherapy effects on growing tooth buds, and indirectly from damage to salivary glands. The severity and frequency of long-term dental complications due to radiotherapy are related to the type of radiotherapy given, the total dose, the size and location of radiotherapy fields and the age of the patient. Tooth bud growth may be arrested by doses of <10 Gy, while doses of >10 Gy can completely destroy buds. Root shortening, abnormal curvature, dwarfism and hypocalcification are noted with doses of 20-40 Gy [M5, S98]. Both chemotherapy and radiotherapy can cause multiple cosmetic and functional abnormalities of dentition, most predominantly in children treated before five years of age who have not yet developed deciduous dentition [A16, H62, H63, K18, K17, K16, O2, P14, P15]. However, even older prepubertal children are at risk. More than 85% of survivors of head and neck rhabdomyosarcoma who receive radiation doses greater than 40 Gy may have significant dental abnormalities, including mandibular or maxillary hypoplasia, increased caries, hypodontia, microdontia, root stunting, and xerostomia [P14, P15]. In Paulino's study, among children with head and neck rhabdomyosarcoma receiving radiotherapy to developing teeth, the alveolar portion of the mandible or the lingual surface of the maxilla developed dental abnormalities, including microdontia, root stunting and dental caries [P15]. Developing teeth are irradiated in the course of treating head and neck sarcomas, Hodgkin's lymphoma, neuroblastoma, CNS leukaemia, and nasopharyngeal cancer, and as a component of whole-body irradiation.

C91. Whole-body irradiation has been linked to the development of short, V-shaped roots, microdontia, enamel hypoplasia, and premature apical closure [D2, H62, H63]. Data regarding dental outcome after bone marrow transplants are limited [D1]. Neuroblastoma patients who received 12 Gy fractionated TBI-based or non-TBI-based transplants were not different in the incidence of microdontia and missing teeth, although TBI was associated with more severe root defects and a higher chance of permanent damage to teeth [H61]. The incidence of tooth abnormalities, including agenesis, was 62.9% in another study in which most of the children were treated with a TBI-based bone marrow transplant regimen [U3]. Tooth breakage due to tooth resorption has been common in patients injected with ^{224}Ra, especially in those injected as teenagers [S99].

IX. SALIVARY GLANDS

C92. The salivary glands include the parotid, submaxillary, and sublingual glands. They each have secretions that enter the oral cavity through a duct. Both the parenchymal cells of the gland and the duct cells are relatively resistant to deterministic effects of radiation exposure. The major exceptions are the relatively large excretory ducts of the parotid, which contain stratified epithelium near the main outlet (similar to that of the oral mucosa) which are relatively radiosensitive. The pathological effects of

radiation on these glands have been well described by Rubin and Casarett [R56], Fajardo [F4], Scherer [S28] and Ang et al. [A20]. Most of the data concerning these structures are derived from radiotherapy experience.

C93. In the months following radiotherapy, the extent of damage varies greatly from person to person. This may be the result of differences in radiotherapy administration, individual susceptibility, and other treatment factors such as sensitizing chemotherapy. Yet, it is clear that salivary gland irradiation incidental to treatment of head and neck malignancies or Hodgkin's lymphoma causes a qualitative and quantitative change in salivary flow, which can be reversible after doses of less than 40 Gy but may be irreversible after higher doses, depending on whether sensitizing chemotherapy is also administered [J14]. There are few specific data concerning the effects of exposure during childhood or adolescence since head and neck tumours are very rare in children. However, available data does suggest that >25 Gy radiotherapy can reduce secretions of the parotid, submaxillary and sublingual glands with resultant dry mouth, but this is generally not pronounced below doses of 40 Gy. Permanent xerostomia occurs in about 80% of persons receiving fractionated doses of 40–60 Gy [F20]. Transient dysfunction of the salivary glands is noted in young patients who have received a single whole-body dose of 10 Gy prior to bone marrow transplantation for leukaemia [D31].

C94. Following administration of very large doses of ^{131}I, radiation sialitis may be observed. Goolden et al. [G21] have calculated that after administration of 5.5–7.4 GBq of ^{131}I, doses to the salivary glands may be as high as 7–9 Gy in 12 hours. Doses from radioiodine therapy for hyperthyroidism (which sometimes occurs in children and adolescents) almost never result in significant xerostomia. When higher administered activities of radioiodine are used for the treatment of thyroid cancer, the doses to the salivary glands are higher. In these circumstances salivary and lachrymal gland dysfunction (sicca syndrome) can occur [S97].

X. THYROID FUNCTION AND THYROIDITIS

C95. There is extensive clinical experience of thyroid irradiation. Human data are available from the survivors of the atomic bombings, from those exposed to fallout from the testing of nuclear weapons, from those exposed as a consequence of accidents, and from those who have undergone radiotherapy for the treatment of tumours of the thyroid or the adjacent neck, or from the treatment of hyperthyroidism.

C96. The deterministic changes in the thyroid following large doses of radiation are primarily mediated by the vasculature, and presumably less so from direct damage to the fully differentiated follicular epithelial cells. Injury may be manifest as inflammatory and oedematous changes, followed later by obliteration of the fine vasculature and, ultimately, by radionecrosis or atrophy. Primary damage to the glands can produce either subclinical or clinically evident hypothyroidism. Damage to the hypothalamic–pituitary axis may produce secondary hypothyroidism.

C97. Late effects on the thyroid after childhood radiotherapy were reviewed in the UNSCEAR 1993 Report [U8]. However, new data concerning those exposed as a consequence of the Chernobyl accident [U15] and patients who have undergone radiotherapy are now available. A large body of literature exists regarding the role of radiation in the development of autoimmune thyroiditis, also known as Hashimoto's thyroiditis. The literature is complicated by the different tests and methodologies used to make the diagnosis, the high prevalence of thyroid abnormalities in the general population and non-radiation aetiological factors.

A. Atomic bombing survivors

C98. Morimoto et al. [M51] reported that in the age group under 20 years of age at the time of the bombings, those who received a dose of 1 Gy or more manifested an increased incidence of thyroid cancer and nodules but no statistically significant difference with regard to hypothyroidism or markers of autoimmune thyroiditis. Thyroid disorders were studied 30 years after exposure in 978 persons who were under 20 years of age at the time of the bombings [M51, M50]. The estimated doses were based on T65 dosimetry. There were 200 males and 277 females in the group exposed to doses of >1.0 Gy, and 219 males and 282 females in the unexposed group. Of these, 128 were aged 0–9 years and 349 were aged 10–19 years at the time of the bombings in the group exposed to doses of >1.0 Gy; 139 subjects were aged 0–9 years and 362 were aged 10–19 years at the time of the bombings in the unexposed group. There were no significant differences in mean scrum TSH levels or mean serum thyroglobulin levels between the unexposed and exposed groups.

C99. In an analysis by Nagataki [N1] of 2,774 subjects of the Nagasaki Adult Health Study cohort, the prevalence of hypothyroidism was 5% in exposed subjects and 2% in controls. Inoue et al. [I37] studied nearly 2,600 subjects from the same cohort and observed hypothyroidism in 3% of the subjects. The fitted relative risk increased from one for those who were less than five years of age to three for those who were 30 years at the time of the bombings.

C100. Fujiwara et al. [F22] reported on the prevalence of various types of immune factors but those associated with autoimmune thyroiditis did not appear to be dose related. An autopsy study by Yoshimoto et al. [Y8] of about 3,800 subjects did not reveal a statistically significant increase in chronic thyroiditis, however, the survivors of the atomic bombings who were under 30 years of age at the time of exposure have shown a dose-dependent excess of thyroid disease, defined to include non-toxic nodular goitre, diffuse goitre, thyrotoxicosis, chronic lymphocytic thyroiditis, and hypothyroidism [W37]. The excess, which became evident within 20 years of exposure and was not detectable in those exposed at older ages, corresponded to a relative risk of 1.24 at 1 Gy (Sv) ($p = 0.003$). Although many of those affected had multiple diagnoses, the exclusion of persons with thyroid cancer or thyroid adenomas did not modify the risk.

C101. The most recent follow-up of thyroid abnormalities among the survivors of the atomic bombings has been published by Imaizumi et al. [I34]. Among 4,091 survivors studied there was no dose–response relationship observed for positive antithyroid antibodies or antithyroid antibody-positive hypothyroidism. There was no analysis by age at exposure.

B. Radiation therapy

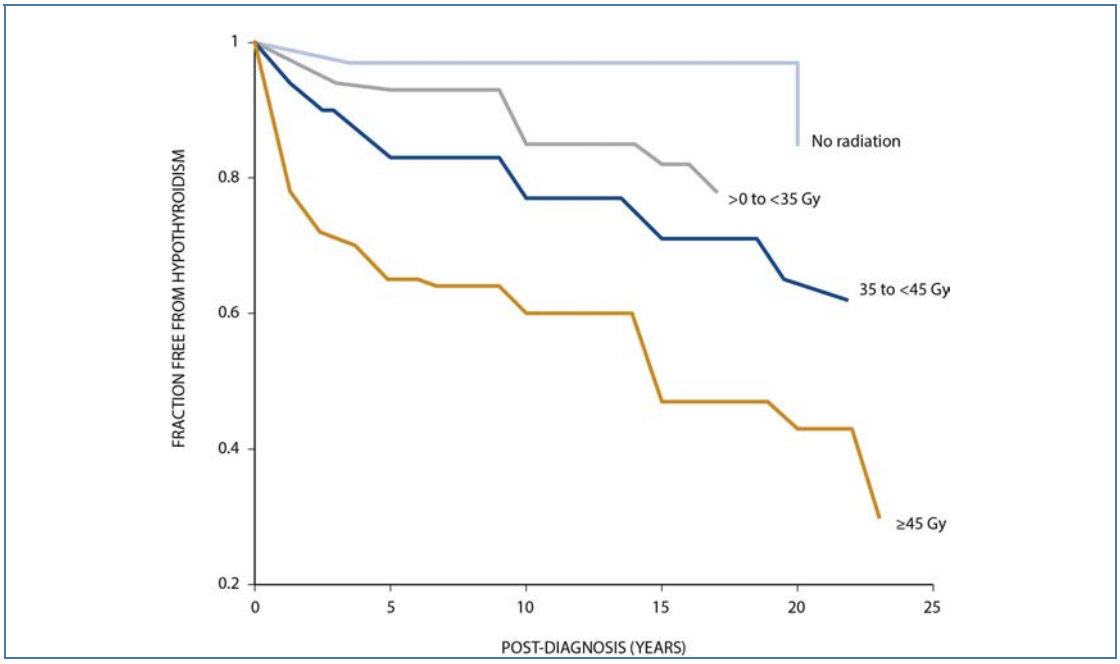
C102. While there are a large number of epidemiological studies of persons who had been treated with radiotherapy in childhood for various benign conditions—such as tinea capitis, presumed thymic enlargement, acne and haemangiomas—none of these studies specifically address the incidence of either hypothyroidism or autoimmune thyroiditis. Spitalnik and Straus [S105] found evidence for chronic lymphocytic thyroiditis, benign thyroid nodules and papillary thyroid cancers in thyroid glands removed for palpable thyroid abnormalities in a cohort of 68 patients who received “low dose” external beam irradiation for benign disease during childhood (thymus, tonsillitis, adenoiditis, acne, and scalp conditions). While the radiation dose to the thyroid was not known, the authors noted that all patients received doses of less than 10 Gy. The NCRP [N18] has pointed out that, given the conditions treated, it is likely that most of the patients received doses between 0.2 and 1.5 Gy as these were the usual doses

received by patients with similar conditions in other studies. Regardless of the dose received, the marked selection bias for cases (all with palpable thyroid disease requiring surgical removal) makes the results not generalizable to patients without palpable thyroid disease. Therefore, no conclusions can be drawn regarding dose–response relationships from this study.

C103. Thyroid dysfunction is a common delayed effect of high-dose radiotherapy fields that include the thyroid gland incidentally in the treatment of Hodgkin's lymphoma, brain tumours, head and neck sarcomas, and acute lymphocytic leukaemia. Of the children treated with radiotherapy, most develop hypothyroidism within the first two–five years post-treatment, but new cases can occur later (figure C-III). Reports of thyroid dysfunction differ depending on the dose of radiation, the length of follow-up, and the biochemical criteria used to make the diagnosis [G15]. The most frequently reported abnormalities include an elevated TSH, produced by the pituitary in response to a depressed thyroxine and stimulating the thyroid gland to compensate with increased output of thyroxine If the thyroid gland is unable to compensate with an increased output, then the thyroxine level will decline below normal [C45, H22, O3, S51, S86].

Figure C-III. Probability of developing an underactive thyroid after diagnosis of hypothyroidism

Adapted from [S83]. Patients are grouped according to dose of thyroid irradiation



C104. The incidence of hypothyroidism should decrease with the lower cumulative doses prescribed in newer protocols for radiotherapy. In a study of 1,677 children and adults with Hodgkin's lymphoma who were treated with radiotherapy between 1961 and 1989, the risk at 26 years post-treatment for overt or subclinical hypothyroidism was 47%, with a peak incidence at two–three years post-treatment [H18]. In a study of children and adults with Hodgkin's lymphoma treated between 1962 and 1979, hypothyroidism occurred in four of 24 patients who received mantle doses less than 26 Gy but in 74 of 95 patients who received doses greater than 26 Gy. The peak incidence occurred three–five years post-treatment, with a median of 4.6 years [C45].

C105. A cohort of survivors of Hodgkin's lymphoma in childhood who had been treated between 1970 and 1986 were evaluated for thyroid disease by use of a self-report questionnaire in the CCSS

[S83]. Among 1,791 survivors, 34% reported that they had been diagnosed with at least one thyroid abnormality. For hypothyroidism, there was a clear dose response, with a 20-year risk of 20% for those who had received a dose of <35 Gy, 30% for those who had received a dose of 35–44.9 Gy, and 50% for those who had received a dose of >45 Gy to the thyroid gland. The relative risks for hypothyroidism, hyperthyroidism and thyroid nodules were 17.1, 8.0 and 27.0, respectively. Elapsed time since diagnosis was a risk factor for both hypothyroidism and hyperthyroidism, where the risk increased in the first three–five years after diagnosis. For nodules, the risk increased beginning at ten years after diagnosis. Females were at increased risk for hypothyroidism and thyroid nodules.

C106. As might be expected, children treated for head and neck malignancies are also at risk for primary hypothyroidism if the neck is irradiated. The German Group of Paediatric Radiation Oncology recently reported on 1,086 patients treated at 62 centres, including 404 patients (median age, 10.9 years) who had received radiotherapy to the thyroid gland/hypophysis. Follow-up information was available for 264 patients (60.9%; median follow-up time was 40 months), with 60 patients (22.7%) showing pathological values. In comparison to patients treated with prophylactic cranial irradiation (median dose, 12 Gy), patients with radiation doses of 15–25 Gy to the thyroid gland had a hazard ratio of 3.072 (p = 0.002) for the development of pathological thyroid blood values. Patients with a dose greater than 25 Gy to the thyroid gland and patients who underwent craniospinal irradiation had a hazard ratio of 3.768 (p = 0.009) and 5.674 (p <0.001), respectively. The cumulative incidence of thyroid hormone substitution therapy did not differ between defined subgroups [B46].

C107. Paediatric patients who have undergone HSCT are at risk of thyroid dysfunction, which is much lower (15–16%) after fractionated whole-body irradiation, as opposed to single-dose irradiation (46–48%). Previously, regimens that did not involve whole-body irradiation were not associated with an increased risk. However, in a report from the Fred Hutchinson Cancer Research Centre, the increased risk of thyroid dysfunction was not different between children receiving whole-body irradiation and those receiving a busulfan-based regimen (p = 0.48) [S19]. Other high-dose therapies have not been studied. While mildly elevated TSH is common, it is usually accompanied by normal thyroxine concentration [B50, S17].

C108. According to the UNSCEAR 1993 Report [U8], the effect of age at the time of radiotherapy on the development of hypothyroidism is a matter of controversy. In one study, 48% of patients with Hodgkin's disease who were younger than 20 years of age at the time of treatment had elevated TSH levels compared to 33% of older patients [G14]. Green et al. [G27] observed that 7 out of 15 children with Hodgkin's disease and irradiated at the age of less than 13 years developed hypothyroidism, compared to 3 out of 12 among those who had been older than 13 years. In a study by Tarbell et al. [T6] of patients irradiated for Hodgkin's disease, the 15-year risk for hypothyroidism was 64% among patients aged 16 years or less, as compared to 29% among those older than 16 years. Constine et al. also identified an influence of age at exposure [C45]. However, other investigators have not identified age as a contributory factor [D36, K9, N23, S92].

C. Fallout

C109. In 1954, a thermonuclear explosion accidentally deposited large amounts of radioiodine on the Marshall Islands [C43, L7, R27]. The estimated thyroid dose varied from 0.3 to 3.4 Gy among those aged ≥18 years to 0.6–20 Gy among those aged <10 years. Many uncertainties were involved in the calculation of doses to the thyroid. The most widespread late effects of radiation exposure among the Marshallese have been related to radiation injury to the thyroid gland.

C110. The incidence of subclinical hypothyroidism was 31% among children of <10 years of age at exposure after an estimated dose to the thyroid of >2 Gy. No case of hypothyroidism occurred in this age group at lower doses. Among subjects who were ≥10 years at exposure, one case (1%) of hypothyroidism was observed in those who had received an estimated dose to the thyroid of <1 Gy, one case (8%) in those who had received a dose of 1 to 2 Gy and four cases (9%) in those who had received a dose of >2 Gy. Only two of the subjects exposed at less than 10 years of age had clinical hypothyroidism. The incidence of hypothyroidism began to increase approximately one decade after exposure. A thorough re-evaluation of the absorbed dose in the thyroid was done by Lessard et al. [L21]. The recalculated cumulative external doses of gamma rays were close to the initial estimates, but the doses from internally deposited radionuclides were much higher. Most of the thyroid dose resulted from short-lived radionuclides. The re-evaluated absorbed doses to the thyroid make the observed results compatible with those of other studies with similar doses [R29].

C111. Long-term follow-up by Takahashi et al. [T1, T2] of the Marshall islanders who received doses to the thyroid up to 4 Gy from the fallout from the testing of nuclear weapons did not show an increase in autoimmune hypothyroidism.

1. Nevada

C112. Although there was an early report by Rallison et al. [R5] of an excess of autoimmune thyroiditis in Nevada and Utah compared to Arizona, a subsequent age- and sex-adjusted study by Kerber et al. [K27] showed no evidence of a relationship between autoimmune thyroiditis or other thyroid diseases and individual doses. After a thorough review of the dosimetry and diagnoses in this study, Lyon et al. [L44] reported a statistically significant association with estimated radiation dose for thyroiditis (ERR Gy^{-1} of 4.9; 95% CI: 2.0, 10.0) and a suggestive association for thyroiditis with hypothyroidism (ERR Gy^{-1} of 2.9; 95% CI: 0.0, 11.7; $p = 0.09$).

2. Chernobyl

C113. The Chernobyl accident also released very large quantities of radioiodine to the environment. Unfortunately, the distribution of radioiodines in the environment and the doses to those exposed as a consequence are not well known. The International Chernobyl Project [I2] did examine the thyroid function of hundreds of persons living in nearby heavily contaminated villages and compared the findings with those of persons living in clean settlements. Five years after the accident, there was no evidence of thyroid hypofunction in the general population as a result of the accident. A large number of subsequent studies have been done on children in the contaminated regions. The majority of the dose initial to the thyroid was from ^{131}I (about 80%) and to a lesser extent from the shorter-lived radioisotopes of iodine. The data is complicated by potential effects of iodine deficiency in some areas and also continuing exposure from ^{137}Cs.

C114. Ostroumova et al. [O19] recently reported on thyroid function among 10,827 children and adolescents exposed to ^{131}I from the accident at the Chernobyl nuclear plant. They reported an association between thyroid dose and hypothyroidism but not for other outcomes including hyperthyroidism and autoimmune thyroiditis. Hypothyroidism was diagnosed on the basis of elevated TSH and not on serum thyroxine levels. As a result, the findings largely refer to subclinical hypothyroidism. The authors mentioned that a linear-quadratic dose-response model fit the data best, but they used a linear model to estimate an excess odds ratio per Gy of 0.34 (95% CI: 0.15, 0.62) for

hypothyroidism. Inspection of the data reveals that there was no statistically significant increase in hypothyroidism at thyroid doses less than about 5 Gy.

C115. The large screening programme conducted by the Chernobyl Sasakawa Health and Medical Cooperation Project from 1991 to 1996 involving 160,000 children who were less than 10 years of age at the time of the accident, found no increased risk of hypothyroidism, hyperthyroidism or goitre that could be related to ionizing radiation [I42, Y4]. Neither was there an increase in thyroid antibodies, which is in contradiction to some other smaller studies. There are quite a number of smaller studies which typically have less than 200 subjects. They are ecological studies based on caesium deposition and are of questionable value. A study from the Russian oblast of Orelby, Kasatkina et al. [K14] found significantly higher antithyroid peroxidase and antithyroglobulin antibody levels in the contaminated region but for those who had a fine needle aspiration performed, the prevalence of autoimmune thyroiditis was the same in the contaminated and control areas.

C116. Studies by Vykhovanets et al. [V19] covered 1,000 children who lived in contaminated areas and were medically screened. However, only 53 had blood tests performed and the results were compared with those obtained with 45 children living in other areas. Differences were reported as significant but inspection of the actual data indicated that this was probably not so. For example, one reported significant finding was that the level of TSH in the controls was 1.6 ± 1.3 and in the group that was presumed to have been exposed it was 6.1 ± 6.2. There are also data on thyroid echogenicity which are subjective and apparently obtained by the observers from a knowledge of where the children were living. Vykhovanets et al. have also reported that there was an increase in thyroid autoimmune disease after Chernobyl in all exposed children in the first decade, but that this effect decreased fourfold and essentially disappeared in the second decade post-exposure in persons who had been exposed to dose of >0.5 Gy [V19].

C117. Pacini et al. [P1] have reported on the prevalence of thyroid autoantibodies in children living around Chernobyl. The blood samples were drawn six–eight years post-exposure. Whether these persons will have a persistent elevation in antibody levels and whether this truly represents autoimmune thyroiditis and might lead to hypothyroidism is unclear. Vermiglio et al. [V17] measured the prevalence of antithyroglobulin antibody and antithyroid peroxidase in 143 children from a contaminated region and compared them with 40 controls. There were statistically significant increases of autoimmune thyroiditis in the exposed group. They also pointed out the possible effects of iodine deficiency on increasing the incidence of thyroid autoimmunity in the Russian Federation.

C118. Increasing the availability of non-radioactive iodine to the thyroid gland can precipitate autoimmune thyroiditis. There were programmes in the former Soviet Union that supplied stable iodine tablets (to combat goitre) to school children even before Chernobyl. In addition, potassium iodide was distributed to the population for use as a thyroid blocking agent in the days after the accident. All these aspects complicate any analysis of the data. The expert summary of the Chernobyl Project based on a review of the literature up to that date concluded that there was no consistent or conclusive evidence of radiation thyroiditis in the populations exposed to the radionuclides released during the Chernobyl accident [W21].

C119. The UNSCEAR 2008 Report [U15] indicated that there had been few studies of significant size addressing the relationship between autoimmune thyroiditis and exposure to radiation from the Chernobyl accident. Some studies report an association between radiation and serum thyroid antibodies, but not with the prevalence of autoimmune thyroiditis [A8]. The largest study by Tronko et al. [T38] could not demonstrate any conclusive evidence of a relationship between dose to the thyroid and autoimmune thyroid disease This is consistent with the findings from studies of other exposed populations.

3. Hanford

C120. A analysis was conducted relative to releases of radioiodine from the Hanford nuclear facility in the United States. The study by Davis et al. [D17] included 3,447 persons who were born between 1940 and 1946 and resident near the Hanford plant. No increased incidences of hypothyroidism or autoimmune thyroiditis related to the estimated doses to the subjects compared to unexposed controls were found. For hypothyroidism and autoimmune thyroiditis, the slopes of the dose–response curves were negative (-0.006 and 0.026, respectively).

4. Mayak

C121. Mushkacheva et al. [M59] have studied those who were exposed to ^{131}I as children as a consequence of discharges from the Mayak weapon facility in the Russian Federation. The study included 894 subjects born in 1952 and 1953. There were 581 subjects born in Ozyorsk and 313 who moved to the area after the exposure had ended. The relative risk for autoimmune thyroiditis was not elevated. The relative risk in males was 0.6 (95% CI: 0.2, 2.1) and for females the relative risk was 0.7 (95% CI: 0.4, 1.2).

D. Radioiodine thyroid therapy

C122. A large amount of information is available on the health effects of exposure of the thyroid gland in humans to ^{131}I, particularly in the treatment of Graves' disease and toxic multinodular goitres. One problem is that the natural course of Graves' disease often terminates in hypothyroidism, whether treated with ^{131}I or not.

C123. The actual absorbed dose to the thyroid is often difficult to calculate in these patients because of uncertainties in the exact size and weight of the gland. Another uncertainty is the biological half-life of the radioiodine in a hyperthyroid and radiation-damaged gland. Hypothyroidism, when it results from high-dose ^{131}I treatment, is usually evident three to four months after therapy; then the patient must be given replacement thyroid hormone. Transient hyperthyroidism due to release of stored hormone following radioiodine therapy for thyrotoxicosis has also been described.

C124. There are only very limited data on the effects of absorbed doses to the thyroid from ^{131}I of <25 Gy, in particular in children. The NCRP Report No. 55 [N15] cited unpublished data from Hamilton and Tompkins, who observed that 8 out of 443 subjects (2%) less than 16 years old and judged to have normal thyroids became hypothyroid after diagnostic ^{131}I tests. The incidence of hypothyroidism was 0% per year in 146 subjects who received a dose of <0.3 Gy to the thyroid, 0.15% per year in 146 subjects who received a dose of 0.3–0.8 Gy and 0.23% per year in 151 subjects after a dose of >0.8 Gy. A linear model with a threshold was postulated for hypothyroidism; owing to the large functional capacity of the thyroid gland, a large number of cells would have to be affected to result in hypothyroidism. Hayek et al. [H36] observed hypothyroidism in 8 out of 30 (26%) patients between the ages of 8 and 18 years who received ^{131}I therapy for hyperthyroidism. The mean amount of ^{131}I administered was 240 MBq, and the mean follow-up was nine years. Freitas et al. [F15] found a 92% prevalence of hypothyroidism in 51 patients aged 6–18 years after ^{131}I therapy for hyperthyroidism (mean ^{131}I activity, 520 MBq). There is one very early report from 1952 that children have more

sensitive glands with regard to the induction of hypothyroidism after repeated diagnostic doses of radioiodine than adults [W18].

E. Summary

C125. Thyroid dysfunction may result from irradiation of the thyroid gland or the hypothalamic–pituitary axis. A substantial proportion of patients receiving radiotherapy for various paediatric tumours have impaired thyroid function. The incidence of hypothyroidism varies with the definition used; it is highest when elevated TSH levels are used to define the impairment. On the basis of very limited external beam radiotherapy data, young children seem to be more sensitive to radiation-induced hypothyroidism. Various studies show that hypothyroidism is dose dependent. The prevalence of hypothyroidism is increased in leukaemic children who have received doses of 18–24 Gy to the cranium from radiotherapy over a period of 2–2.5 weeks. The doses to the thyroid in these cases have been calculated to be 3–8% of those to the brain (i.e. 1–2 Gy). However, the children also received associated chemotherapy, which may affect the risk for hypothyroidism.

C126. No epidemiological study has demonstrated hypothyroidism in children after a thyroid dose from external irradiation of <1 Gy. There is limited evidence that dose rate may be of importance and that the risk of hypothyroidism is reduced when fraction size is reduced. There are insufficient data on the effects of ^{131}I to determine whether there is a threshold dose for the induction of hypothyroidism. Some data from the Chernobyl accident do indicate an increase in antithyroid antibodies in the more contaminated regions. The available data, which are well documented, indicate that autoimmune thyroiditis is unlikely to have been induced by exposure to radiation in childhood. This includes recent data from the survivors of the atomic bombings, those exposed in the Marshall Islands following the testing of a nuclear weapon, those exposed as a consequence of the Chernobyl accident and those exposed as a consequence of discharges from the Mayak facility.

XI. BENIGN THYROID NODULES

C127. There are a large number of studies regarding the induction of benign thyroid nodules in children. These include those related to the use of radiotherapy for benign and malignant conditions, the survivors of the atomic bombings, environmental exposures, and medical use of ^{131}I. A recent review was published in 2008 by the NCRP [N18]. The data on risk for radiation-induced benign nodules has greater uncertainty than the data for induction of thyroid cancer. This is due to the high spontaneous rate of thyroid nodules in the population (which increases with age), differences in detection methods, and somewhat poorer characterization of the doses to the thyroid.

C128. In the general population, thyroid nodules are more common in adults than in children and about twice as common in females as in males. The prevalence of palpable nodules in non-exposed children ranges between 0.2% and 1.5%. In adults, palpable nodules are present in 4–7% of the population. The prevalence of nodules detected by ultrasound can be three–tenfold higher than when based on data from physical examinations.

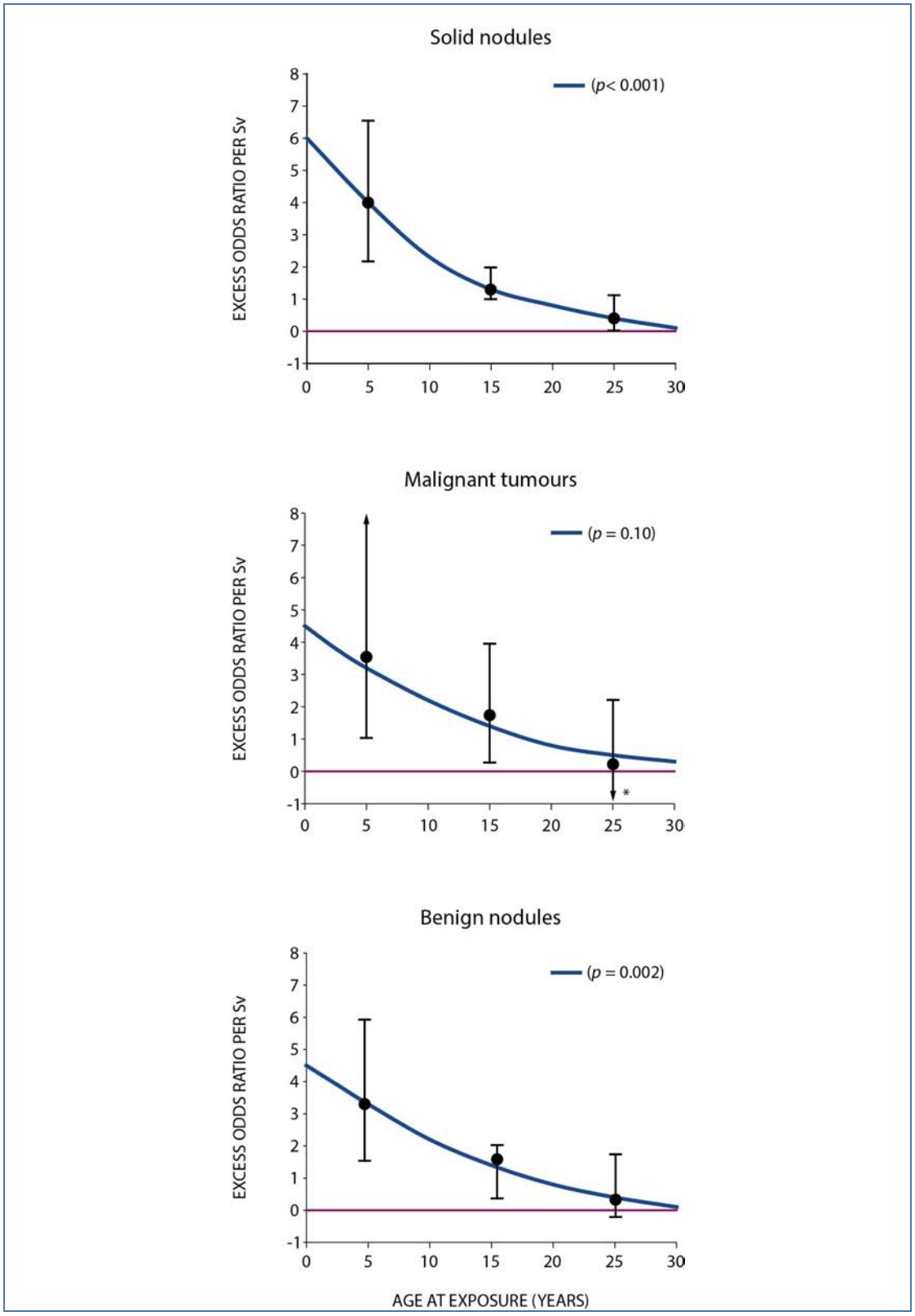
A. Atomic bombing survivors

C129. In a study of the incidence of non-cancer disease in the survivors of the atomic bombings by Yamada et al. [Y2], dose–response relationships were found for thyroid disease. The radiation risk was highest for subjects exposed at younger ages. The relative risk at 1 Gy for subjects exposed at less than 20 years of age was 1.54 (p <0.0001; 95% CI: 1.33, 1.81). For those exposed after 20 years of age, the relative risk at 1 Gy was not statistically significant, being 1.11 (95% CI: 0.96, 1.30; p <0.18).

C130. Imaizumi et al. [I34] studied thyroid disease in a cohort of 4,091 survivors of the atomic bombings 55–58 years after exposure. A significant dose response was found for all solid nodules, cancer and benign nodules. Nodules were all 1 cm or larger. There was a clear age-at-exposure effect with those exposed at younger ages being more at risk for both solid nodules (p <0.001) and benign nodules (p = 0.002) (see figure C-IV). The excess odds ratio for benign nodules was 2.89 (95% CI: 1.32, 5.77) for those exposed at 0–9 years of age, 0.83 (95% CI: 0.28, 1.70) for those exposed at 10–19 years of age, and 0.25 (95% CI: –0.20, 1.21) for those exposed at or above 20 years of age.

Figure C-IV. Trend at age of exposure in radiation response of thyroid diseases

Adapted from [I34]. *P* values are calculated by likelihood ratio test; * indicates detectable limit



B. Medical radiation uses

1. Tinea capitis

C131. Ron et al. [R39] studied the incidence of thyroid neoplasia among 10,834 Israeli persons who received X-ray therapy for ringworm of the scalp. All were less than 16 years old at the time of treatment. The mean dose to the thyroid was estimated to be 90 mSv, the relative risk for adenomas was 2.3 and the ERR per unit dose was 14.4 (95% CI: 2.9, 35) Gy^{-1}. In 1992, Shore et al. [S71] studied New York children who were treated with X-rays for tinea capitis. The mean dose to the thyroid was estimated to be 60 mSv. The relative risk for adenomas was 6.6 and the ERR per unit dose was 93 (95% CI: 1.7, 647) Gy^{-1}.

2. Presumed thymic enlargement

C132. Janower and Miettinen [J13] studied children treated for presumed thymic enlargement. The estimated dose to the thyroid was about 400 mSv and the relative risk was 4.6 and the ERR per unit dose was 8.9 (95% CI: 2.3, 25) Gy^{-1}. Shore et al. [S66, S67, S63] studied a cohort of 2,657 exposed children compared to 4,833 siblings using a questionnaire. There were 86 cases in the irradiated group and 11 in the sibling controls. The estimated thyroid dose was 1,360 mSv. The ERR per unit dose was 6.3 (90% CI: 3.7, 11.2) Gy^{-1}. Elevation in risk was seen even in the group exposed to a dose of <0.25 Gy. There was no increase in risk of nodules in less than 13 years after exposure; the mean latency was 38 years.

3. Lymphoid hyperplasia

C133. Children who had been irradiated for lymphoid hyperplasia between 1938 and 1969 were followed up by Pottern et al. [P40] and compared with surgically treated subjects. The mean dose to the thyroid was estimated to be 240 mGy. This was a very interesting study in that the results were obtained both by questionnaire and by clinical examination. A much higher relative risk of thyroid nodules was estimated from the questionnaire (RR = 15.8) than from clinical examination (RR = 2.7). This study indicates that there are major differences in risk estimates that can be obtained solely upon the basis of the study design and that questionnaire studies may substantially overestimate the true risk. Palpation by two physicians was used for the clinical evaluation, and nodules were found in 10.3% of the exposed persons compared with 4.2% in the controls. The ERR was estimated to be 7% (95% CI: 3, 20) per 0.01 Gy. This can be compared with risks of 10–30% per 0.01 Gy obtained in the Israeli tinea capitis study.

C134. Wong et al. [W38] reported the results of a telephone interview with 590 adults who, as children, had received head and neck (tonsillar) irradiation with an estimated dose to the thyroid of 570 mSv. The ERR per unit dose for nodules was 11.0 Gy^{-1}. There was a strong effect of age at irradiation (p = 0.006).

4. Haemangioma

C135. A cohort of 5,032 patients who were treated by radiotherapy for skin haemangioma between 1941 and 1973 in France was studied by de Vathaire et al. [D26]. Approximately 1,480 of these patients were less than 14 years old at the time of irradiation and were considered to have received exposure of thyroid (they were treated with ^{32}P, ^{90}Sr or ^{90}Y for haemangiomas that were located less than 5 cm from the thyroid or with ^{226}Ra or X-rays at other locations of the haemangioma). The authors calculated the absolute risk of thyroid nodules (benign and malignant) to be 1.8×10^{-3} PY Gy. Two studies from Sweden examined the risk of benign nodules following the treatment of skin haemangiomas with ^{226}Ra during infancy [L26, L40]. The mean estimated doses to the thyroid were 116 and 260 mGy, respectively. The ERRs per unit dose were 7.5 (95% CI: 0.4, 18.1) Gy^{-1} and 4.92 (95% CI: 1.26, 10.19) Gy^{-1}, respectively.

5. Hodgkin's disease

C136. Treatment of Hodgkin's disease with radiotherapy during childhood has been the subject of study relative to thyroid nodules. Hancock et al. [H18] have reported on 1,787 patients treated at Stanford University with radiation alone (810 patients), radiation and chemotherapy (920 patients), and chemotherapy alone (57 patients). Palpable abnormalities were found in 48 patients, 1.5–25 years after therapy. Thyroidectomy was performed on 26 patients. The patients had benign adenomas, six had adenomatous nodules, 4 had multinodular goitres, and six had cancer. The cancers occurred 9–19 years after therapy. No risk estimates for nodule induction were given. In a limited ultrasound study of the thyroids of 30 patients who had previous treatment for Hodgkin's disease using mantle radiotherapy, abnormalities were described in 24 patients [S115]. Nine of these appeared to have nodular lesions that would meet usual criteria. Other abnormalities included atrophy of the gland.

C137. A cohort of survivors of Hodgkin's lymphoma in childhood who were treated between 1970 and 1986 were evaluated for thyroid disease by use of a self-report questionnaire in the CCSS. Among 1,791 survivors, 34% reported that they had been diagnosed with at least one thyroid abnormality. The relative risk for thyroid nodules was 27.0 with the risk increase beginning at 10 years after diagnosis. Females were at increased risk for both hypothyroidism and thyroid nodules [S83].

C138. In a recent study of children treated with fractionated TBI between 1989 and 2009 for the treatment of haematological diseases, and with a median age of 8.2 years (5.7–11.4), the 10 year cumulative incidence of benign and malignant thyroid nodules was 16% and 8%, respectively [V18].

6. Radioiodine in diagnosis

C139. Hamilton et al. [H14] conducted a cohort study of 3,503 persons who had received diagnostic doses of radioiodine as children. The mean and median thyroid doses were estimated to be about 0.9 and 0.30 Gy, respectively, but the authors stated that the doses were probably higher because examinations for which some data were lacking were not included in the dosimetric calculations. In addition, the number of tumours was too small to estimate the ERR for benign nodules. Hall et al. [H7] examined 1,005 women who had received a diagnostic dose of ^{131}I. Within the exposed group there was a dose–response relationship with an ERR per unit dose of 0.9 (95% CI: 0.2, 2.3) Gy^{-1}. The ERR was similar for those irradiated before and after age 20.

C. Environmental and accidental exposures

1. Fallout from nuclear weapon testing

C140. The 1954 BRAVO thermonuclear test exposed residents of the Marshall Islands to fallout. A number of reports [C43, R29] indicated a higher than expected incidence of thyroid cancer and thyroid nodules. Data through 1986 indicated that 51 patients had nodules in the exposed group and 10 in the control group. The first nodule was found in a nine-year-old girl after the accident. Nodules were palpated in 2.6% of the control group of children under the age of 10 and in 7.8% of those over the age of 10. On Rongelap Atoll, nodules were palpated in over 60% of persons exposed at age less than 10 and in 13% of those over age 10 at exposure. The percentages were smaller for the Ailingae and Utirik atolls. Analysis of these data reveals virtually no excess of nodules at doses to the thyroid of less than 3 Gy. The risk in females was about 3.7 times that of males. Pathological diagnosis of the nodules indicated that most were adenomatous and frequently multiple.

C141. In another study, Hamilton et al. [H15] screened 2,273 Marshall Islanders using palpation, defining a nodule as being 1 cm or greater. The prevalence of thyroid nodules ranged from 0.9 to 10.6% and decreased with distance from the test site. A risk estimate was reported of 1,100 cases per Gy per year per million persons (11 excess cases per rad per year per million persons). This risk factor is complicated by the fact that there are wide variations in the natural incidence of thyroid cancer in Polynesian populations, and the spontaneous prevalence of thyroid nodules is not well known. Given these factors, the risk estimates from this population should be viewed with caution.

C142. An analysis of thyroid nodules in Utah has been conducted to examine the potential effect of fallout from the Nevada Test Site. Using palpation, Rallison et al. [R4] did not find any significant difference between 5,179 children in Utah and Nevada exposed to fallout and 3,453 in a control group. Many of the study participants were subsequently screened again for thyroid disease. Lyon et al. [L44] conducted a thorough review of the dosimetry and diagnoses in that study. They found that about 7% of the study participants had estimated thyroid doses of ≥400 mGy and another 10% had doses of 250-400 mGy. For the revised data they reported an ERR Gy^{-1} of 4.65 (95% CI: 1.1, 12.3) for thyroid nodules.

2. Hanford

C143. An analysis was conducted relative to releases of radioiodine from the Hanford nuclear facility in the United States. The study included 3,447 subjects who were children at the time of exposure, born between 1940 and 1946 and resident near the Hanford plant. The result reported by Davis et al. [D16, D17, K44] did not find an increased incidence of benign nodules. The estimated slope per unit dose was actually negative at −0.008 (95% CI: <0.022, 0.041) Gy^{-1}. The relative risk detectable with an 80% or greater power at 170 mGy was 1.37.

3. Mayak

C144. Mushkacheva et al. [M59] evaluated data on those who had been exposed as children to ^{131}I that had been discharged from the Mayak weapon facility in the Russian Federation. The study included 894 subjects who were born in 1952–1953. There were 581 subjects born in Ozyorsk and 313 who

moved to the area after the exposure had ended. The prevalence of nodular disease was significantly higher in the exposed group (20.7%) than in the control group (14.4%) with a relative risk of 1.4 (95% CI: 1.1, 1.9).

4. Semipalatinsk

C145. Land et al. [L6] reported the results of ultrasound findings of thyroid nodules among a group of 2,994 residents of villages close to the Semipalatinsk test site who were children at the time of the main radioiodine fallout event from the testing of a nuclear weapon in 1949. Nodules—diagnosed if they were above 3 mm—were found in 30.6% of the subjects. The vast majority were benign. The prevalence of nodules increased with dose (p = 0.001) and the linear-model excess odds ratio per unit dose was 0.74 (95% CI: 0.22, 1.24) Gy^{-1}. Of interest is that estimates of both external and internal radiation doses were strongly and independently associated with nodule prevalence and that internal irradiation was about one quarter to one third as causative (per unit exposure) as external photons but the data were consistent with ratios anywhere from 0.3 to 2.

5. Chernobyl

C146. The population living in the contaminated areas around the Chernobyl nuclear power plant were studied as part of the International Chernobyl Project [I2] and additional results were reported by Mettler et al. [M34]. Both palpation and high-resolution ultrasound were performed in seven highly contaminated villages and compared with results from five clean villages. In contaminated and control populations, both methods yielded less than 1.2% of children at five and ten years of age with a thyroid nodule. This, however, was at about only five years post-exposure. Longer follow-up was conducted as a part of the Sasakawa Project [I42, Y4]. Ivanov et al. [I46] reported on non-cancer thyroid diseases among 2,457 persons exposed as children in the Kaluga and Bryansk regions of the Russian Federation. Thyroid nodules were diagnosed if their diameter exceeded 3 mm. Solid nodules were found in 2.5% of those examined; however, the ERR for risk of nodules was not estimated.

D. Summary

C147. The incidence of benign thyroid nodules increases following radiation exposure. Those exposed at younger ages and females appear to be at greater risk. The estimated dose associated with the induction of benign nodules varies widely among the many published epidemiological studies. This is, in part, due to differences in the low signal-to-noise ratio, the detection methods used, the criteria for diagnosis and the uncertainties in the estimation of dose to the thyroid. On the basis of data from the survivors of the atomic bombings, the excess odds ratios per unit dose at different ages for thyroid cancer and benign nodules are broadly similar. The major difference occurs in prevalence as a result the large background of spontaneous benign nodules in unexposed populations. The vast majority of benign thyroid nodules do not become malignant.

XII. PARATHYROID GLANDS

C148. In spite of the extensive experience from studies of the effects of neck irradiation for the treatment of the thyroid for both benign and malignant conditions, no clinically-significant deterministic effects upon the parathyroid glands have been identified. Both Rubin and Casarett [R57] and Fajardo [F4] have reviewed the literature; the only effect reported has been atrophy of some glands embedded within the thyroid tissue when large doses of radioiodine had been administered. This result indicates the relative resistance of the parathyroid parenchymal cells to radiation, and perhaps a significant reserve capacity such that minor injury is well compensated. There have been reports of hyperfunction of the parathyroids following irradiation of the neck for benign and malignant conditions [C28].

C149. Fujiwara et al. [F23] reported increased levels of parathyroid hormone of 6.8% per unit dose (grays) but the dose response levelled off at a dose of about 1 Gy. Calcitonin levels were also increased. The mechanism remains unclear, and there is little, if any, clinical significance since normal individual variation is much greater than the potential radiation effect. There are occasional reports of calcitonin deficiency after radioiodine therapy [B35]; however, in most of these cases, there had been previous surgery for thyroid carcinoma and the removal of parathyroid glands. There is no literature specifically related to children that addresses susceptibility.

XIII.FEMALE BREAST

C150. Effects of radiation on breast tissue following radiotherapy have been well described. In general, adult breast tissue is quite radioresistant, with the major changes occurring in the skin, although ultimately atrophy of the gland may occur. Breast development is readily inhibited by radiotherapy in infancy and severe hypoplasia of the breast has been reported in women who have had a history of breast irradiation in childhood [D22, G34, K41, U5]. Doses to the breast of an infant in excess of 2–3 Gy may produce later deformity or hypoplasia. Rubin and Casarett [R58] reported that in infants and children, a dose exceeding 10 Gy of conventionally fractionated radiotherapy may result in absence of breast development in 1–5% of patients, but with hypoplasia occurring in most patients. This observation is supported by experience treating young children with doses of greater than 12 Gy for metastatic Wilms' tumour.

C151. Furst et al. [F26] reviewed the effect of radiation on the breast in 129 women who had received about 2.3 Gy to the chest as children for the treatment of haemangioma. The children were treated with flat ^{226}Ra applicators and were less than four years of age at the time of treatment. The mean absorbed dose to the breast for the cohort was 2.3 Gy (range 0.01–18.3 Gy). Breast hypoplasia was reported on the treated side by 57% of the patients and on the contralateral side by 8% of patients.

XIV. HEART

C152. All structural and functional components of the heart including the pericardium, myocardium, valves, conduction system, and coronary arteries are susceptible to deterministic effects by irradiation

although the thresholds are slightly different. No effects are evident at doses below 0.5 Gy. The pathophysiology of radiation-induced injury has been extensively studied and reviewed [A4].

C153. Myocardial injury is marked by non-specific, diffuse interstitial fibrosis [F2]. Lesions can measure from a few millimetres to several centimetres in diameter but usually do not involve the entire myocardium. Severity of fibrosis from one region to another can be markedly different. At a microscopic level, collagen not only increases as a whole but the proportion of type I collagen increases proportionally to type III [C11]. This change is thought to alter the compliance of the myocardium, and thus, contribute to the diastolic dysfunction seen after cardiac irradiation. Cells of the myocardium involved with conduction also appear to be sensitive to radiation-induced fibrosis, as demonstrated by the multiple reports of arrhythmias occurring after chest radiotherapy [C34, O16], and also correlations between pathological and electrophysiological changes [C11]. A common pathophysiological pathway of damage to the heart appears to be microcirculatory damage.

C154. Essentially all studies document an increased incidence or mortality from cardiovascular disease after exposure to ionizing radiation; however, these studies are complicated by significant limitations. Prominent among these is the fact that there is a wide range of cardiovascular and circulatory diseases, which may or may not be interrelated (including stroke, valvular disease, arteritis, atherosclerosis, hypertension, ischaemic disease, myocardial hypertrophy, myocardial infarction, myocarditis, hypercholesterolemia and pericarditis). Many studies use self-reported surveys, and those which examine the subjects often do not provide the criteria used for diagnosis of specific end points. There are also many confounding factors which are rarely accounted for, including misclassification of injury, and detailed analysis of other known cardiac risk factors such as family history, hypertension, obesity, and diabetes. Other risk factors are also clearly relevant, such as socioeconomic status, tobacco use, cardiotoxic medications, diet and genetics.

C155. Cardiovascular effects after exposure to ionizing radiation have been reviewed in the UNSCEAR 1993 Report (annex I) [U8], which summarized the late cardiovascular effects after irradiation of childhood cancer patients. It was concluded that radiation exposure causes occlusion of both small and large blood vessels. Cardiac abnormalities were observed particularly following irradiation of the mediastinum. The few data available at that time suggested that a dose of 40 Gy with conventional fractionation can be considered as a critical dose for clinical cardiomyopathy in both children and adults.

C156. The UNSCEAR 2006 Report (annex B) [U12] reviewed the epidemiological evidence of cardiovascular disease after radiation exposure and indicated that there was clear evidence of cardiovascular disease after absorbed doses in the radiotherapeutic range, but that the only evidence for fatal cardiovascular disease at doses of less than 1–2 Gy came from the data on the survivors of the atomic bombings. More recent reviews are available from Darby et al. [D9] and the NCRP [N19]. The review by Darby et al. [D9] indicates that there is a higher risk with younger age at irradiation. The data related to children is derived from studies of the survivors of the atomic bombings and the survivors of childhood cancer. Data related to stroke and cerebrovascular disease are discussed elsewhere in this annex.

A. External exposure

C157. Non-cancer disease mortality in the survivors of the atomic bombings was studied in the AHS by Yamada et al. [Y2], who found it to be increased for some categories of disease, including

cardiovascular. In particular, they reported a statistically significant quadratic association of radiation dose and myocardial infarction among those who were under age 40 at the time of irradiation. Positive effects of radiation exposure have also been reported for the incidence of hypertension and cardiovascular disease in the cohort exposed in childhood [T7]. For hypertension, the ERR/Gy was 0.15 (95% CI: −0.01, 0.34; $p = 0.06$) and for cardiovascular disease (which included both heart disease and stroke) it was 0.72 (0.24, 1.40).

C158. More recently, mortality from heart disease was studied in the LSS cohort [S57], based on about 8,400 heart disease deaths. It was found that possible confounders—smoking, alcohol intake, education, occupation, obesity and diabetes—had almost no impact on the risk estimate although adjusting for the misdiagnosis of cancers as heart disease slightly reduced the risk estimate but it was still statistically significant. They found an approximately linear dose response over the dose range of 0 to about 3 Gy; a test for quadratic curvature yielded a *p*-value >0.5. The estimated linear dose-response risk estimate was an ERR Gy^{-1} of 0.14 (95% CI: 0.06, 0.23; $p<0.001$), and EAR of 3.2 (1.3, 5.2) $(10^4$ PY $Sv)^{-1}$. The dose response over the dose range 0 to 1 Gy was statistically significant, but over the range 0 to 0.5 Gy it was not. A formal analysis for a dose-effect threshold gave a best estimate of 0 Gy (95% CI: <0, 0.5 Gy), suggesting no dose threshold. Nevertheless, the erratic nature of the data points in the lower dose range leaves considerable uncertainty about dose effects below about 0.5 Gy. There was no significant modification of risk by age at exposure. The risk estimates (ERR/Gy) were 0.24, 0.08, 0.10 and 0.17 for exposure ages of <10, 10–19, 20–40 and >40 years, respectively.

C159. Late effects of radiotherapy on the cardiovascular system include cardiomyopathy, coronary artery disease, pericardial effusions, valvular injury, conduction defects and pericarditis [S38]. Radiation, chemotherapy, and biological agents, both independently and in combination, increase the risk of cardiovascular disease in survivors of childhood cancer. In fact, cardiovascular disease is the leading cause of non-cancer mortality among the survivors of some cancers such as Hodgkin's lymphoma [H74, H73, R18]. The highest risks are from therapeutic exposures involving the use of the anthracyclines (doxorubicin, daunorubicin, idarubicin, epirubicin, mitoxantrone) and thoracic irradiation. The risks to the heart are related to the cumulative dose from anthracycline, the method of administration, the amount of radiation delivered to different depths of the heart, the volume and specific areas of the heart irradiated, the total and fractional irradiation dose, the age at exposure, the latency period, and the sex.

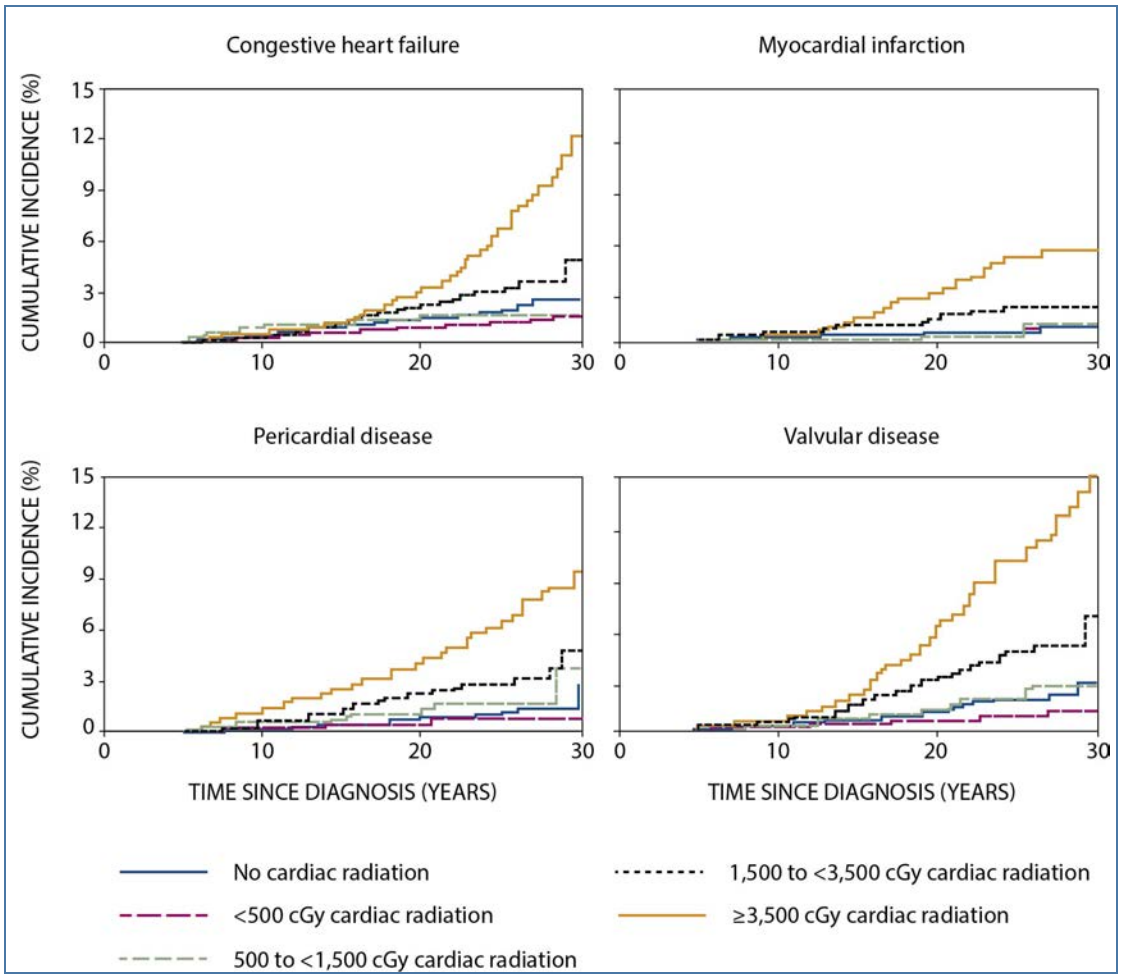
C160. The effects of thoracic irradiation are difficult to separate from those of anthracyclines because few children undergo thoracic irradiation without the use of anthracyclines. However, the pathogenesis of injury differs, with radiation primarily affecting the fine vasculature of the heart and anthracyclines directly damaging the myocytes [F3].

C161. Mulrooney et al. [M58] recently conducted a very large study of cardiac outcomes among 14,358 survivors of childhood and adolescent cancer. This group was found to be significantly more likely than a group of siblings to report congestive heart failure, myocardial infarction and pericardial disease or valvular abnormalities. The risk was slightly higher with younger age at exposure. Treatment with anthracyclines and cisplatin caused some of the increased risk. However, a dose to the heart of 15 Gy or more increased the relative hazard of congestive heart failure, myocardial infarction, pericardial disease and valvular abnormalities by two- to sixfold compared to non-irradiated survivors. The hazard ratios for congestive heart failure at doses of <5 Gy, 5–<15 Gy, 15–<35 Gy and >35 Gy were 0.9 (95% CI: 0.6, 1.4), 1.3 (95% CI: 0.7, 2.5), 2.2 (95% CI: 1.4, 3.5), and 4.5 (95% CI: 2.8, 7.2), respectively. The hazard ratios for myocardial infarction with the same dose intervals were 0.7 (95% CI: 0.4, 1.4), 0.6 (95% CI: 0.1, 2.5), 2.4 (95% CI: 1.2, 4.9) and 3.6 (95% CI: 1.9, 6.9), respectively. The values for pericardial disease were 0.7 (95% CI: 0.4, 1.1), 1.9 (95% CI: 0.9, 3.9), 2.2 (95% CI: 1.3, 3.9) and 4.8 (95% CI: 2.8, 8.3), respectively. For valvular abnormalities, the values were 0.6 (95% CI: 0.4,

1.0), 1.4 (95% CI: 0.7, 2.9), 3.3 (95% CI: 2.1, 5.1) and 5.5 (95% CI: 3.5, 8.6), respectively. The risk of incurring these effects continued to increase for at least 30 years (see figure C-V).

Figure C-V. Cumulative incidence of cardiac disorders among childhood cancer survivors by average cardiac radiation doses

Adapted from [M58]



C162. A European study of 4,122 five-year survivors of childhood cancer diagnosed before 1986 also provides evidence for an association between radiation dose and risk of cardiovascular disease [T50]. After 86,453 person-years of follow-up (average, 27 years), 603 deaths had occurred. The overall standardized mortality ratio was 8.3-fold (95% CI: 7.6, 9.0) higher in relation to the general populations of France and the United Kingdom. Thirty-two patients had died of cardiovascular disease, and this is fivefold (95% CI: 3.3, 6.7) greater than expected. The risk of dying of cardiac disease (n = 21) was significantly higher in people who had received a cumulative dose of anthracyclines greater than 360 mg/m^2 (RR = 4.4; 95% CI: 1.3, 15.3), with or without irradiation, and following radiation doses between 5 and 14.9 Gy (RR = 12.5) and greater than 15 Gy (RR = 25.1) to the heart. A linear relationship was found between the average dose of radiation to the heart and the risk of cardiac mortality (ERR at 1 Gy is 60%).

C163. Subclinical cardiac dysfunction was evaluated by a group from the Netherlands. Of 601 eligible adult five-year survivors of childhood cancer, 525 (87%) had an echocardiogram performed, of which 514 were evaluable for assessment of the left ventricular shortening fraction (LVSF) [V2]. The

median overall LVSF in the whole group of survivors of childhood cancer was 33.1% (range 13.0–56.0%). Subclinical cardiac dysfunction (LVSF <30%) was identified in 139 patients (27%). In a multivariate linear regression model, the LVSF was reduced with younger age at diagnosis, higher cumulative anthracycline dose, and higher radiation dose to the thorax. High-dose cyclophosphamide and ifosfamide were not associated with a reduction of the LVSF. This group also studied the occurrence of symptomatic cardiac abnormalities in a hospital-based cohort of 1,362 five-year childhood cancer survivors diagnosed between 1966 and 1996 and treated in the Netherlands [V3]. Fifty cardiac events, including 27 cases of congestive heart failure, were observed in 42 survivors at a median attained age of 27.1 years. The 30 year cause-specific cumulative incidence of cardiac events was significantly increased after treatment with both anthracyclines and cardiac irradiation (12.6%; 95% CI: 4.3, 20.3), after anthracyclines (7.3%; 95% CI: 3.8, 10.7), and after cardiac irradiation (4.0%; 95% CI: 0.5, 7.4) compared to other treatments; an exponential relationship between anthracycline and irradiation doses with risk was observed.

C164. Because cardiovascular disease is a leading cause of morbidity and mortality in survivors of childhood Hodgkin's lymphoma, this disease deserves special attention. An early case–control study by Boivin et al. [B44] of Hodgkin's lymphoma patients found the relative risks of myocardial infarction associated with mediastinal irradiation to be relatively homogenous among subgroups categorized by age at diagnosis of Hodgkin's lymphoma (0–39, 40–59 and 60+ years) or by number of years after diagnosis (0–4, 5–9, and 10+ years). However, variations in the radiation-related risk of heart disease were evident in the Stanford Hodgkin's lymphoma data [H21], which included a large number of patients treated at a wide range of ages and followed for varying time intervals. Most remarkably, the relative risk of acute myocardial infarction was highest (RR = 44) among those treated at age <20 years and decreased significantly with increasing age at irradiation. The absolute risk (i.e. the excess number of cases per 10,000 persons) increased significantly with increasing age at treatment, reflecting the increasing background rate for this disease with increasing age. The relative risk of acute myocardial infarction was already significantly elevated during the first five years after the initiation of therapy and remained increased 20 years or more after treatment, and the risk increased with time after treatment. Generally, similar patterns were observed for the risk of heart diseases other than myocardial infarction. The relative risk of heart disease other than myocardial infarction was highest among patients treated at age <20 years, decreasing significantly with increasing age at treatment, and increased significantly with increasing years after treatment.

C165. With current techniques and the fact that reduced doses are now used in radiotherapy for Hodgkin's lymphoma and other paediatric malignancies, these effects are unlikely to be so frequently observed following treatment for childhood cancer. Recent data from the German-Austrian DAL–HD studies show a dose response for cardiac diseases in children treated for Hodgkin's lymphoma with combined radiation and anthracycline-based chemotherapy (cumulative doxorubicin dose was uniformly 160 mg/m^2). The 25-year cumulative incidence of cardiac diseases was 3% with no radiotherapy, 5% after a dose of 20 Gy, 6% after a dose of 25 Gy, 10% after a dose of 30 Gy, and 21% after a dose of 36 Gy [S27]. An older study of 635 patients treated for childhood Hodgkin's lymphoma confirms the risks that occur after higher-dose radiation therapy that is no longer used in current treatment regimens. Yet, in that study's report, the risk of pericarditis requiring pericardiectomy was 4% at 17 years post-treatment (occurring only in children treated with higher radiation doses). Only 12 patients died of cardiac disease, including seven deaths from acute myocardial infarction; however, these deaths occurred only in children treated with a dose of 42–45 Gy [H19]. In an analysis of 48 patients treated for Hodgkin's lymphoma from 1970 to 1991 with mediastinal therapy (median dose 40 Gy), 43% had valvular abnormalities, 75% had a conduction abnormality or arrhythmia, and 30% had reduced oxygen consumption during exercise testing. Among children treated with a dose of 15–

26 Gy, none developed radiation-associated cardiac problems [A5] although this finding is contradicted by the much larger Mulrooney study discussed previously[M58].

C166. Data from the CCSS demonstrate the significant cardiovascular morbidity that occurs after treatment of a large variety of childhood cancers in addition to Hodgkin's lymphoma, with the caveat that the data were based on self-reporting. In a study of self-reported late effects among 1,607 survivors of childhood brain tumours [G39], 18% reported a heart or circulatory late effect. The risk was higher among those treated with combined surgery, radiotherapy, and chemotherapy compared to those treated with surgery and radiotherapy alone, suggesting a potential added vascular injury from chemotherapy. Children who received spinal irradiation for the treatment of CNS tumours have been demonstrated to show a low maximum cardiac index on exercise testing and pathological Q-waves in inferior leads on electrocardiogram testing, and higher posterior-wall stress [J10]. Among survivors of non-Hodgkin's lymphoma, the standard mortality ratio for cardiac disease was 6.9. A recent follow-up study of survivors of Wilms' tumour reported a cumulative risk of congestive heart failure of 4.4% at 20 years for those who had received doxorubicin as part of their initial therapy, and 17.4% at 20 years where doxorubicin was received as part of the therapy for relapsed disease. The risk factors for congestive heart failure in this cohort included female sex, lung irradiation with doses of 20 Gy or higher, left-sided abdominal irradiation, and doxorubicin dosage of 300 mg/m^2 or more [G28]. Finally, cardiac complications after bone marrow transplantation may occur with arrhythmias, pericarditis, and myopathies predominating. High-dose cyclophosphamide is clearly a causative agent. Whole-body irradiation is a secondary contributing factor [A23, E1, H55, S27].

C167. There have been a number of claims in the popular media concerning "Chernobyl heart disease in children" with the allegation that this is due to caesium contamination. Similar concern has also been raised as a result of caesium contamination from Fukushima. Extensive review of the health effects of the Chernobyl accident was included in both annex D of the UNSCEAR 2008 Report [U15] and the 2005 Chernobyl Forum Report [W21]. There was neither scientific evidence nor apparent biological mechanism to support such an entity.

XV. RESPIRATORY SYSTEM

C168. The lung is the most radiosensitive organ in the thorax. The data on lung injury following childhood exposure are almost exclusively derived from information obtained from radiotherapy treated patients, and interpretation of these data is complicated because of the use of chemotherapeutic agents in most of these patients. The mechanism for radiation-induced respiratory damage in young children may be different from that in adults or in adolescents. Specific radiation effects in children can include the impaired formation of new alveoli or failure in the development of the thoracic skeleton (chest wall) and thus a reduced size of the lung [B13, R59]. Overall, respiratory damage in young children is somewhat less than in adults at the same doses. The reasons for this are that children have less pre-existing disease, fewer co-morbid conditions and better repair capability. Children are able to develop additional alveoli up to the age of two years. No deterministic effects are seen at doses of less than 1 Gy.

C169. Acute and chronic pulmonary complications reported after treatment for paediatric malignancies include radiation pneumonitis, pulmonary fibrosis, and spontaneous pneumothorax. These sequelae are uncommon following contemporary therapy and most often result in subclinical injury that is detected only by imaging or formal pulmonary function testing. Chemotherapy agents with potential

pulmonary toxicity commonly used in the treatment of paediatric malignancies include bleomycin, busulfan, and the nitrosoureas (carmustine and lomustine). These agents induce lung damage on their own or potentiate the damaging effects of radiation to the lung. Thus, the potential for acute or chronic pulmonary sequelae must be considered in the context of the specific chemotherapeutic agents and the radiation dose administered, the volume of lung irradiated, and the fractionation of the doses used in radiotherapy [N14].

C170. Acute pneumonitis manifested by fever, congestion, cough, and dyspnea can follow radiotherapy alone at doses greater than 40 Gy to focal lung volumes, or after lower doses when combined with dactinomycin or anthracyclines. Fatal pneumonitis is possible after radiotherapy alone at doses to the whole lung greater than 20 Gy, but is possible after lower doses when combined with chemotherapy. Infection, GVHD in the setting of bone marrow transplant, and pre-existing pulmonary compromise (e.g. asthma) all may influence this risk. Changes in lung function have been reported in children treated with whole-lung radiotherapy for metastatic Wilms' tumour. A dose of 12–14 Gy reduced the total lung and vital capacity to about 70% of the predicted values and even lower if the patient had undergone thoracotomy.

C171. In a study of 48 survivors of paediatric malignant solid tumours with a median follow-up of 9.7 years following median whole lung irradiation doses of 12 Gy (range 10.5–18 Gy), only nine patients (18.8%) reported respiratory symptoms. However, abnormalities in forced vital capacity, forced expiratory volume in one second, total lung capacity, and diffusion capacity were common (58-73%). Focal boost irradiation was also significantly associated with additional abnormalities [M53]. Reducing the size of the daily radiation fractions (e.g. from 1.8 Gy per day to 1.5 Gy per day) decreases this risk [M15, M16]. Administration of bleomycin alone can produce pulmonary toxicity and, when combined with radiotherapy, can intensify its effects. Chemotherapeutic agents such as doxorubicin, dactinomycin, and busulfan are radiomimetic agents and can reactivate latent radiation damage [K51, M15, M16].

C172. The development of bleomycin-associated pulmonary fibrosis with permanent restrictive disease is dose dependent, usually occurring at doses of bleomycin greater than 200–400 U/m^2, which is higher than those used in most treatment protocols for paediatric malignancies [B51, F21, K51]. Nevertheless, more current paediatric regimens for Hodgkin lymphoma using radiotherapy and adriamycin/doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) have shown a significant incidence of asymptomatic pulmonary dysfunction after treatment, which appears to improve with time [H72, H76, M6]. However, more severe and symptomatic grade 3 and 4 pulmonary toxicity has been reported in 9% of children receiving 12 cycles of ABVD (an amount no longer used) followed by a radiation dose of 21 Gy [F21]. In addition, ABVD-related pulmonary toxicity may result from fibrosis induced by bleomycin or "radiation recall" (terminology for the first manifestation or re-expression of subclinical or clinical radiation-induced injury, respectively, when certain chemotherapeutic agents are administered) pneumonitis related to administration of doxorubicin. Pulmonary veno-occlusive disease has been observed rarely and has been attributed to bleomycin chemotherapy [P37].

C173. Patients undergoing HSCT are at increased risk of pulmonary toxicity related to: *(a)* pre-existing pulmonary dysfunction (e.g. asthma, pre-transplant therapy); *(b)* the preparative regimen that may include cyclophosphamide, busulfan, carmustine; *(c)* whole-body irradiation; and *(d)* the presence of GVHD [C10, K8, L20, M7, N24, N46]. Although most survivors of transplant are not clinically compromised, restrictive lung disease may occur. Obstructive disease is less common, as is late onset pulmonary syndrome, which includes the spectrum of restrictive and obstructive disease. Bronchiolitis obliterans with or without organizing pneumonia, diffuse alveolar damage, and interstitial pneumonia may occur as a component of this syndrome, generally between 6 and 12 months post-transplant.

Cough, dyspnea, or wheezing may occur with either normal chest X-rays or diffuse/patchy infiltrates; however, most patients are symptom free [L20, S40, U4, Y7].

C174. Additional factors contributing to chronic pulmonary toxicity include superimposed infection, underlying pneumonopathy (e.g. asthma), cigarette use, respiratory toxicity, chronic GVHD, and the effects of chronic pulmonary involvement by tumour or reaction to tumour. Lung lobectomy during childhood appears to have no significant impact on long-term pulmonary function [K50] but the long-term effect of lung surgery for children with cancer is not well defined.

C175. The true prevalence or incidence of pulmonary dysfunction in childhood cancer survivors is not clear. For children treated with HSCT, there is significant clinical disease. No large cohort studies have been performed with clinical evaluations coupled with functional and quality-of-life assessments. An analysis of self-reported pulmonary complications of 12,390 survivors of common childhood malignancies has been reported by the CCSS [M31]. This cohort includes children treated with both conventional and myeloablative therapies. Compared with siblings, the survivors had an increased relative risk of lung fibrosis, recurrent pneumonia, chronic cough, pleurisy, use of supplemental oxygen therapy, abnormal chest wall, exercise-induced shortness of breath, and bronchitis, with RRs ranging from 1.2 to 13.0 (highest for lung fibrosis and lowest for bronchitis). The 25-year cumulative incidence of lung fibrosis was 5% for those who had received chest irradiation and less than 1% for those who had received pulmonary toxic chemotherapy. With changes in the doses of radiotherapy used since the late 1980s, the incidence of these abnormalities is likely to decrease.

XVI. OESOPHAGUS

C176. The squamous epithelium of the oesophagus has approximately the same turnover rate as oral mucosa. In spite of this, the oesophagus is extremely resistant to radiation when compared with the remainder of the gastrointestinal tract. Oesophagitis, dysphasia, and later stricture following radiotherapy have been reported. Early changes are primarily due to mucosal damage while late damage is primarily related to changes in the muscle wall although mucosal changes may be present.

C177. The appearance of mucositis in the oesophagus is very similar to its appearance in the oropharynx. There is little information on early effects after irradiation of the oesophagus in children to indicate a significant difference in sensitivity from adults. There is a report of a child with ataxia telangiectasia being more sensitive during radiotherapy for Hodgkin's disease [P57].

C178. Early symptoms include mild to moderate substernal burning and difficulty in swallowing, beginning in the second or third week after initiation of radiotherapy at absorbed dose levels as low as 20 Gy. Doses of 20–30 Gy over 2 weeks lead to clinical symptoms of oesophagitis; however, they are transient. The oesophagus can tolerate fractionated doses up to 60 Gy. Strictures have been reported to develop 4–8 months after completion of radiotherapy at doses from 30 Gy in 2 weeks to 65 Gy in 6.5 weeks. Strictures may occur at lower doses in very young patients. Rare late delayed effects including tracheoesophageal fistula and stricture have been reported after radiotherapy for Hodgkin's disease [H2, M52].

XVII. SMALL INTESTINE

C179. Donaldson et al. [D42] reviewed the late complications in children after whole abdominal radiotherapy for Wilms' tumour, teratoma, or lymphoma. Of 14 long-term survivors, five developed severe radiation injury, with small bowel obstruction, within two months of the completion of therapy. The average age at treatment was six years, and the dose was 31 Gy in 7–20 fractions over 11–39 days. Coia and Hanks [C35] reviewed the complications in 1,026 patients treated with large-field infradiaphragmatic radiotherapy for Hodgkin's disease and seminoma. The most frequent complications were gastrointestinal injury, such as peptic ulceration, haemorrhage, chronic diarrhoea, and intestinal obstruction. The bowel complications occurred in 1% of patients at doses of <35 Gy and 3% at doses of ≥35 Gy. Major bowel complications were increasingly likely when large portions of the bowel received fractionated doses above 50–55 Gy. Histologically, during the subacute and chronic period, the villae of the mucosa are often blunt and thickened, and the mucosal cells are often flattened. The lamina propria may be normal or may demonstrate severe fibrosis. Telangiectasia may occasionally occur as well. Overall, collagen deposition throughout the submucosa is demonstrated most consistently.

C180. Upper gastrointestinal, hepatic, and lower gastrointestinal adverse outcomes were assessed in cases from participants in the CCSS of 14,358 survivors of childhood cancer who were diagnosed between 1970 and 1986. Data were compared with those from randomly selected siblings. The median age at cancer diagnosis was 6.8 years (range, 0–21.0 years), and the median age at outcome assessment was 23.2 years (5.6–48.9 years) for survivors and 26.6 years (1.8–56.2 years) for siblings. Rates of self-reported late gastrointestinal complications (occurring five or more years after cancer diagnosis) were determined and associated with patient characteristics and cancer treatment, adjusting for age, sex, and ethnic group. Older age at diagnosis, intensified therapy, abdominal radiation, and abdominal surgery increased the risk of certain gastrointestinal complications [G19].

XVIII. HEPATOBILIARY AND PANCREAS

A. Liver

C181. Data on hepatobiliary effects following childhood radiation exposure are derived primarily from its therapeutic use for malignancies. At fractionated absorbed doses to the liver of <10 Gy, no radiation-induced clinical effects (i.e. in the absence of chemotherapy) have been reported. Radiation and specific chemotherapeutic agents may produce hepatic toxicity that is acute and transient in most affected patients but, rarely, can be delayed in onset and be persistent. Recipients of HSCT are the exception to this rule as these persons frequently experience chronic liver dysfunction related to microvascular, immunological, infectious, metabolic, and toxic aetiologies. Acute radiation-induced liver disease also causes endothelial cell injury that is characteristic of veno-occlusive disease/ sinusoidal obstruction syndrome [D20].

C182. Tefft [T14] observed liver abnormalities in children after radiotherapy that included a dose to the liver of 12–30 Gy. The whole liver in adults has a tolerance of up to 30–35 Gy with conventional fractionation. Chou et al. [C22] reported that about 75% of children receiving 7–12 Gy whole-body

irradiation for conditioning in the setting of bone marrow transplant develop acute liver dysfunction, and about 25% show signs of hepatic veno-occlusive disease. Thomas et al. [T21, T22] reported hepatic fibrosis in 3 of 26 long-term survivors of Wilms' tumours who had received a dose of at least 30 Gy in 1.5 to 2 Gy fractions.

C183. On the basis of limited data from paediatric cohorts treated in the 1970s and 1980s, persistent radiation hepatopathy after contemporary treatment appears to be uncommon in long-term survivors without predisposing conditions such as viral hepatitis or iron overload [P7]. The risk of injury in children increases with radiation dose, hepatic volume, younger age at treatment, prior partial hepatectomy, and concomitant use of radiomimetic chemotherapy like dactinomycin and doxorubicin [B23, F8, K54, T14]. Survivors who received radiation doses of 40 Gy to at least one third of the liver volume, or doses of ≥30 Gy to the whole abdomen or to the upper abdomen that included the entire liver, are at the highest risk for hepatic dysfunction.

C184. Hepatitis following irradiation and chemotherapy at doses and volumes of irradiation ordinarily considered within the tolerance of hepatic function has been reported [K54]. Fatal liver damage occurred in a 13-year-old boy who had received adriamycin before and during radiotherapy involving a dose of 24 Gy in 17 fractions over 28 days to the upper abdomen including the entire liver. A 13-year-old girl had moderate clinical liver changes following a dose of 25 Gy in 23 fractions over 32 days with adriamycin administered before and during irradiation. In this case, much of the right lobe was shielded during radiotherapy. About 20 patients have been reported to have developed liver disease after fractionated radiotherapy involving a total dose of 12–40 Gy to the liver in childhood together with chemotherapy [C7, J16]. Viral hepatitis B and C may complicate the treatment course of childhood cancer and result in chronic hepatic dysfunction.

C185. Nodular regenerative hyperplasia (NRH) is a rare condition characterized by the development of multiple monoacinar regenerative hepatic nodules and mild fibrosis. The pathogenesis is not well established, but may represent a non-specific tissue adaptation to heterogeneous hepatic blood flow [W14]. NRH has rarely been observed in survivors of childhood cancer treated with chemotherapy, with or without liver irradiation [B63, C29]. Biopsy may be necessary to distinguish NRH from a second malignancy.

C186. In a cohort who recently completed intensified therapy for ALL, histological evidence of fatty infiltration was noted in 93% and siderosis in up to 70% of the patients [H11]. Fibrosis developed in 11% and was associated with a higher serum low-density lipoprotein cholesterol level.

C187. Prospective studies are needed to define whether acute post-therapy fatty liver change contributes to the development of steatohepatitis or the metabolic syndrome in this population. Likewise, information about the long-term outcomes of transfusion-related iron overload is lacking, especially among cohorts of survivors who did not undergo haematopoietic cell transplantation.

B. Pancreas

C188. The pancreas has been thought to be relatively radioresistant because of a paucity of information on late pancreatic-related effects. However, children and young adults treated with total body or abdominal radiation are known to have an increased risk of insulin resistance and diabetes mellitus. A retrospective cohort study, based on self-report, on 2,520 five-year survivors of childhood cancer treated in France and the United Kingdom investigated the relation between radiation dose to the

pancreas and risk of a subsequent diabetes diagnosis. Sixty-five cases of diabetes were validated with the risk increasing with radiation dose to the tail of the pancreas where the islets of Langerhans are concentrated. Risk increased up to 20–29 Gy and then plateaued. The estimated relative risk at one Gy was 1.61, and the relative risk of diabetes was 11.5 in patients who received more than 10 Gy to the tail of the pancreas. Radiation dose to the other parts of the pancreas did not have a significant effect compared with patients who did not receive radiation. Children younger than two at the time of exposure were more sensitive compared with older patients (relative risk at one gray was 2.1 for this young age group versus 1.4 for older patients). For the 511 patients who received more than 10 Gy, the cumulative incidence of diabetes was 16% [D29, N14].

XIX. REPRODUCTIVE SYSTEM AND FERTILITY

A. Testes

C189. The effects of radiation on the testes are age and dose dependent. Radiation appears to have its greatest effect on the germ cells rather than on Leydig cells. Testicular function may be compromised at doses as low as 0.5 Gy. Leydig cell function appears more resistant to radiation, and impaired function occurs after a dose of ≥10 Gy. Testicular function is also impaired by chemotherapy and may be abnormal prior to therapy for malignancy that does not involve the testes. Irradiation to the prepubertal gonads may not always result in irreversible damage. Whole-body irradiation has been shown to produce primary gonadal failure of various degrees in the majority of boys who had received doses of 10 Gy, regardless of pubertal status. In most of these patients, Leydig cell function appeared adequate. A recent review of this was reported by members of the United States Children's Oncology Group [K26].

1. Radiotherapy

C190. Surgery, radiotherapy, and/or chemotherapy may damage testicular function. Patients who undergo unilateral orchiectomy for testicular torsion may have subnormal sperm counts at long-term follow-up [A21, T43]. Retrograde ejaculation is a frequent complication of bilateral retroperitoneal lymph node dissection performed on males with testicular neoplasms [N9, N31] and impotence may occur following extensive pelvic dissections to remove a rhabdomyosarcoma of the prostate [S30].

C191. Most data on the sensitivity of the testes to radiation are historical, but demonstrate that men treated with whole-abdomen irradiation during childhood frequently develop gonadal dysfunction. For example, in one study, five of ten men evaluated at ages 17–36 years were azoospermic, and two were severely oligospermic, after whole-abdomen irradiation for Wilms' tumour at ages 1–11 years. This occurred even though the penis and scrotum were either excluded from the treatment volume, or shielded with 3 mm of lead. The doses to the testes varied from 7.96 Gy to 9.83 Gy [S49]. Others reported azoospermia in 100% of ten men 2–40 months after radiotherapy doses of 1.4–3 Gy to both testes [S100]. Similarly, azoospermia was demonstrated in 100% of ten men following radiotherapy doses to the testes of 1.18–2.28 Gy. Recovery of spermatogenesis occurred after 44–77 weeks in 50% of the men, although three of the five with recovery had sperm counts below 20×10^6 ml^{-1} [H3].

Oligospermia or azoospermia was reported in 33% of 18 men evaluated 6–70 months after receiving testicular radiation doses of 0.28–1.35 Gy [P23].

C192. In another report, none of five men who had received doses to the testes of <0.20 Gy became azoospermic. By contrast, two who had received doses to the testes of 0.55–0.70 Gy developed temporary oligospermia, with recovery to sperm counts greater than 20×10^6 ml^{-1} 18–24 months after treatment [K34]. In summary, a decrease in sperm counts can be seen three–six weeks after irradiation and, depending on the dose, recovery may take one–three years. The germinal epithelium is damaged by much lower doses (<1 Gy) than those that damage Leydig cells (20–30 Gy). Complete sterilization may occur with fractionated irradiation above doses of 2 to 4 Gy.

C193. Administration of higher radiation doses, such as 24 Gy, which was used for the treatment of testicular relapse of ALL, results in both sterilization and Leydig cell dysfunction [B28]. Craniospinal irradiation produced primary germ cell damage in 17% of 23 children with ALL [S84] but in none of four children with medulloblastoma [A9]. This difference may be related to the concurrent administration of chemotherapy in the children with ALL, and also to techniques used to shield or avoid the testes in the medulloblastoma children. Whole-body irradiation involving doses of 9.50-15.75 Gy combined with cyclophosphamide (60 mg/kg each day for two days) produced azoospermia in almost all men treated [S15]. Male survivors of non-Hodgkin's lymphoma who underwent pelvic radiotherapy and received a cumulative cyclophosphamide dose greater than 9.5 g/m^2 were at increased risk for failure to recover spermatogenesis [N14, P61].

2. Accidents and incidents

C194. A case of child abuse involving industrial radiography sources has been reported by Collins and Gaulden [C36]. In this particular instance, a divorced petroleum engineer had intermittent custody of his two sons. He had possession of at least a 37 GBq ^{137}Cs source used for oil and gas well logging. The dose rate in contact with such a source is approximately 5 Gy/min. One of the sons was subjected to various occasions in which "shiny silver pellets" were placed in the earpieces of headphones that he was told to wear, in a pillow he was told to use, and in a sock he found on his bed. After more than a year, a plastic surgeon recognized the lesions as radiation necrosis. Both testes had effectively been destroyed and the boy had been functionally castrated.

B. Ovary

C195. The majority of post-pubertal females who receive whole-body irradiation prior to bone marrow transplantation develop amenorrhea. Recovery of normal ovarian function occurred in only 9 of 144 patients in one series and was highly correlated with age at irradiation; those who demonstrated recovery were younger than 25 years [S16]. In a series restricted to patients who were prepubertal at the time of bone marrow transplantation, 44% (7 out of 16) had clinical and biochemical evidence of ovarian failure [M12].

C196. As previously suggested, the frequency of ovarian failure following abdominal radiotherapy is related to both the age of the woman at the time of irradiation, and the radiotherapy dose received by the ovaries. Whole-abdomen irradiation produces severe ovarian damage. Seventy-one per cent of women in one series failed to enter puberty, and 26% had premature menopause following whole-

abdominal radiotherapy doses of 20 to 30 Gy [W9]. Other studies reported similar results in women treated with whole-abdomen irradiation [S45] or craniospinal irradiation [H17, W10] during childhood.

C197. Of 3,390 eligible participants in the CCSS, 215 (6.3%) developed acute ovarian failure (AOF). Survivors with AOF were older at cancer diagnosis (aged 13–20 years versus those aged 0–12 years), more likely to have been treated for Hodgkin's lymphoma, or to have received abdominal or pelvic radiotherapy than survivors without AOF [C12]. Of the survivors who developed AOF, 75% had received abdominal–pelvic irradiation. Radiation doses to the ovary of at least 20 Gy were associated with the highest rate of AOF, with over 70% of such patients developing AOF [C12]. In a multivariable logistic regression model, increasing doses of ovarian irradiation, exposure to procarbazine at any age, and exposure to cyclophosphamide at 13–20 years of age were independent risk factors for AOF.

C198. The presence of apparently normal ovarian function at the completion of chemotherapy should not be interpreted as evidence that no ovarian injury has occurred. Premature menopause is well documented in survivors of childhood cancer, especially in women treated with both an alkylating agent and abdominal irradiation [B74, C18, S87]. A total of 126 survivors of childhood cancer and 33 control siblings who participated in the CCSS developed premature menopause. Of these women, 61 survivors (48%) and 31 siblings (94%) had surgically-induced menopause (RR = 0.8; 95% CI: 0.52, 1.23). However, the cumulative incidence of non-surgical premature menopause was substantially higher for survivors than for siblings (8% versus 0.8%; RR = 13.21; 95% CI: 3.26, 53.51; p <0.001) [S87].

C199. A multiple Poisson regression model showed that the risk factors for non-surgical premature menopause included attained age, exposure to increasing doses of radiation to the ovaries, increasing alkylating agent dose score, and a diagnosis of Hodgkin's lymphoma. For survivors who were treated with alkylating agents plus abdominal–pelvic irradiation, the cumulative incidence of non-surgical premature menopause approached 30% [S87]. A recent review of ovarian function following cancer therapy in children was performed by Metzger et al. [M36].

C. Fertility

C200. Fertility was evaluated among the 6,224 male CCSS participants aged 15–44 years who were not surgically sterile. They were less likely to sire a pregnancy than siblings (hazard ratio = 0.56; 95% CI: 0.49, 0.63). Among survivors, the hazard ratio of siring a pregnancy was decreased by radiotherapy doses greater than 7.50 Gy to the testes (hazard ratio = 0.12; 95% CI: 0.02, 0.64). Compared with siblings, the hazard ratio for ever siring a pregnancy for survivors who had not been treated with alkylating agents, and had no measureable radiation doses to the hypothalamic/pituitary axis or testes, was 0.91 (95% CI: 0.73, 1.14; p = 0.41) [G32].

C201. Fertility was evaluated among the 5,149 female CCSS participants and 1,441 female siblings of CCSS participants, aged 15–44 years. The RR for ever being pregnant was 0.81 (95% CI: 0.73, 0.90; p <0.001) compared with female siblings. In multivariate models among childhood cancer survivors, those who had received a hypothalamic/pituitary radiation dose greater than 30 Gy (RR = 0.61; 95% CI: 0.44, 0.83) or an ovarian/uterine radiation dose greater than 5 Gy were less likely to have ever been pregnant (RR = 0.56 for a uterine dose of 5–10 Gy; 95% CI: 0.37, 0.85; RR = 0.18 for a uterine dose >10 Gy; 95% CI: 0.13, 0.26).

C202. Fertility may be impaired by factors other than the absence of sperm and ova. Conception requires delivery of sperm to the uterine cervix, patency of the fallopian tubes for fertilization to occur, and appropriate conditions in the uterus for implantation. Retrograde ejaculation occurs with significant frequency in men who undergo bilateral retroperitoneal lymph node dissection. Uterine structure may be affected by abdominal irradiation. A recent study demonstrated that uterine length was significantly shorter in ten women with ovarian failure who had been treated with whole abdomen irradiation. Endometrial thickness did not increase in response to hormone replacement therapy in three women who underwent weekly ultrasound examination. No flow was detectable with Doppler ultrasound through either uterine artery in five women, and through one uterine artery in three additional women [G30].

C203. In summary, fertility and reproduction can be reduced by a number of factors, including those outlined above for the testes, ovary and uterus. Other factors would include patency of fallopian tubes and dysfunction of the pituitary/hypothalamic axis. While there is no data that radiation susceptibility of the neuroendocrine axis is greater at younger age, uterine development is clearly compromised by pelvic irradiation and is, thus, age dependent. Conversely, the ovary, and perhaps the testes, may be more resistant to radiation at younger age [K26, M36].

D. Reproduction

C204. For survivors of childhood cancer who maintain fertility, numerous investigations have evaluated the prevalence of and risk factors for pregnancy complications in adulthood. Pregnancy complications including hypertension, foetal malposition, foetal loss/miscarriage, pre-term labour, and low birth weight have been observed in association with specific diagnostic and treatment groups [B73, C18, C26, C52, C60, G32, G33, H32, M4, M54, R17, W31]. Studies regarding heritable effects were presented earlier in the annex.

C205. In a study of 4,029 pregnancies among 1,915 women followed in the CCSS, there were 63% live births, 1% stillbirths, 15% miscarriages, 17% abortions, and 3% unknown or in gestation. Risk of miscarriage was 3.6-fold higher in women treated with craniospinal irradiation and 1.7-fold higher in those treated with pelvic irradiation. Chemotherapy exposure alone did not increase the risk of miscarriage. Compared with siblings, survivors were less likely to have live births, more likely to have medical abortions, and more likely to have low birth-weight babies [C52]. In the same cohort, another study evaluated pregnancy outcomes of partners of male survivors. Among 4,106 sexually active males, 1,227 reported that they had sired 2,323 pregnancies, which resulted in 69% live births, 13% miscarriages, 13% abortions, and 5% unknown or in gestation at the time of analysis. Compared with partners of male siblings, there was a decreased incidence of live births (RR = 0.77), but no significant differences of pregnancy outcome by treatment [G32].

C206. In the National Wilms Tumor Study, records were obtained for 1,021 pregnancies of more than 20-weeks duration. In this group, there were 955 single live births. Hypertension complicating pregnancy, early or threatened labour, malposition of the foetus, lower birth weight (<2,500 g), and premature delivery (<36 weeks) were more frequent among women who had received flank irradiation, in a dose-dependent manner [G33]. Results from a Danish radiotherapy study confirm the association of uterine irradiation with spontaneous (but not other types of abortion). Thirty-four thousand pregnancies were evaluated in a population of 1,688 female survivors of childhood cancer in the Danish Cancer Registry. The pregnancy outcomes of survivors, 2,737 sisters, and 16,700 comparison women in the population were identified. No significant differences were seen between survivors and comparison

women in the proportions of live births, stillbirths, or all types of abortions combined. Survivors with a history of neuroendocrine or abdominal radiotherapy had an increased risk of miscarriage. Thus, the pregnancy outcomes of survivors were similar to those of comparison women with the exception of miscarriage [W31].

C207. Preservation of fertility and successful pregnancies may occur after HSCT, though the conditioning regimens that include whole-body irradiation, and treatment with cyclophosphamide, and busulfan are highly gonadotoxic. In a group of 21 females who had received bone marrow transplantation in the prepubertal years, 12 (57%) were found to have ovarian failure when examined between ages 11 and 21 years, and the association with busulfan was significant [T15]. One study evaluated pregnancy outcomes in a group of females who had undergone bone marrow transplantation. Among 708 women who were post-pubertal at the time of transplant, 116 regained normal ovarian function and 32 became pregnant. Among 82 women who were prepubertal at the time of transplant, 23 had normal ovarian function and nine became pregnant. Of the 72 pregnancies in these 41 women, 16 occurred in those treated with whole-body irradiation and 50% resulted in early termination. Among the 56 pregnancies in women treated with cyclophosphamide without either whole-body irradiation or treatment with busulfan, 21% resulted in early termination. There were no pregnancies among the 73 women treated with both busulfan and cyclophosphamide, and only one retained ovarian function [S18].

C208. For survivors of childhood cancer who have offspring, there is concern about congenital anomalies, genetic disease, and risk of cancer in the offspring. In an early analysis [G29] of information from the National Wilms Tumor Study Group, congenital anomalies were marginally increased in offspring of females who had received radiotherapy of the flank. In a later analysis [G33], the offspring of the partners of males who had received radiotherapy to the flank raised the possibility that one or both findings were spurious.

C209. In a report on 2,198 offspring of adult survivors who were treated for childhood cancer between 1945 and 1975 compared with 4,544 offspring of sibling controls, there were no differences in the proportion of offspring with cytogenetic syndromes, single-gene defects, or simple malformations. There was similarly no effect on the occurrence of genetic disease in the offspring regardless of the type of treatment for childhood cancer that had been used. A population-based study of 2,630 live-born offspring of the survivors of childhood cancer versus 5,504 live-born offspring of the siblings of the survivors found no differences in the proportion of abnormal karyotypes or incidence of Down's syndrome or Turner's syndrome between the two groups [W30]. Survivors treated with abdominal radiotherapy and/or alkylating agents did not have an increased risk of offspring with genetic disease, compared with survivors not exposed to these agents [B75].

C210. In a study of 5,847 offspring of survivors of childhood cancer treated in five Scandinavian countries, in the absence of a hereditary cancer syndrome (such as hereditary retinoblastoma), there was no increased risk of cancer [S22]. A study by Byrne et al. also indicated no excess risk of single-gene disorders, congenital malformations, or chromosomal syndromes among the offspring of former patients compared with the offspring of siblings [B75].

C211. In summary, treatment for childhood malignancy with select chemotherapeutic agents, primarily alkylators, or radiation therapy that exposes the ovaries or testes, is associated with an impairment in fertility and this is both chemotherapy and radiation-dose related. Radiation therapy that exposes the uterus is associated with miscarriages and premature or small-for-date babies, and this is also dose related.

XX. SKIN

C212. The skin is considered to be a body organ. It serves not only as a barrier against the environment but is also involved in immune function, in control of the body's temperature, and as a medium to provide sensory input. A vast literature describes the effects of radiation exposure on the skin. In general, children's skin is not significantly more radiosensitive than that of adults [F5, I12, R56, T42]. When large areas of skin are exposed, the "cutaneous radiation syndrome" [G24, P26] may appear.

C213. Single acute doses of low-LET radiation of 0–2 Gy to the skin produce no clinically observable effects in adults. At a dose of 2–5 Gy, there is transient erythema followed by temporary epilation in 2-8 weeks. Doses of 5–10 Gy result in transient and delayed erythema and permanent partial epilation. Acute single doses of 10–15 Gy will cause the same erythematous changes but with dry or moist desquamation and long-term telangiectasia and dermal atrophy. With single acute doses >15 Gy, moist desquamation at 2–8 weeks followed by ulceration and necrosis may occur [B3]. Erythema in children has been documented as a result of accidental overexposures from CT scans. Children appear to be less sensitive than adults for some skin effects such as moist desquamation (perhaps owing to the faster repair by the skin cells) [G16].

C214. With radiotherapy, temporary loss of hair (epilation) occurs in about three weeks with doses of 3-5 Gy; hair begins to return during the second month and continues for up to one year. Single doses of 7 Gy may cause permanent epilation, with the latent period being less than three weeks. Not all body areas have the same radiosensitivity for epilation. Hair follicles of children are more sensitive than those of adults. Exacerbated acute skin reactions can be seen when radiotherapy is combined with chemotherapy. Late effects of radiotherapy include telangiectasia, pigmentation changes and skin atrophy. There is significant individual variation in expression of these effects.

C215. Skin effects have been reported in children following accidental exposure to radionuclides. The circumstances have included fallout from the testing of atomic weapons in the Marshall Islands, the Goiania accident involving a source of ^{137}Cs and many accidents with orphan industrial radiography sources. Most reports, however, do not provide information on the difference in skin reactions by age of patient.

C216. The effects on the skin of various deposited radionuclides depend significantly on the half-life of the radionuclide and the energy spectrum of the emitted radiation. A number of reports and books on the occurrence and treatment of such lesions are available [G43, I1, O13].

XXI. MUSCULOSKELETAL SYSTEM

C217. The majority of data concerning deterministic effects on the musculoskeletal system are derived from studies of those who had undergone external beam radiotherapy; some were previously summarized in the UNSCEAR 1993 Report [U8]. Essentially all forms of cancer therapy, including surgery, chemotherapy, and radiotherapy, can affect the musculoskeletal system of a growing child or adolescent. Outcomes affecting the musculoskeletal system are discussed below, including late effects on the bone and joints (abnormal bone and muscle growth, amputation/limb-sparing surgery, joint contracture, osteoporosis/fractures, osteonecrosis) and changes in body composition (obesity and body fatness). There are a few studies of childhood exposure relating to growth and the musculoskeletal

system involving those exposed to ^{224}Ra, the survivors of the atomic bombings and those exposed as a consequence of radiation in the environment (e.g. following the Chernobyl accident).

A. Abnormal bone growth

C218. Otake et al. [O22] have studied growth retardation as a potential radiation effect following in utero exposure of the survivors of the atomic bombings. Overall, the effect, if any, was small. Similar results have been reported by Nakashima [N5]. There are no data among the survivors of the atomic bombings indicating that there was a direct effect on the musculoskeletal system in those who were exposed as children.

C219. Anthropometric analyses were performed in 1990 on children who were living in the former Soviet Union at the time of the accident at the Chernobyl nuclear plant in 1986, and in children born in 1989 [I2]. The main conclusion from these studies was that there were no significant differences in height or weight between those living in the control and contaminated regions.

C220. In cancer patients up to six years of age, a dose of 10 Gy produces mild osseous changes, whereas a dose of 10–20 Gy in fractionated radiotherapy produces severe changes (impaired growth and development, including asymmetrical bone growth if only part of the bone is irradiated). In general, the higher the dose and the younger the child, the more deformity results. Although animal data indicate that irradiation of bone causes a reduction in the number of blood vessels, it is not thought to be the primary cause of reduction in growth.

C221. In an age- and dose-dependent fashion, radiotherapy can inhibit normal bone and muscle maturation and development. Radiation to the head (e.g. cranial, orbital, infratemporal, nasopharyngeal radiotherapy) can cause craniofacial abnormalities, particularly in children treated before the age of five or with radiation doses of 20 Gy or more [D34, E13, G9, K13, K15]. Soft tissue sarcomas, such as orbital rhabdomyosarcoma, and retinoblastoma are two of the more common cancer groups with these head and neck radiation fields. Often, in addition to the cosmetic impact of the craniofacial abnormalities, there can be related dental and sinus problems as previously discussed.

C222. Radiotherapy can also directly affect the growth of the spine and long bones (and associated muscle groups), and can cause premature closure of the epiphyses, leading to short stature, scoliosis/kyphosis, or limb-length discrepancy depending on the radiation field treated [F9, H56, K19, M27, P58, W25]. Orthovoltage, commonly used before 1970, delivered higher doses of radiation to the bone and was commonly related to abnormalities in bone growth. However, even with contemporary radiotherapy, if the location of the solid tumour is near an epiphysis or the spine, alterations in normal bone development can be difficult to avoid.

C223. The effects of radiation on stature in survivors of Wilms' tumour was assessed in the National Wilms Tumor Studies [H56]. Stature loss in 2,778 children treated on these studies was evaluated. Repeated height measurements were collected during long-term follow-up. The effects of radiation dose, chemotherapy, and age at treatment on stature were analysed using statistical models that accounted for the normal variation in height with sex and advancing age. Predictions from the model were validated by descriptive analysis of heights measured at age 17–18 years for 205 patients. For those under 12 months of age at diagnosis who received a dose of more than 10 Gy, the estimated deficit in adult height was 7.7 cm when contrasted with the unexposed group. For those who received a dose of 10 Gy, the estimated shortening of the trunk was 2.8 cm or less. Among those whose height

measurements in the teenage years were available, patients who received a dose of more than 15 Gy were 4–7 cm shorter on average than their unexposed counterparts, and there was an evident dose–response relationship. Chemotherapy did not confer an additional risk.

C224. The effects of radiation on the development of scoliosis have also been recently re-evaluated. In a group of 42 children treated for Wilms' tumour from 1968 to 1994, scoliosis was seen in 18, with only one patient needing orthopaedic intervention [P16]. Median time to development of scoliosis was 102 months (range 16–146 months). A clear dose–response relationship was seen, with children treated with lower doses (<24 Gy) having a significantly lower incidence of scoliosis than those who received a dose of more than 24 Gy. There was also a suggestion that the incidence was lower in patients who received a dose of 10–12 Gy, the doses that are currently used for the treatment of Wilms' tumour. Also, cranial and whole-body radiotherapy damages the hypothalamic–pituitary axis in an age– and dose–response fashion, often leading to growth hormone deficiency. This has been discussed in the text on neuroendocrine effects.

C225. In children, radiotherapeutic fractionated doses in excess of 25 Gy to the ends of long bones have occasionally been shown to cause slipped capital epiphyses. Slippage is rare with fractionated doses of less than 25 Gy [B5, W7]. The risk in children irradiated under the age of four is about 47%, and about 5% in older children [S79]. This effect apparently results from an arrest in chondrogenesis and vascular changes. Chemotherapy may play a minor role because many patients have received doxorubicin, which has been shown to arrest chondrogenesis temporarily [E7, P9, S79, W7]. In addition to slippage of the femoral epiphysis, there also can be aseptic necrosis in some patients. Usually, these are children who have received doses in excess of 30–40 Gy and chemotherapy [P54].

C226. Growth retardation has also been observed in children injected with ^{224}Ra for the treatment of tuberculosis of bone and soft tissue [M13, S104]. Spiess et al. [S104] obtained the adult heights of 133 patients injected as juveniles. ^{224}Ra-induced growth retardation was greatest in young children, who had the greatest amount of potential growth after exposure. The growth retardation increased with radiation dose, and there was a 2% decrease in potential growth post-irradiation per Gy for average skeletal doses up to 20-25 Gy.

B. Osteoporosis/fractures

C227. Chemotherapy (e.g. methotrexate) can have a cytotoxic effect on osteoblasts, resulting in a reduction of bone volume and the formation of new bone. This effect may be exacerbated by the chronic use of corticosteroids [P36]. Radiation-related endocrinopathies, such as growth hormone deficiency or hypogonadism, may contribute to ongoing bone-mineral loss. Radiation-induced fractures can occur with fractionated doses of radiation of 50 Gy or more, as is often used in the treatment of Ewing's sarcoma of the extremity [P18, W3].

C. Osteochondroma

C228. Radiation-induced osteochondromas have been reported in 6% of long-term surviving children who received radiotherapy. These benign "tumours" have been noted in the spine, pelvis, scapula, and ribs [N28]. Approximately 5% of children undergoing myeloablative stem cell transplantation will

develop osteochondroma, which most commonly presents in the metaphyseal regions of long bones. Osteochondroma generally occurs as a single lesion; however, multiple lesions may develop in the context of hereditary multiple osteochondromatosis [B55]. A large Italian study reported a 6.1% cumulative risk of developing osteochondroma at 15 years post-transplant, with increased risk associated with younger age at transplant (≤3 years) and use of whole-body irradiation [F6]. Growth hormone therapy may influence the onset and pace of growth of osteochondromas [B48]. Malignant degeneration of these lesions is exceptionally rare.

D. Joints and muscle

C229. Cartilage, like adult bone, is fairly radioresistant. Doses of 60 to 70 Gy in a prolonged radiotherapy treatment scheme can be tolerated by cartilage. Unless there is stress to the cartilage, clinical manifestations of deterministic radiation effects are rare with the exception of delayed necrosis of the larynx.

C230. Deterministic effects of radiation on muscle are distinctly unusual. Acute radionecrosis of skeletal muscle requires absorbed doses in excess of 500 Gy [G7]. The most common late effect on developing muscle tissues secondary to irradiation is their diminished development (hypoplasia). The muscles treated are smaller and functionally not as strong as the patient's non-irradiated muscle tissues. Studies have shown that the functional outcome after radiotherapy to the limb is related to the radiotherapy volume and the size of the non-irradiated corridor [A15]. The total dose and dose per fraction of radiotherapy used is also significant in determining range of movement, muscle power, and limb function [K28]. At lower fractionated doses, from 22 to 54 Gy, atrophy of fibres can be identified. Finally, ischaemia due to arterial narrowing may result in fibrosis [Z4]. The ultimate clinical result of muscle irradiation probably depends not only on the absorbed dose but on the length of the muscle segment irradiated. If the muscle is short and is entirely included in the radiation field, the resultant detriment may be substantially greater than if only a portion of a long muscle is irradiated. Heterotopic calcification of soft tissue has been reported as a late radiation effect although it is usually seen in combination with other late effects such as tissue ulceration, fibrosis, nerve damage or bone necrosis [C5].

E. Changes in body composition

C231. The primary cancer groups recognized with an increased incidence of treatment-related obesity are survivors of acute lymphocytic leukaemia [C24, G5, M40, O8, R11, W36] and of CNS tumour in childhood treated with cranial radiotherapy [G39, P34]. In addition, craniopharyngioma survivors also have a substantially increased risk of extreme obesity [C47, M22, N10]. Moderate-dose cranial radiotherapy (18–24 Gy) among survivors of acute lymphocytic leukaemia is associated with obesity, particularly in females treated at a young age [D39, G5, O8].

C232. Female adult survivors of acute lymphocytic leukaemia in childhood who were treated with cranial radiotherapy with a dose of 24 Gy prior to the age of five are four times more likely to be obese in comparison with women who have not been treated for cancer [O8]. In addition, women treated with cranial radiotherapy with doses of 18–24 Gy prior to the age of 10 have a substantially greater rate of increase in their body mass index through their young adult years in comparison with women who were

treated for acute lymphocytic leukaemia with only chemotherapy or with women in the general population [G5]. It appears that these women also have a significantly increased visceral adiposity and associated insulin resistance [J11, O11]. These outcomes are attenuated in males. Interestingly, among survivors of brain tumours treated with higher doses of cranial radiotherapy, only females treated at a younger age appear to be at increased risk for obesity [G40].

C233. The development of obesity following cranial radiotherapy is multifactorial, with factors including growth hormone deficiency, leptin sensitivity, reduced levels of physical activity, and energy expenditure [B59, G5, O10]. Importantly, survivors of childhood cancer treated with whole-body irradiation in preparation for an allogenic HSCT have increased measures of body fatness (percentage of fat) while often having a normal body mass index [N29, N47]. It remains controversial whether contemporary acute lymphocytic leukaemia therapy, without cranial radiotherapy, is associated with a sustained increase in body mass index.

F. Metabolic syndrome

C234. The metabolic syndrome is highly associated with cardiovascular events and mortality. Definitions of the metabolic syndrome are evolving, and generally include a combination of central (abdominal) obesity with at least two other components, namely:

- hypertension;
- atherogenic dyslipidemia (elevated triglycerides, reduced high-density level cholesterol);
- abnormal glucose metabolism (fasting hyperglycaemia, hyperinsulinism, insulin resistance, diabetes mellitus type II) [N12].

C235. An increased risk of metabolic syndrome or its components has been observed in cancer survivors. Long-term survivors of acute lymphocytic leukaemia, especially those treated with cranial irradiation, may have a higher prevalence of some, potentially modifiable, risk factors for cardiovascular disease such as impaired glucose tolerance or overt diabetes, dyslipidemia, hypertension, and obesity [C27].

C236. In a young adult cohort of survivors of acute lymphocytic leukaemia (mean age 30 years), 62% had at least one cardiovascular risk factor and 30% had two or more [O7]. Another study observed no difference in prevalence of metabolic syndrome in 75 survivors of acute lymphocytic leukaemia compared to a population-based control group [G42]. However, survivors with metabolic syndrome were more likely to have growth hormone insufficiency or deficiency. Those treated with cranial radiotherapy also had an association with growth hormone abnormalities and were more likely to have two or more components of the metabolic syndrome compared to survivors who were not treated with cranial radiotherapy.

C237. A high frequency of cardiovascular risk factors has also been observed among haematopoietic cell transplant recipients [S52]. French investigators reported an overall 9.2% (95% CI: 5.5, 14.4) prevalence of metabolic syndrome in a cohort of 184 survivors of acute lymphocytic leukaemia (median age 21.2 years) [O24]. Sex, age at diagnosis, corticosteroid therapy or cranial irradiation were not significant predictors of metabolic syndrome. However, haematopoietic cell transplantation with whole-body irradiation was a major risk factor for metabolic syndrome (OR = 3.9; $p = 0.03$).

C238. Other investigators have reported a significantly increased risk of hyperinsulinemia, impaired glucose tolerance, or diabetes mellitus associated with exposure to whole-body irradiation [N29]. The association between whole-body irradiation and excess risk for diabetes has also been observed by other investigators [N14].

G. Summary

C239. No radiation-related effect on height has been observed in children living in the former Soviet Union at the time of the Chernobyl accident nor among those exposed as children to the atomic bombings. In childhood cancer patients, growth can be adversely affected by direct radiation damage and by malnutrition, other treatment modalities, the presence of residual tumour, and endocrine chronic radiation effects. Most clinical data are based on small and heterogeneous groups of patients treated in different ways at varying ages. The skeletal effects have also been assessed in a variety of ways, and it is not possible to give any estimates of late deterministic effects based on large-scale epidemiological data.

C240. Skeletal changes in children generally occur at doses exceeding fractionated doses of 20 Gy and include scoliosis, kyphosis, slipped femoral epiphyses, hypoplasia, growth retardation, and dental problems. However, even doses lower than 20 Gy can impair muscle and skeletal development in young children and infants. Absolute shortening of the long bone depends on the absorbed radiation dose and the age at the time of irradiation. Scoliosis and kyphosis are common after spinal or flank irradiation with doses of >20 Gy. Slipped femoral capital epiphysis does not occur below a dose of 20 Gy, and this late effect is more common in children under four years of age at the time of irradiation. A dose exceeding 20 Gy is required to arrest endochondral bone formation, and doses of 10–20 Gy cause the partial arrest of bone growth. There is little alteration in bone growth below a fractionated dose of 10 Gy to the bone. Exposure at less than six years of age and during puberty appears to have the greatest effect on growth retardation. Clearly, several factors—including radiation dose, radiation volume, age at irradiation, concomitant chemotherapy, and patient genetics (i.e. the expected size to which the patient might grow)—are all important variables in determining final growth.

XXII. URINARY SYSTEM

C241. The urinary system shows a wide range in radiosensitivity, with the kidney being the most sensitive organ, the bladder having an intermediate sensitivity and the urethra being more resistant. All available data on deterministic effects comes from high doses associated with radiotherapy and are complicated by chemotherapy and by the primary tumour.

A. Kidney

C242. The kidney is a relatively radiosensitive organ when compared with the other intra-abdominal organs and tissues. The kidney consists of three major cell groups of interest, those forming: *(a)* the glomerulus; *(b)* the renal tubules; and *(c)* the vascular supply system. The vascular system is

particularly important because about one fifth of the body's blood passes through the kidneys each minute. The arterioles supply a rich network about the glomeruli and the renal tubules. The epithelia of the tubules and the glomerular capsule are long-lived, composed of reverting post-mitotic cells that rarely divide. The nephrons themselves are unable to regenerate and are constantly being reduced in number with age and injury; however, if an injury is focal, the remaining nephrons may hypertrophy. Acute nephritis may occur in 6–13 months associated with proteinuria and hypertension. Chronic radiation nephritis (associated with protein casts in the urine) and hypertension usually has a latent period of 1.5–4 years [D21, P16].

C243. Cancer treatment predisposing to late renal injury and hypertension includes specific chemotherapeutic drugs (cisplatin, carboplatin, and ifosfamide), renal radiotherapy, and nephrectomy [J17]. The tolerance dose for the adult kidney appears to be approximately 23 Gy in five weeks to the parenchyma of both kidneys. Doses of 28 Gy to both kidneys in five weeks carry a high risk of severe radiation nephritis [L43]. In some studies, renal injury appears to be more severe in children, and they have limited tolerance for combined chemotherapy and radiotherapy. Reduced creatinine clearance has been reported by Mitus et al. [M42] in 18% of 108 children who had nephrectomy for malignant disease and received a dose of less than 12 Gy to the remaining kidney, and in 33% of those who received a dose of 12–24 Gy. Doses greater than 20 Gy can result in significant nephropathy [D21]. In a recent report from the German Registry for the Evaluation of Side Effects after Radiation in Childhood and Adolescence (RISK consortium), 126 patients who underwent radiotherapy to parts of the kidneys for various cancers were evaluated. All patients also received potentially nephrotoxic chemotherapy. Whole kidney volumes exposed to doses greater than 20 Gy (p = 0.031) or 30 Gy (p = 0.003) were associated with a greater risk for mild degrees of nephrotoxicity [B45].

C244. The effect of radiotherapy on the kidney has best been examined in the survivors of paediatric Wilms' tumour. Generally, studies have shown that the risk of renal insufficiency is higher among children receiving higher doses of radiation [B2, R25, S88]. A correlation between functional impairment and the dose to the kidneys was reported in a study of 100 children treated for Wilms' tumour. The incidence of impaired creatinine clearance was significantly higher for children receiving doses of more than 12 Gy to the remaining kidney, and all cases of overt renal failure occurred after a dose of more than 23 Gy [M42]. In a cohort of survivors of Wilms' tumour evaluated five years after receiving abdominal irradiation, the prevalence of renal insufficiency, as defined by hypertension, was approximately 7% [P16].

C245. Data from the National Wilms Tumor Study Group and the United States renal data system indicate that the 20-year cumulative incidence of end-stage renal disease in children with unilateral Wilms' tumour and Denys–Drash syndrome is 74%, 36% for those with WAGR (Wilms' tumour, aniridia, genitourinary abnormalities, mental retardation) syndrome, 7% for male patients with genitourinary anomalies and 0.6% for 5,347 patients with none of these conditions [B61]. For patients with bilateral Wilms' tumours, the incidence of end-stage renal disease is 50% for the Denys-Drash syndrome, 90% for WAGR syndrome, 25% for genitourinary anomaly and 12% for patients for all others [B61, H16]. End-stage renal disease in patients with WAGR syndrome and genitourinary anomalies tended to occur relatively late, and often during or after adolescence. Treatment for Wilms' tumour without flank or abdominal radiotherapy was not associated with significant nephrotoxicity in a study of 40 survivors of Wilms' tumour treated in England [B2].

C246. Radiation nephropathy has also been reported in children receiving bone marrow transplantation therapy [T6, V11]. After a dose of 12–14 Gy given in six–eight fractions over three–four days, there was haematuria and elevated creatinine. This is probably the result of both radiation and chemotherapy since long-term studies revealed abnormalities in less than 10% of patients receiving doses of only 12 Gy in six fractions to the whole body [B49]. The risk is related to the nephrotoxic

agents used and the total dose to the whole body, fractionation scheme and interfraction interval. More specifically, the radiation-associated risk rises when the total dose exceeds 12 Gy, or the individual fraction size is greater than 2 Gy, or the interval-fraction is less than four–six hours [A2, E12, H54, L20]. Obviously, if only one kidney is irradiated, there is substantially less clinical effect. Radiation of only one kidney did not cause radiation nephropathy in any of 13 patients receiving doses between 25 Gy in six weeks and 49 Gy in five weeks [K31].

B. Urethras and bladder

C247. The bladder is relatively more radioresistant than the kidneys, with the most resistant portion of the genitourinary system being the urethras. Survivors of childhood cancer treated with pelvic or CNS surgery, alkylator-containing chemotherapy including cyclophosphamide or ifosfamide, or pelvic radiotherapy may experience late effects in the urinary bladder including haemorrhagic cystitis, bladder fibrosis, neurogenic/dysfunctional bladder, and bladder cancer [R24]. Bladder dysfunction after irradiation for bladder and prostate sarcomas (median dose of 40 Gy) is reported to be 27% [R7]. This includes incontinence, urinary frequency and nocturia. It should be noted that most of these patients also received cyclophosphamide. Bladder damage, including haemorrhagic cystitis, fbrosis and occasional bladder shrinkage, can occur following chronic administration of alkylating agents such as cyclophosphamide [L23].

C248. In summary, late effects following irradiation of the kidney include nephritis, tissue necrosis and fibrosis, renal dysfunction and hypertension. Available data do not indicate that children are more susceptible to radiation-induced renal injury than adults. Radiation nephritis has been reported after fractionated doses of 14 Gy, and decreased creatinine clearance has occurred after doses around 12 Gy. The seemingly higher sensitivity of the kidney in children can probably be explained by the combination of radiotherapy and chemotherapy, which can enhance the side effects in the kidney [R60].

XXIII. IMMUNE FUNCTION

C249. The effects of radiation on the immune system have been extensively reviewed in the UNSCEAR 2006 Report (annex D) [U13]. The material presented here summarizes the information contained in that report and from newer data sources relative to potential differences that may result from exposure during adulthood versus that during childhood. Those studies that relate to the possible interaction of the immune system and autoimmune thyroiditis and cardiovascular disease are discussed elsewhere in this annex.

A. Atomic bombing survivors

C250. Immune mechanisms have consistently been associated with either resistance to or development of numerous tumours. Also, an association between non-cancer mortality and radiation dose has been observed among the survivors of the atomic bombings, cardiovascular, thyroid and liver

diseases being the more frequently reported causes. Kusunoki et al. [K56] have suggested that long-lasting inflammation may be considered an important contributory factor for the development of some of these diseases.

C251. While there are several studies showing increased changes in the immune system with increasing age, few studies have examined the effect of age at exposure. Several studies indicate an increased perturbation of the immune system in survivors exposed at older age compared to those exposed as children. Investigating T-cell immunity among the survivors of the atomic bombings, in an early paper Akiyama et al. [A11] looked at the responsiveness of peripheral blood lymphocytes to allogenic antigens in mixed lymphocyte cultures (MLCs) from 139 survivors. This study revealed a significant decrease in MLC response with increasing radiation dose and increasing age. The decline was most marked in the survivors who were >15 years old at the time of the initial exposure. These results were interpreted as an impaired thymic function as it affects the immune system.

C252. The numbers of peripheral blood lymphocytes belonging to different subsets were studied in 1,328 survivors of the atomic bombings using immunocytochemistry (fluorescent antibodies) [K55]. The number of CD5+ B-lymphocytes was significantly lower in those persons exposed to doses >1 Gy within the group exposed at the age of 30 or later. A similar tendency towards decreased numbers of CD4+, CD8+, and CD19+ cells was observed in these older survivors, although the differences were not statistically significant. These results suggest that ageing of the T-cell-related immune system is accelerated in people irradiated at advanced age. Due to the age-related decrease in thymic function, subjects who were older at the time of the bombings may have decreased functional capability of the immune system for recovery after radiation injury.

C253. The major histocompatibility complex (MHC) gene seems to be a particularly important genetic factor that can affect host immune responses. Significant differences in type 2 diabetes prevalence were found by Hayashi et al. [H35] between heavily exposed (those who received doses of >1.5 Gy) and low-dose/non-exposed survivors of the atomic bomb dropped on Hiroshima with different class II MHC DQA1 and DRB1 alleles. The prevalence was higher for heavily-exposed people who were less than 20 years old at the time of the bombings and who presented DQA1*0401 and DRB1*08 alleles or DQA1*0301 and DRB1*09. These results suggest that certain class II MHC genes regulate one or more components of the immune system related with the risk of diabetes development among the younger and more heavily-exposed survivors.

B. Chernobyl

C254. Studies relating to the immune system of those exposed as a consequence of the Chernobyl accident have yielded conflicting results and are often at variance with the results reported in survivors of the atomic bombings. Also, children evacuated from Pripyat did not have significant differences in immunological parameters from those of the control groups [B9, B8]. Children examined two years after the accident from Mogilev and Gomel did not show abnormalities in levels of T-lymphocytes, but showed a minor increase in B-lymphocytes [G3]. The UNSCEAR 2000 Report (annex J) [U10] pointed out that: *(a)* the levels of radiation that Chernobyl populations were exposed to had not been shown to affect the immune system in prior non-Chernobyl studies; *(b)* the findings of Chernobyl studies were not consistent with the known mechanisms and temporal effects of radiation on the immune system. The UNSCEAR 2000 Report concluded that immunological effects in the general population could not be associated with Chernobyl and, when observed, were likely due to other causes [U10].

C255. Titov et al. [T27] investigated the production of immunoglobulins in children living around the Chernobyl nuclear power plant. They found a decrease in B-cell numbers, a transient decrease of immunoglobulin M (IgM) and immunoglobulin G (IgG) and an increase of immunoglobulin A (IgA) levels (both in serum and saliva) during the first months following the accident. Over a six-year period, children living in the contaminated areas exhibited increasing production of IgG and IgM.

C256. Chernyshov et al. [C15] examined peripheral blood lymphocyte subsets in children living around the Chernobyl nuclear power plant eight years after the accident. Differences were found in children who had recurrent respiratory disease. Children with this disease from the contaminated areas had higher levels of CD3– CD56+ CD16+ natural killer (NK) cells compared to children with recurrent respiratory disease living in non-contaminated areas. Healthy children without recurrent respiratory disease from contaminated areas had the same mean values for lymphocyte subsets as healthy children from non-contaminated areas.

C257. Koike et al. [K39] compared NK cell activity from children living in Gomel, a highly contaminated area, with that of children living in non-contaminated areas. While children living in non-contaminated areas exhibited a narrow range of NK cell cytotoxicity percentages, a wider range of NK cell cytotoxicity percentages was found in children from contaminated areas. NK cell cytotoxicity of these children was correlated with neither NK cell number nor with the amount of internal contamination by ^{137}Cs. The authors interpreted these findings as a loss of normal regulatory mechanism to maintain a correlation between the cytotoxic activity and the number of NK cells. This seems to be a rather speculative conclusion for this ecological study. Even if such dysregulation exists, the Committee concluded it cannot be attributed to ionizing radiation. There are few if any immunological studies of residents of the contaminated areas that have shown a significant difference in immune function as a result of age at exposure.

C. Techa River

C258. About 30,000 inhabitants living near the Techa River were exposed, predominantly during the early 1950s, to external gamma radiation from fission products associated with discharges of high and medium level wastes from the Mayak nuclear facility into the river. In the early period, cases of chronic radiation sickness (940 people in total, including 242 under the age of 19 years) were diagnosed. The diagnosis was based on occurrence of changes in blood parameters (leucopoenia, thrombocytopenia, granulocytopoenia); nervous system disorders; ostealgia; cardiovascular syndrome; and changes in immunity (inhibition of innate immunity, autoimmunity). The subjects who were initially exposed in utero or at one–two years of age showed the greatest changes in the immune system parameters. Haematopoietic disturbances developed almost at the same time as the signs of immune insufficiency [K47]. Complete recovery from the haematological and neurological effects, respectively, occurred within 13–16 and 14–20 years following the beginning of exposure. The duration of the disease was presumably dependent on the patient age at exposure. A specific feature of chronic radiation syndrome in children was the prevalence of neurological disorders while in adults it was haemopoiesis that was most frequently recorded. Recovery processes developed more slowly in children and teenagers who received the highest doses.

D. Radiotherapy

C259. Blomgren et al. [B33] studied the lymphocyte count and serum immunoglobulin level in children irradiated for treatment of either Wilms' tumour or non-Hodgkin's lymphoma. Doses to the tumours were from 7 to 32 Gy, and all children received chemotherapy. With the exception of a slightly decreased serum level of immunoglobulin E (IgE) in patients treated for lymphoma, there was no difference from healthy controls in immunoglobulin levels, lymphocyte count, or frequency of rosette-forming cells.

C260. A long-term deficit in total CD4+ T-cell counts after radiation treatment for Hodgkin's disease was reported by Posner et al. [P38]. Watanabe et al. [W15] found a marked depletion in both CD4+ and CD8+ naive T-cell counts in patients who received mediastinal irradiation for Hodgkin's disease, which persisted up to 30 years after completion of treatment. In contrast, CD4+ and CD8+ memory T-cell subsets and total CD8+ T-cells recovered to normal or above normal levels by five years post-treatment with different kinetics (early expansion of CD8+ memory T-cells versus gradual recovery of the others). Thus, the long-term deficit in total CD4+ T-cell counts in irradiated patients with Hodgkin's disease was due to specific depletion of naive T-cell subset. Similarly, total CD8+ T-cell counts return to normal values within five years, particularly because CD8+ memory T-cells expand to higher than normal levels. As the thymus is the main source of naive T-cells, these findings suggest that mediastinal irradiation results in a long-term depletion of the CD4+ naive cell pool, probably because of thymus impairment. This dysregulation of T-cell subset homeostasis may explain the altered T-cell function observed in patients who were treated for Hodgkin's disease, including the poor response to immunization after treatment. An extrathymic (peripheral) expansion of mature T-cells may partially compensate for the loss of thymic-derived T-cells, but this expansion is restricted primarily to the memory population, thus resulting in a selective expansion of memory T-cells, while the naive T-cell number remains low [W15].

C261. Although the immune system appears to recover from the effects of active chemotherapy and irradiation, there is some evidence that lymphoid subsets may not always normalize. Innate immunity, thymopoiesis, and DNA damage responses to radiation were shown to be abnormal in survivors of childhood leukaemia [S43]. Antibody levels resulting from previous vaccinations are also reduced in patients who have completed chemotherapy for ALL for at least one year [A29, L22].

C262. In summary, there is only sparse literature concerning potential differences in immune function following exposure in adulthood and childhood. The data from the survivors of the atomic bombings suggest that some effects are greater during exposure at older ages. The data from those exposed as a consequence of the Chernobyl accident generally do not compare adults and children and, when age at exposure is considered, the results are often contradictory. The radiotherapy data are complicated by concurrent disease and chemotherapy. Overall, there does not appear to be a major or clinically significant difference regarding age at exposure.

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This publication contains:

VOLUME II Scientific findings on effects of radiation exposure of children

Scientific Annex with appendices
Annex B.: Effects of radiation exposure of children

Appendix A. Dosimetry
Appendix B. Malignant neoplasms
Appendix C. Deterministic effects

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.

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