

# **RADIATION**

**VOLUME 100 D**  
**A REVIEW OF HUMAN CARCINOGENS**

This publication represents the views and expert  
opinions of an IARC Working Group on the  
Evaluation of Carcinogenic Risks to Humans,  
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**IARC MONOGRAPHS**  
**ON THE EVALUATION**  
**OF CARCINOGENIC RISKS**  
**TO HUMANS**

**RADIOACTIVE MATERIAL**

# X- AND $\gamma$ -RADIATION

X- and  $\gamma$ -radiation were considered by a previous IARC Working Group in 1999 ([IARC, 2000](#)). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

## 1. Exposure Data

### 1.1 Physical properties

Radiation sources can be either external to the body, such as medical X-rays, or through deposition on the Earth's surface, or internal. Internal exposure can result from the ingestion of contaminated foods, inhalation, dermal absorption, or injection of radionuclides. The effects of radiation are directly related to the dose that an organ receives, and any differences between the effects of external and internal sources is in large part related to the distribution of dose within and among body organs ([IARC, 2001](#)).

The activity of a radionuclide is defined as the number of nuclear transformations occurring per unit of time. The standard unit is the becquerel (Bq), which is 1 disintegration per second. Historically, the curie (Ci) ( $1 \text{ Ci} = 3.7 \times 10^{10} \text{ Bq}$ ) was also used. The energy of radiation emitted during the nuclear transformation is normally measured in units of electron-volts (eV), as this is a small unit, it is commonly represented as kilo eV (keV) (1000 eV) or mega eV (MeV) ( $10^6 \text{ eV}$ ).

#### 1.1.1 X- and $\gamma$ -rays

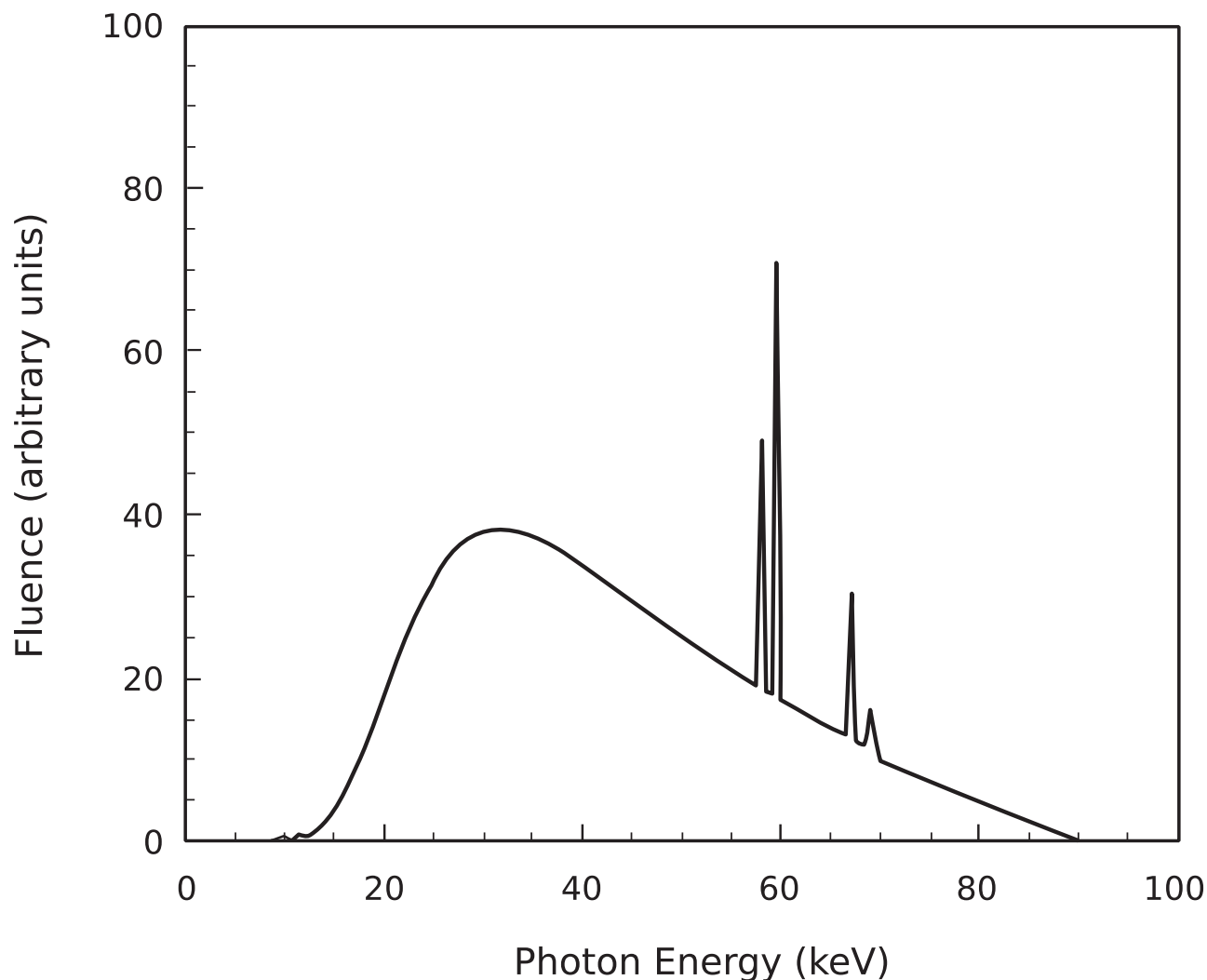
X- and  $\gamma$ -rays are both electromagnetic radiations distinguished mainly by their origin. X-rays are photons emitted from the electron shells surrounding the atomic nucleus or during the slowing down of electrons or other charged particles. The term  $\gamma$ -rays is usually applied to radiation originating from the atomic nucleus, and from particle annihilation. The energy ranges of X- and  $\gamma$ -rays overlap considerably with X-rays having energies upwards from a few tens of eV (the shortest ultraviolet wavelengths), and  $\gamma$ -ray energies extending up to a few tens of MeV.

##### (a) X-rays

Characteristic X-rays are emitted during transitions of electrons in excited atomic shells to lower energy states: they have line spectra characteristic of the corresponding element. A continuous X-ray spectrum is produced when charged particles, normally electrons, are decelerated or deflected (in an electric or magnetic field such as that close to a nucleus). This is known as 'bremsstrahlung' from the German for 'braking radiation'.

For example, X-ray tubes generate bremsstrahlung and characteristic X-rays (see Fig. 1.1). X-rays for medical exposures are classified,

**Fig. 1.1 Bremsstrahlung X-ray spectrum from a tungsten target at 90 kVp with 1 mm aluminium filtration. The peaks between 57 and 70 keV are due to characteristic X-rays of tungsten**



Adapted from [IPEM \(1997\)](#)

according to their kVp (the peak applied voltage for an exposure) from ultrasoft (5–20 kVp), to very hard (> 250 kVp). Extremely hard X-rays are generated with betatrons, synchrotrons, and linear accelerators in the MeV range.

X-rays are used in many medical and technical applications. The most common are diagnostic X-ray examinations of the human body, and the analysis of materials. In X-ray therapy, the biological effect of X-rays is used to destroy malignant tissue. It is applied mainly to treat cancer patients, when high doses are delivered to

a limited area of the body, with restricted irradiation of adjacent tissue ([IARC, 2000](#)).

#### (b) $\gamma$ -Rays

$\gamma$ -Ray photons are usually emitted during transformations in atomic nuclei. They have widely different energies in the range of 0.01–17.6 MeV. Such radiation can also be produced by the decay of elementary particles, the annihilation of electron–positron pairs, and the acceleration and deceleration of high-energy electrons in

cosmic magnetic fields or in elementary particle accelerators.

### 1.1.2 Neutrons

Neutrons are uncharged particles which, along with protons, form the nuclei of atoms. Whereas X- and  $\gamma$ -rays interact primarily with orbital electrons, neutrons interact with the nucleus of atoms. Neutrons are emitted from nuclei in several ways, in the interaction of high-energy cosmic radiation with the Earth's atmosphere, and in the fission or fusion of nuclei. Fission neutrons have energies up to several MeV, and fusion neutrons approximately 10 MeV. Neutrons can also be produced by the collision of energetic charged particles (e.g.  $\alpha$ -particles, ions from an accelerator) with a suitable target material. The neutrons emitted are used for radiography and radiotherapy.

### 1.1.3 $\alpha$ -particles

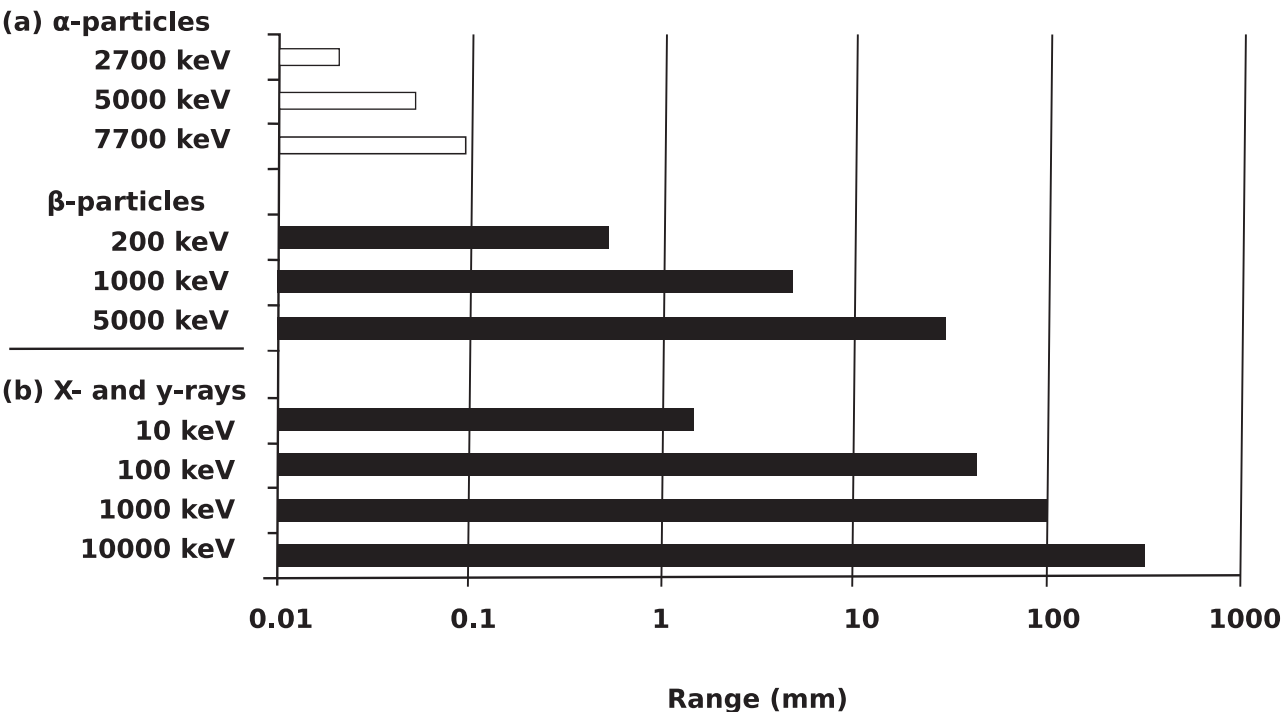
$\alpha$ -particles are emitted from the nucleus of a radionuclide and consist of two protons, giving them a +2 charge, and two neutrons bound together, resulting in an atomic mass of 4, so they are, in effect, high energy helium-4 ( $^4\text{He}$ ) atoms. The energy of  $\alpha$ -particles typically varies between 4 and 8 MeV, the energy increasing with the mass of the parent nucleus which emitted it. Consequently, emissions from any particular radionuclide are mono-energetic and have a characteristic energy. Because the energy and mass of an  $\alpha$ -particle are significant on an atomic scale, the emission of an  $\alpha$ -particle causes the parent/daughter nucleus to recoil. This  $\alpha$ -recoil effect represents a small, but not negligible, percentage (~2%) of the overall energy released during a decay.  $\alpha$ -particles rapidly lose energy and acquire electrons from the surrounding environment to become inert Helium-4 (their typical lifetime is a few picoseconds).

### 1.1.4 $\beta$ -Particles

$\beta$ -Particles are emitted from the nucleus of a radionuclide and consist of electrons or anti-electrons, these electrons have a mass of approximately 0.00055 of an atomic mass unit.  $\beta^-$  (negatron) radiation is the result of the conversion of a neutron into a proton, a negatively charged electron being emitted as a result.  $\beta^+$  (positron) radiation is a result of the opposite conversion, a proton is converted to a neutron and an anti-electron, the positively charged equivalent of an electron, known as a positron, is emitted.  $\beta$  radiation also results in the production of a third body, the first two bodies being the daughter nuclide and the electron/positron. The third body is an anti-neutrino in the case of  $\beta^-$  emission and a neutrino in the case of  $\beta^+$  emission. Because the energy from  $\beta$  radiation is shared between the emitted particle and the third body, the energy of  $\beta$ -particles varies, even when the parent radionuclide is the same (i.e. their energy is not characteristic). The continuum of energies for a  $\beta$ -particle goes from a lower energy limit of zero to an upper limit set by the maximum available energy from the transmutation of the parent into the daughter (the reaction energy 'Q', typically around 1 MeV). Many  $\beta$  emitters also emit  $\gamma$ -rays, those that do not are known as 'pure'  $\beta$  emitters. High-energy  $\beta$ -particles can produce bremsstrahlung. Emitted  $\beta^-$  particles quickly (in a few tens of picoseconds) lose their excess energy, and are then indistinguishable from other electrons in the environment. As positrons are anti-electrons, they are normally rapidly annihilated after they are emitted as a result of collisions with electrons in the surrounding environment, which are also annihilated. The released energy manifests itself as two characteristic 0.511 MeV  $\gamma$ -rays.

For the sake of clarity,  $\beta^-$  particles will henceforth be referred to as  $\beta$ -particles and  $\beta^+$  particles as positrons.

**Fig. 1.2 (a) Depth of penetration of  $\alpha$  and  $\beta$ -particles in tissue, for selected energy values; (b) depth of penetration of X- and  $\gamma$ -rays in tissue in which 50% of the radiation energy is lost**



From [IARC \(2000\)](#)

## 1.2 Interactions with matter

Different radiation types penetrate matter to a different extent and in different ways (Fig. 1.2). X- and  $\gamma$ -rays, especially those with high energy, can penetrate matter easily, while  $\alpha$ - and  $\beta$ -particles are much less penetrating.

Ultimately, virtually all the radiation energy from ionizing radiation is transferred to electrons, which lose their energy by ionizing the irradiated medium.

For radiation protection purposes, the International Committee for Radiation Protection ([ICRP, 2007](#)) introduced radiation-weighting factors to take into account the fact the various radiation types have different relative biological effects (RBE). The primary dosimetric quantity unit of dose taking radiation-weighting factors into account is the sievert (Sv), which should be used with caution (note that values of

radiation-weighting factors have changed over the years). For epidemiological purposes, the basic physics quantity of the gray (Gy, i.e. joule per kilogram) should be used where possible. For X- and  $\gamma$ -rays, the radiation-weighting factor has always been 1, and values for individual organs could therefore equally well be expressed in terms of absorbed dose in grays or equivalent dose in sieverts.

Doses may be expressed in terms of effective (whole-body equivalent) dose ([ICRP, 2007](#)). Effective doses should only be used for radiation protection and regulatory purposes, and with caution for general comparisons.

### 1.2.1 X- and $\gamma$ -rays

The interaction of X- and  $\gamma$ -rays with matter is described by the photoelectric effect, Compton scattering, and pair production. Photoelectric

absorption dominates at low energies followed by Compton scattering, and then pair production as the energy increases. Absorption of very high energy photons results in nuclear disintegration. The intensity of X- and  $\gamma$ -rays generally decreases with depth. The ability to penetrate matter increases with increasing energy and decreases with increasing atomic number of the absorbing material.

The above processes (apart from photodisintegration) all result in the production of electrons (or their anti-matter equivalent, positrons) and lower energy X-rays, which undergo further absorption and scattering. The energy of the initial photon is thus transferred to electrons that create ionization leading to significant chemical and biological effects such as degradation of DNA.

### 1.2.2 Neutrons

Neutrons are captured or scattered by matter. The likelihood of interactions occurring between neutrons and atoms of a material (i.e. the neutron cross-section) is unique for each nuclide, and the nature of these interactions are complex. Thermal neutron-capture cross-sections are generally much greater than those at higher energies: in nuclear power reactors, neutron energies must be reduced by collisions with a moderating medium (usually water or graphite) to thermal energies where the cross-sections allow a chain reaction to proceed.

The mean free path of neutrons in tissues varies with their energy from a fraction of, to several tens of centimetres. In tissue, neutrons interact with hydrogen nuclei. The recoiling nuclei (low-energy proton) form densely ionizing tracks, with a high linear energy transfer (LET) which are efficient in producing biological injury. The [ICRP \(2007\)](#) has therefore defined radiation-weighting factors for estimating the risks associated with exposure to neutrons, which are larger

than those for X- or  $\gamma$ -rays for the same tissue dose.

In tissue, neutrons with energy  $> 50$  MeV interact mainly with nuclei such as C, N, O, and Ca, producing many lower energy particles such as  $\alpha$ -particles, protons, and other neutrons with a broad distribution of LET. Exposure to high-energy neutrons is thus quite distinct from exposure to low-energy neutrons. Neutrons as they interact with matter generate  $\gamma$ -rays.

### 1.2.3 $\alpha$ and $\beta$ Radiation

Charged particle radiation, such as  $\alpha$  and  $\beta$  radiation, is not very penetrating, the maximum range of an  $\alpha$ -particle in tissue is less than 100 microns and for  $\beta$ -particles only about a centimetre. This means that, for external exposures, these types of radiation are often a much lower or, in the case of  $\alpha$ -particles, insignificant radiological hazard when compared to highly penetrating radiation such as X- and  $\gamma$ -rays. However, when  $\alpha$ - and  $\beta$ -particle emitters become internally deposited within living tissues, their radiations deposit most, if not all, of their energy within that tissue.  $\alpha$ -particles in particular are relatively massive, doubly charged, and very densely ionizing. Consequently, they have a substantially enhanced effect on living tissues per unit energy, compared to X- and  $\gamma$ -rays, and  $\beta$ -particles. There is also some evidence, from radionuclides such as tritium, that  $\beta$ -particle radiation may have a slightly greater radiological effect per unit energy than X- and  $\gamma$ -rays.

Neutrinos and anti-neutrinos interact very weakly with matter, therefore present no radiological hazard, and will not be considered further.

### 1.2.4 Others

Other types of ionizing radiation that interact with matter include cosmic rays, protons, muons, and heavy ions. As for the other forms of radiation described above, these will all ultimately produce ionizing electrons.

### 1.2.5 Energy loss process

As described above, the indirectly ionizing radiations all interact to produce ionizing particles; electrons, protons,  $\alpha$ -particles, and heavy ions.

All ionizing particles interact with the atomic electrons of the medium through which they pass to produce secondary electrons with a range of energies. In turn, these electrons create more electrons (mainly low energy) until all electrons are completely slowed down in the medium. At the end of their tracks, electrons of less than about 500 eV form clusters of ionization. An analysis of low-energy electron track structure in liquid water is given by [Wilson et al. \(2004\)](#).

### 1.2.6 Radionuclides, internally deposited

For the purposes of this *IARC Monograph*, internally deposited radionuclides are defined as radionuclides that have been taken into the body (encapsulated radionuclides entering the body, as in brachytherapy, are not discussed in this *Monograph* because they are considered as external exposure). These radionuclides may emit any form of radiation, but in practice it is those that emit charged particles,  $\alpha$  ( $\alpha$ ) and  $\beta$  ( $\beta^-$ )/( $\beta^+$ ) radiation, that tend to be the most radiologically significant.

In theory, any radionuclide could become internally deposited but only a subset of radionuclides which are relatively available from nuclear weapons tests, the Chernobyl accident, or from radiotherapy and radiodiagnosis, and known to have the potential to affect cancer risks are considered here. To understand the occurrence of radionuclides within the environment and their potential to result in significant individual exposures, it is necessary to have some knowledge of their physical and chemical properties as well as their abundance—this information has been collated from various sources: The CRC ‘Handbook of Chemistry

and Physics’ ([Lide, 2005–2006](#)), World Nuclear Association Reference Documents ‘Radiological and Chemical Fact Sheets to Support Health Risk Analyses for Contaminated Areas’ ([Argonne National Laboratory, 2007](#)) and [ICRP \(1983, 2008\)](#). The information provided is not intended to be definitive or comprehensive.

#### (a) Tritium

Tritium ( $^3\text{H}$ ) is an isotope of the hydrogen atom.  $^3\text{H}$  is naturally produced by interactions between cosmic radiation and nitrogen and oxygen in the atmosphere at a rate of approximately 0.4 kg/year. However, environmental concentrations of naturally occurring  $^3\text{H}$  are low (the total steady-state global inventory from this route of production is  $\sim 7$  kg) due to global dispersal, and because they are constantly being depleted by radioactive decay as a result of its comparatively short half-life.  $^3\text{H}$  gas will tend to bond with any available moisture to form tritiated water, which, from a biochemical perspective, behaves like any other water in the environment.

$^3\text{H}$  is a pure, low energy,  $\beta$  emitter that has a half-life of 12.35 years, it decays to helium-3, which is stable.

Although  $^3\text{H}$  is not a particularly abundant fission product (uranium-235 fission yield is 0.01%) and the atmospheric testing of nuclear weapons has largely ceased, the quantity of  $^3\text{H}$  in the environment from previous tests still exceeds that from natural cosmogenic production. However, once again due to global dispersal of this material, concentrations involved are low.

$^3\text{H}$  is a strategic material in the production of nuclear weapons; and because of the nature of this application, specific information on the amounts of  $^3\text{H}$  generated and used for this purpose are difficult to obtain. Production of  $^3\text{H}$  for weapon purposes involves neutron bombardment of lithium-6 in nuclear reactors. The  $^6\text{Li}$  atom, with three protons and three neutrons and the captured neutron combine to form a lithium-7 atom, with three protons and four neutrons,

which instantaneously splits to an atom of  $^3\text{H}$  (one proton and two neutrons) and one atom of  $^4\text{He}$  (two protons and two neutrons). The United States of America is thought to have produced over 200 kg of  $^3\text{H}$  for military purposes but much of this has now decayed to  $^3\text{He}$ , and only  $\sim 75$  kg remains ([Argonne National Laboratory, 2007](#)).

Heavy water ( $^2\text{H}_2\text{O}$ ) moderated reactors, such as the CANada Deuterium Uranium (CANDU) designs, produce substantial amounts of  $^3\text{H}$  as a by-product, due to neutron capture in the moderator.  $^3\text{H}$  is routinely removed from the heavy water used in CANDU reactors in Canada, and approximately 1–2 kg are recovered per year.

$^3\text{H}$  can be produced in a particle accelerator by bombarding  $^3\text{He}$  with neutrons. In addition,  $^3\text{H}$  is used in the manufacture of radionuclide-labelled materials for application in medicine, research and industry (and can be released from such manufacturing plants), and in the use and disposal of these materials.  $^3\text{H}$  has also been used in luminous paint used in some wristwatches and compasses, and in emergency exit signs, and gun-sights ([HPA, 2007](#)).

#### (b) Phosphorus-32

Phosphorus is an abundant, naturally occurring, reactive non-metal, and is never found in its elemental form in the environment. Compounds containing phosphorus are essential to life and are involved in many metabolic processes. Only one phosphorus isotope is not radioactive,  $^{31}\text{P}$ , and this is the only isotope found in nature.

$^{32}\text{P}$  is a man-made isotope, generally used for medical purposes. It is produced by neutron bombardment of sulfur-32 ( $^{32}\text{S}$ , this involves a 'n,p' reaction, where a neutron is captured and a proton is ejected), is a pure  $\beta$  particle emitter with a half-life of 14.29 days, and decays back to  $^{32}\text{S}$ , which is stable. Because of its short radioactive half-life  $^{32}\text{P}$  must be used relatively quickly after it is produced, and it cannot be stockpiled.

#### (c) Strontium-90

Strontium is a relatively abundant, chemically reactive metal, which oxidizes readily. Naturally occurring strontium has four stable isotopes  $^{84}\text{Sr}$ ,  $^{86}\text{Sr}$ ,  $^{87}\text{Sr}$ , and  $^{88}\text{Sr}$ . The chemistry of strontium has similarities to that of calcium.

$^{90}\text{Sr}$  is a man-made isotope that is a pure  $\beta$  particle emitter with a half-life of 29.12 years. It decays to Yttrium-90, which is a short-lived high energy  $\beta$  particle emitter, which greatly increases the radiological effect of  $^{90}\text{Sr}$  exposures.  $^{90}\text{Sr}$  is mostly produced as a result of nuclear fission, either in nuclear weapons or batteries/reactors, and is one of the most commonly occurring fission products ( $^{235}\text{U}$  fission yield is  $\sim 6\%$ ). Its relatively long half-life results in it being persistent in the environment if it is released. Levels of  $^{90}\text{Sr}$  in surface soil due to fallout from atmospheric nuclear weapons tests are around 3.7 Bq/kg on average.

#### (d) Iodine-131

Iodine is a halogen, it is both volatile and reactive, and is not found in its elemental form in nature but rather, most commonly, as iodide ions. Only one isotope of iodine is stable,  $^{127}\text{I}$ . Iodine is an essential element and the human body contains about 20 mg mainly in the thyroid gland.

$^{131}\text{I}$  is a man-made isotope that is a  $\beta$  and  $\gamma$  emitter with a short half-life of 8.04 days. It decays to xenon-131, a small percentage to its metastable state, which is a  $\gamma$  emitter, but mostly ( $\sim 99\%$ ) to its ground state, which is stable.

As it is a common fission product ( $^{235}\text{U}$  fission yield is  $\sim 3\%$ ),  $^{131}\text{I}$  is produced by nuclear weapons and in nuclear batteries/reactors. Because it is volatile,  $^{131}\text{I}$  can more readily escape from containment than other fission products, but its relatively short half-life means it does not persist in the environment for long periods.

$^{131}\text{I}$  is also produced via neutron bombardment of tellurium-130 for medical diagnostic and

treatment purposes. Because of its short half-life, it cannot be stockpiled for this purpose. Global demand for  $^{131}\text{I}$  for medical purposes is approximately 600 tera (T)Bq ( $600 \times 10^{12}$  Bq).

#### (e) *Caesium-137*

Caesium is a rare naturally occurring, highly reactive alkali metal with only one stable isotope  $^{133}\text{Cs}$ . The chemistry of caesium has some similarities to that of potassium.

$^{137}\text{Cs}$  is a man-made isotope that is a  $\beta$  and  $\gamma$  emitter with a half life of 30 years. It decays to barium-137, mostly (~95%) to its metastable state, which is a short-lived energetic gamma emitter, but also to its ground state, which is stable.  $^{137}\text{Cs}$  is mostly produced as a result of nuclear fission, either in nuclear weapons or batteries/reactors, and is one of the most commonly occurring fission products ( $^{235}\text{U}$  fission yield is ~6%). Its relatively long half-life results in it being persistent in the environment if released. Levels of  $^{137}\text{Cs}$  in surface soil due to fallout from atmospheric nuclear weapons tests are around 15 Bq/kg on average.

#### (f) *Radon*

Radon is a noble (chemically inert) gas mostly produced through the radioactive decay of environmental uranium/thorium and their radioactive daughters. All of the isotopes of radon are radioactive:  $^{222}\text{Rn}$  is the isotope with the longest radioactive half-life, and its naturally abundant parent is  $^{226}\text{Ra}$ , itself a daughter of  $^{238}\text{U}$  (see Fig. 1.3),  $^{222}\text{Rn}$  is the most prevalent in the environment.  $^{220}\text{Rn}$  (also known as thoron) is the only other isotope of radon that is found in any significant quantity in nature. That isotope and its radioactive daughters typically contribute less than 20% of the total dose from radon, and its contribution is often not included in radon exposure assessments. Henceforth, the term radon should be taken as referring to Radon-222 unless otherwise indicated.

$^{222}\text{Rn}$  is an  $\alpha$ -particle emitter with a short half-life of 3.82 days, it decays to polonium-218, which is also an  $\alpha$ -emitter, and has in turn further short-lived radioactive daughter products (see Fig. 1.3). The presence of this decay chain greatly increases the overall radiological significance of this isotope. Although  $^{222}\text{Rn}$  is a gas, its short-lived progeny are electrically charged particles that can become attached to environmental dust particles in the air, the existence and extent of this 'attached' fraction has a considerable impact on dose to the upper airways of the lung.

Like its parent radionuclides (see Fig. 1.3),  $^{222}\text{Rn}$  is omnipresent in nature but levels vary because certain types of rocks and soils (e.g. granite, phosphate rocks, and alum shales) contain more of its parents than others ([Appleton, 2007](#)).  $^{222}\text{Rn}$  rapidly disperses into the troposphere when it escapes into the free atmosphere, i.e. outside of enclosed spaces. Consequently, concentrations of  $^{222}\text{Rn}$  in breathing air in open spaces is relatively low, typically around 10 Bq/m<sup>3</sup>.

$^{222}\text{Rn}$  can also be found in building materials albeit at low concentrations ([de Jong et al., 2006](#)). Building materials such as concrete, wallboard, brick and tile usually have concentrations similar to those of major rock types used for their manufacture, and levels also vary according to the type of rock used for construction ([Mustonen, 1984](#); [Ackers et al., 1985](#)). Although building materials generally contribute only a very small percentage of the indoor air  $^{222}\text{Rn}$  concentrations, in a few areas, concrete, blocks, or wallboard incorporating radioactive shale or waste products from uranium mining can make an important contribution to the indoor  $^{222}\text{Rn}$  levels ([Man & Yeung, 1998](#); [Åkerblom et al., 2005](#)).

#### (g) *Radium*

Radium is a naturally occurring rare earth metal. Ubiquitous in the environment, in small quantities, it is found in soils, uranium/thorium ores (e.g. pitchblende), minerals, ground water, and seawater, because the common radium

**Fig. 1.3 Uranium-238 decay chain**

| Radionuclide       | Half-life           |
|--------------------|---------------------|
| <b>Uranium-238</b> | 4,468,000,000 years |
| ↓ α-particle       |                     |
| Thorium-234        | 24.1 days           |
| ↓ β-particle       |                     |
| Protactinium-234m  | 1.17 minutes        |
| ↓ β-particle       |                     |
| Uranium-234        | 2,444,500 years     |
| ↓ α-particle       |                     |
| Thorium-230        | 75,400 years        |
| ↓ α-particle       |                     |
| <b>Radium-226</b>  | 1,600 years         |
| ↓ α-particle       |                     |
| <b>Radon-222</b>   | 3.82 days           |
| ↓ α-particle       |                     |
| Polonium-218       | 3.11 minutes        |
| ↓ α-particle       |                     |
| Lead-214           | 26.8 minutes        |
| ↓ β-particle       |                     |
| Bismuth-214        | 19.9 minutes        |
| ↓ β-particle       |                     |
| Polonium-214       | 0.000163 seconds    |
| ↓ α-particle       |                     |
| Lead-210           | 22.3 years          |
| ↓ β-particle       |                     |
| Bismuth-210        | 5.01 days           |
| ↓ β-particle       |                     |
| Polonium-210       | 138 days            |
| ↓ α-particle       |                     |
| <b>Lead-206</b>    | <b>Stable</b>       |

isotopes are products of the main uranium/thorium decay chains. All the isotopes of radium are radioactive,  $^{226}\text{Ra}$  has the longest half-life, and therefore is the predominant isotope found in nature.

$^{226}\text{Ra}$  is an α-particle emitter with a half-life of 1600 years, and decays to  $^{222}\text{Rn}$ , which is also an α-particle emitter.

$^{228}\text{Ra}$  is a β and gamma emitter with a half-life of 5.75 years, and decays to actinium-228, which is a β-particle and gamma emitter.

$^{226}\text{Ra}$  concentrations in soil vary considerably, typically between 10–50 Bq/kg, with approximately 25 Bq/kg considered to be average ([UNSCEAR, 1982](#)), concentration in seawater is 4–5 orders of magnitude lower than this.

$^{223}\text{Ra}$  and  $^{224}\text{Ra}$  are both α-particle emitters with a half-life of 11.43 days and 3.6 days, respectively.  $^{224}\text{Ra}$  can be found in ground water.

#### (h) Thorium-232

Thorium is a naturally occurring dense metal that is usually found in minerals such as monazite, thorite, and thorianite. Thorium is thought to be about three times more abundant than uranium in the environment. All of the isotopes of thorium are radioactive, therefore the isotope with the longest radioactive half-life,  $^{232}\text{Th}$ , is by far the most prevalent in nature.

$^{232}\text{Th}$  is an α-particle emitter with a half-life of  $1.41 \times 10^{10}$  years, and decays to  $^{228}\text{Ra}$ , which is a β-particle emitter.

$^{230}\text{Th}$  is present in soil and ores with  $^{232}\text{Th}$ .  $^{230}\text{Th}$  is a decay product of  $^{234}\text{U}$ .  $^{230}\text{Th}$  is an α-particle emitter with a half-life of  $7.54 \times 10^4$  years.

#### (i) Uranium

Uranium is a naturally occurring very dense metal, which is widespread in the environment, including seawater, at low concentrations. All of the isotopes of uranium are radioactive, therefore the isotopes with the longest radioactive half-lives are the most prevalent in nature. Environmental uranium is made up of three

isotopes:  $^{234}\text{U}$ ,  $^{235}\text{U}$ , and  $^{238}\text{U}$ .  $^{238}\text{U}$  is predominant by mass at 99.284%;  $^{235}\text{U}$ , accounting for 0.711%; and,  $^{234}\text{U}$  only 0.005% (it should be noted that natural isotopic composition can vary slightly).

$^{234}\text{U}$  is an  $\alpha$ -particle emitter with a half-life of  $2.445 \times 10^5$  years, and decays to  $^{230}\text{Th}$ , which is also an  $\alpha$ -particle emitter.

$^{235}\text{U}$  is an  $\alpha$ -particle and gamma emitter with a half-life of  $7.03 \times 10^8$  years, and decays to  $^{231}\text{Th}$ , which is a  $\beta$ -particle and gamma emitter.

$^{238}\text{U}$  is an  $\alpha$ -particle emitter with a half-life of  $4.468 \times 10^9$  years, and decays to  $^{234}\text{Th}$ , which is a  $\beta$ -particle and gamma emitter.

Of the three naturally occurring uranium isotopes, only  $^{235}\text{U}$  has the capacity to support sustained nuclear fission through a chain reaction. Hence, uranium is commonly classified into types depending on the percentage of  $^{235}\text{U}$  it contains, as compared to that in naturally occurring uranium ores (0.711% by mass). Natural uranium, as its name would suggest, has the same percentage of  $^{235}\text{U}$  as uranium ores. Depleted uranium, which is a common by-product of the nuclear fuel cycle, has a lower percentage of  $^{235}\text{U}$  than natural uranium. Enriched uranium typically contains about 2.5–3.5% by mass of  $^{235}\text{U}$ , and is widely produced on an industrial scale for use in the manufacture of power reactor fuel assemblies. Highly enriched uranium is almost all  $^{235}\text{U}$ , greater than 80% by mass, and is produced in much more limited quantities than normal enriched uranium for use in nuclear propulsion reactor systems, and for nuclear weapons.

Approximately 50000 tonnes of natural uranium are mined annually, about more than half of this amount is produced by mines in Kazakhstan, Canada, and Australia with the remainder coming from mines in many countries throughout the world.

World stockpiles of depleted uranium are currently more than 1 million tonnes, with over 50000 tonnes being added per year.

Approximately 60000 tonnes of enriched uranium is produced for nuclear fuel production

purposes annually by facilities in the USA, Canada, France, the Russian Federation, and the United Kingdom.

A total of over 2000 tonnes of highly enriched uranium are thought to have been produced for military purposes ([World Nuclear Association, 2009](#)).

#### (j) *Plutonium*

Plutonium is a man-made (predominantly), very dense, rare earth metal, which has a complex chemistry. All the isotopes of plutonium are radioactive, the most commonly occurring isotopes are the  $\alpha$ -particle emitters  $^{239}\text{Pu}$ ,  $^{240}\text{Pu}$  and, increasingly, the  $\beta$ -particle emitter,  $^{241}\text{Pu}$ . Shortly after its discovery,  $^{239}\text{Pu}$  was identified as a strategic material for nuclear weapons production, because it has the capacity (greater than that of  $^{235}\text{U}$ ) to support sustained nuclear fission. Most of the plutonium now in existence has been man-made as a result of nuclear weapons and power production programmes. However, small quantities of plutonium have also been found at the site of the so-called ‘natural reactor’ at Oklo in Gabon West Africa.  $^{239}\text{Pu}$  is produced through neutron capture by  $^{238}\text{U}$ , within nuclear batteries/reactors. This yields  $^{239}\text{U}$  which decays to  $^{239}\text{Np}$  by  $\beta$ -particle emission, which decays further to  $^{239}\text{Pu}$ , also by  $\beta$ -particle emission. The longer that nuclear fuel is used (‘burned’) in a reactor, the greater the number of plutonium isotopes that appear in increasing quantities, e.g. neutron capture by  $^{239}\text{Pu}$  yields  $^{240}\text{Pu}$ , which can, in turn, capture neutrons to produce  $^{241}\text{Pu}$ .  $^{238}\text{Pu}$  is also increasingly produced from  $^{235}\text{U}$  through neutron-capture reactions and radioactive decay.

$^{238}\text{Pu}$  is a high-energy  $\alpha$ -particle emitter with a half-life of 88 years, and decays to  $^{234}\text{U}$ , which is also an  $\alpha$ -particle emitter.

$^{239}\text{Pu}$  is an  $\alpha$ -particle emitter with a half-life of 24065 years, and decays to  $^{235}\text{U}$ , which is also an  $\alpha$ -particle emitter.

$^{240}\text{Pu}$  is an  $\alpha$ -particle emitter with a half-life of 6500 years, and decays to  $^{236}\text{U}$ , which is also an  $\alpha$ -particle emitter.

$^{241}\text{Pu}$  is primarily a  $\beta$ -particle emitter with a half-life of 14 years, and decays to  $^{241}\text{Am}$ , which is a radiologically significant  $\alpha$ -particle emitter.

The only plutonium isotope required for nuclear weapons purposes is  $^{239}\text{Pu}$ , and the presence of other isotopes of plutonium, such as  $^{240}\text{Pu}$ , can also be a hindrance to this application. Therefore, plutonium is classified into different grades depending on its  $^{239}\text{Pu}$  and  $^{240}\text{Pu}$  content. The primary distinction is between weapons-grade material, which is more than 93%  $^{239}\text{Pu}$ , and other grades, for example reactor grade, which contain lower percentages of  $^{239}\text{Pu}$ .

Because of the secrecy surrounding nuclear weapons, precise figures on weapons-grade plutonium production are difficult to obtain, however, total worldwide production is thought to have been of the order of several hundred tonnes. Global stockpiles of weapons-grade plutonium have diminished as a result of strategic arms limitation agreements, and are currently believed to be about 250 tonnes.

Approximately 70 tonnes of reactor-grade plutonium are produced by power-generating nuclear reactors every year, this adds to an existing inventory of about 1300 tonnes globally, much of this is still contained in spent fuel ([World Nuclear Association, 2009](#)).

$^{238}\text{Pu}$  is used as a heat source in radiothermal generators to produce electricity for a variety of purposes ([Argonne National Laboratory, 2007](#)).

## 1.3 Exposure

### 1.3.1 X-rays, $\gamma$ -rays and neutrons

Detailed information on the different methods of measurement (present and historical) of all types of external radiation and their associated uncertainty can be found in [NCRP \(2007\)](#). Estimates of neutron dose are uncertain

because good personal neutron dosimetry is difficult to achieve over all energy ranges (energies of importance cover a range  $> 10^9$  eV), and detection thresholds are often high, particularly in the early days of monitoring.

#### (a) Accidents

The production and transport of nuclear weapons have resulted in several accidents. The two most serious accidents in nuclear weapons production were at the Mayak complex near Kyshtym in the Russian Federation (formerly the Soviet Union), and at the Windscale plant at Sellafield in the United Kingdom. A major accident in a nuclear power plant occurred in Chernobyl, Ukraine.

#### (i) Southern urals

Mayak, the former Soviet Union's main production facility for weapons-grade plutonium was built near the town of Ozersk in the southern urals, the Russian Federation, in the 1940s. Operations at this facility resulted in several major, and persistent minor, uncontrolled releases of activity into the surrounding environment, particularly the Techa river.

In 1957, a Mayak waste storage facility located near Kyshtym exploded as a result of a chemical reaction, this incident is referred to as the Kyshtym accident. The region contaminated by this accident had a population of approximately 273000 people and around 11000 of these had to be relocated, including 1500 people who had previously been resettled from the Techa River area. In Mayak, the total collective effective dose to an exposed population of 273000 was 2500 man.Sv ([UNSCEAR, 2000a](#)). This and other discharges from the plant (routine and accidental) resulted in substantial doses to workers (see [Vasilenko et al., 2007](#)) and to the local population ([Degteva et al., 2006](#)).

As a result of a drought in 1967, Karachay Lake, which had been used as an open depot for liquid radioactive waste from Mayak, dried

up and the winds associated with a subsequent storm picked up radionuclide-loaded sediments from the lake and distributed them over a wide area.

(ii) *Windscale fire*

In October 1957, at the Windscale Works, now part of the Sellafield site, in the United Kingdom, a nuclear reactor used to produce plutonium for weapons caught fire. Before the fire could be extinguished, damage occurred to the irradiated fuel contained in the reactor, and radionuclides were released in the environment. Because of the design of this reactor, which incorporated the filtration of exhausted coolant air, mainly gaseous and volatile radioisotopes escaped. In the Windscale accident, doses were mainly due to internal ingestion, and are reported in Section 1.3.

(iii) *Three Mile Island*

Failure to maintain coolant fluid in a commercial light-water reactor at Three Mile Island in the USA resulted in the reactor core becoming exposed to the air, and led to a partial meltdown of the fuel load.

(iv) *Chernobyl*

In the accident at Chernobyl in the Ukraine in April 1986, a Russian reactor Bolshoy Moschnosti Kanalniy (RMBK) became uncontrollable creating a steam explosion and a subsequent fire, which resulted in a loss of containment and ultimately to the complete destruction of the reactor. In the Chernobyl accident, the main contributor to the dose from external irradiation was  $^{137}\text{Cs}$ . The doses to individuals throughout the northern hemisphere varied widely, some staff and rescue workers on duty during the accident receiving fatal doses  $> 4$  Sv ([Savkin et al., 1996](#)). Yearly averaged doses to operation recovery workers of Belarus, the Russian Federation, and Ukraine were in the range of 20–185 mGy during 1986–89 ([UNSCEAR, 2008a](#)).

(b) *External exposure*

(i) *Natural sources*

Exposure to external radiation accounts for about 40% of the average worldwide natural radiation dose, the rest being due to internal exposure, mainly from  $^{222}\text{Rn}$  ([Table 1.1](#)).

Most of the natural exposure to X- and  $\gamma$ -rays is from terrestrial sources, and depends on the concentration of (natural) radioactive materials in the soil and building materials. Cosmic rays contribute substantially to the effective dose and are practically the only natural source of neutron exposure. Cosmic ray dose at sea level is mainly from muons, electrons, and photons with about 8% of the effective dose from neutron interactions. The neutron fraction increases to a peak of about 40% at a height of around 4000 m. The cosmic ray dose increases with altitude and also is greater at higher latitudes ([UNSCEAR, 2000a](#)).

[UNSCEAR \(2000a\)](#) gives detailed data for exposure in various regions of the world. Average outdoor external dose rates for different countries cover the range 18–93 nGy/h. The population-weighted average is 59 nGy/h (0.52 mSv per year). Areas of very high dose rates above ~10000 nGy/h have been reported from various sites throughout the world.

The population-weighted average effective dose of neutrons was estimated to be 100  $\mu\text{Sv}$  per year by [UNSCEAR \(2000a\)](#).

(ii) *Medical uses*

The medical uses of radiation include diagnostic examinations and therapy. Radiotherapy is intended to deliver high doses to target organs of the order of tens of Gy ([UNSCEAR, 2000a](#)). Assessing the risk to non-target organs may be important in some cases.

The dose per medical diagnostic examination is generally of the order of 0.1–20 mGy. While lower than doses from radiotherapy, diagnostic examinations are the main source of radiation from medical use. The use of X- and  $\gamma$ -rays for

medical purposes is distributed very unevenly throughout the world (Table 1.2). UNSCEAR (2000a) reported an increase in the overall frequency of diagnostic X-ray examinations but the frequency was static or had shown decreases in some countries (Fig. 1.4). The majority of the world population receives no exposure in a given year from X- and γ-irradiation in medical diagnosis, while the effective dose may be up to 100 mSv for a small number of people. Doses due to diagnostic X-rays are changing rapidly with time as technologies develop (NCRP, 2009).

The average levels of radiation exposure due to the medical uses of radiation has been increasing (Fig. 1.5; UNSCEAR, 2000a), in particular due to increasing use of computed tomography (CT), angiography, and interventional procedures in developed countries (Fig. 1.6). The estimated global annual effective dose from all diagnostic uses of radiation was estimated to be 1.2 mSv per person in 1991–96, compared to 1.0 mSv in 1985–90. In 2006, US citizens received a collective effective dose from medical procedures 7.3 times greater than was the case in the early 1980s (NCRP, 2009).

For the same examination, doses may vary by an order of magnitude, and reducing the highest doses can reduce collective dose without a reduction in diagnostic information (Watson *et al.*, 2005).

Conventional radiographs form the majority of radiographic examinations with doses from < 0.01 up to ~10 mSv per procedure (Watson *et al.*, 2005). The use of digital imaging techniques to replace film-screen combinations has become widespread in some countries (see e.g. Hart *et al.* (2005) for a detailed review of practices in the United Kingdom).

Doses to the breast from mammography examinations are of the order of 1.5 mGy with large variations depending on breast characteristics (Young & Burch, 2000; Schubauer-Berigan *et al.*, 2002). In Germany, 18% of first mammographies were on women less than 30 years old and

**Table 1.1 Average radiation dose from natural sources**

| Source                    | Worldwide average annual effective dose (mSv) | Typical range (mSv)  |
|---------------------------|-----------------------------------------------|----------------------|
| <b>External exposure</b>  |                                               |                      |
| Cosmic rays               | 0.4                                           | 0.3–1.0 <sup>a</sup> |
| Terrestrial γ-rays        | 0.5                                           | 0.3–0.6 <sup>b</sup> |
| <b>Internal exposure</b>  |                                               |                      |
| Inhalation (mainly radon) | 1.2                                           | 0.2–10 <sup>c</sup>  |
| Ingestion                 | 0.3                                           | 0.2–0.8 <sup>d</sup> |
| <b>Total</b>              | <b>2.4</b>                                    | <b>1–10</b>          |

<sup>a</sup> Range from sea level to high-ground elevation

<sup>b</sup> Depending on radionuclide composition of soil and building materials

<sup>c</sup> Depending on indoor accumulation of radon gas

<sup>d</sup> Depending on radionuclide composition of foods and drinking-water

From UNSCEAR (2000a)

31% on women 30–39 years old (Klug *et al.*, 2005). In USA, 60% of women had their first mammography exams by the age of their 40<sup>th</sup> year, and in France 45.8% during the age of 45–50 years (Spyckerelle *et al.*, 2002; Colbert *et al.*, 2004).

Computed tomography scanning has become widely available in many developed countries. The effective dose per examination is considerably higher than that from most conventional radiographic procedures, and its use is increasing (Brenner & Hall, 2007). Doses per procedure are in the range of 1.5 mSv to over 25 mSv (UNSCEAR, 2000a).

Fluoroscopy results in much higher doses than radiography. The doses may vary widely: modern equipment with image amplifiers results in lower doses than older equipment with fluorescent screens, but high doses may still be received. Advances in technology have facilitated the development of increasingly complex radiological procedures for angiography and interventional radiology, and effective doses per procedure from under 10 to over 80 mSv, depending on the complexity of the procedure, have been reported (UNSCEAR, 2000a).

**Table 1.2 Radiation exposures from diagnostic medical examinations**

| Population per physician | Annual number of examinations per 1000 population | Average annual effective dose to population (mSv) |
|--------------------------|---------------------------------------------------|---------------------------------------------------|
| < 1000                   | 920                                               | 1.2                                               |
| 1000–3000                | 150                                               | 0.14                                              |
| 3000–10000               | 20                                                | 0.02                                              |
| > 10000                  | < 20                                              | < 0.02                                            |
| <b>Worldwide average</b> | <b>330</b>                                        | <b>0.4</b>                                        |

From [UNSCEAR \(2000a\)](#)

The medical use of neutrons and protons in radiotherapy is limited at present.

### (iii) General population

Estimates of the average doses received by the general population are reviewed regularly by the United Nations Scientific Committee on the Effects of Atomic Radiation ([UNSCEAR, 2000a](#)), and by many national bodies, such as the Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit in Germany ([BMU, 2007](#)), the National Council on Radiation Protection and Measurements in the USA ([NCRP, 2009](#)), and the Radiation Protection Division of the Health Protection Agency in the United Kingdom ([Watson et al., 2005](#)).

Fig. 1.7 shows in a) the distribution of average exposures to ionizing radiation in the United Kingdom ([Watson et al., 2005](#)) and in b) and c) how the distribution in the USA has changed between the early 1980s and 2006 ([NCRP, 2009](#)). The distribution of some of the components in different countries may vary by an order of magnitude.

### (iv) Nuclear explosions and production of nuclear weapons

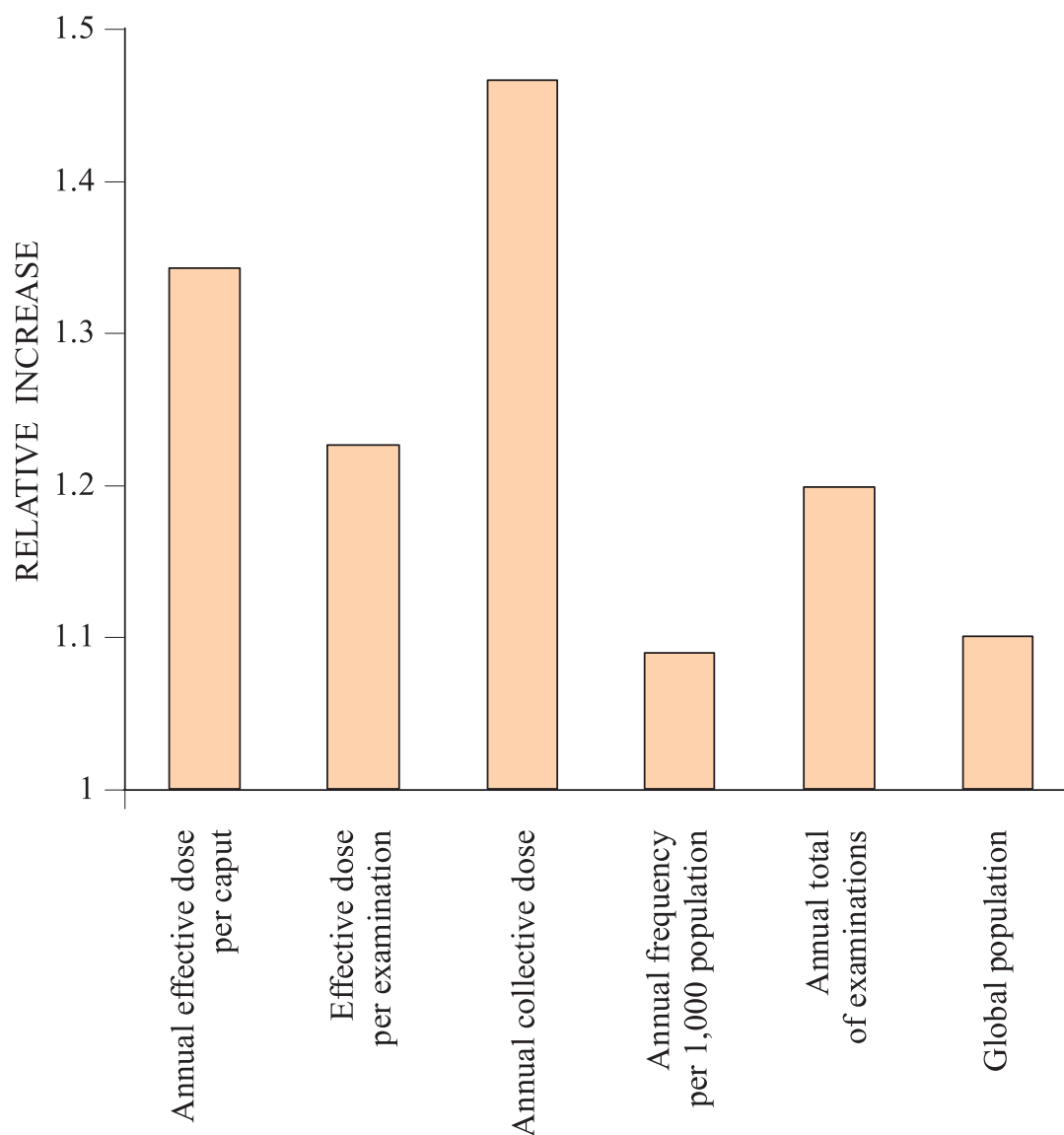
The atomic bombings of Hiroshima and Nagasaki, Japan, in 1945 exposed hundreds of thousands of people to substantial doses of external radiation from  $\gamma$ -rays with a small

fraction due to neutrons (~1%) and some internal exposure. For the survivors, the latest estimates of the doses using dosimetry system DS02 ([Young & Kerr, 2005](#)) are available for 113251 persons in the Life Span Study of whom 93741 were within 10 km of the hypocentres. Of these, 44464 had doses < 0.5 mGy and 35393 had doses > 10 mGy ([Cullings et al., 2006](#)). The mean of known doses for survivors at about 1600 m was roughly 170 mGy ([Preston et al., 2004](#)).

Atmospheric nuclear explosions were carried out, mostly in the northern hemisphere, between 1945 and 1980. The most intense period of testing was between 1952 and 1962. In all, approximately 543 atmospheric tests have been carried out, with a total yield of 440 Mt (megatonne) explosive power ([UNSCEAR, 2000a](#)). Since 1963, nuclear tests have been conducted mainly underground, and the principal source of worldwide exposure due to weapons testing is the earlier atmospheric tests. The global average committed effective dose (which includes the sum of all doses that will be received over a period of 50 years from internal irradiation) is 3.5 mSv, of which, 0.5 mSv is from external irradiation ([UNSCEAR, 2000a](#)). Annual average total radiation doses are currently ~8  $\mu$ Sv per year, of which, < 3  $\mu$ Sv per year is from external irradiation.

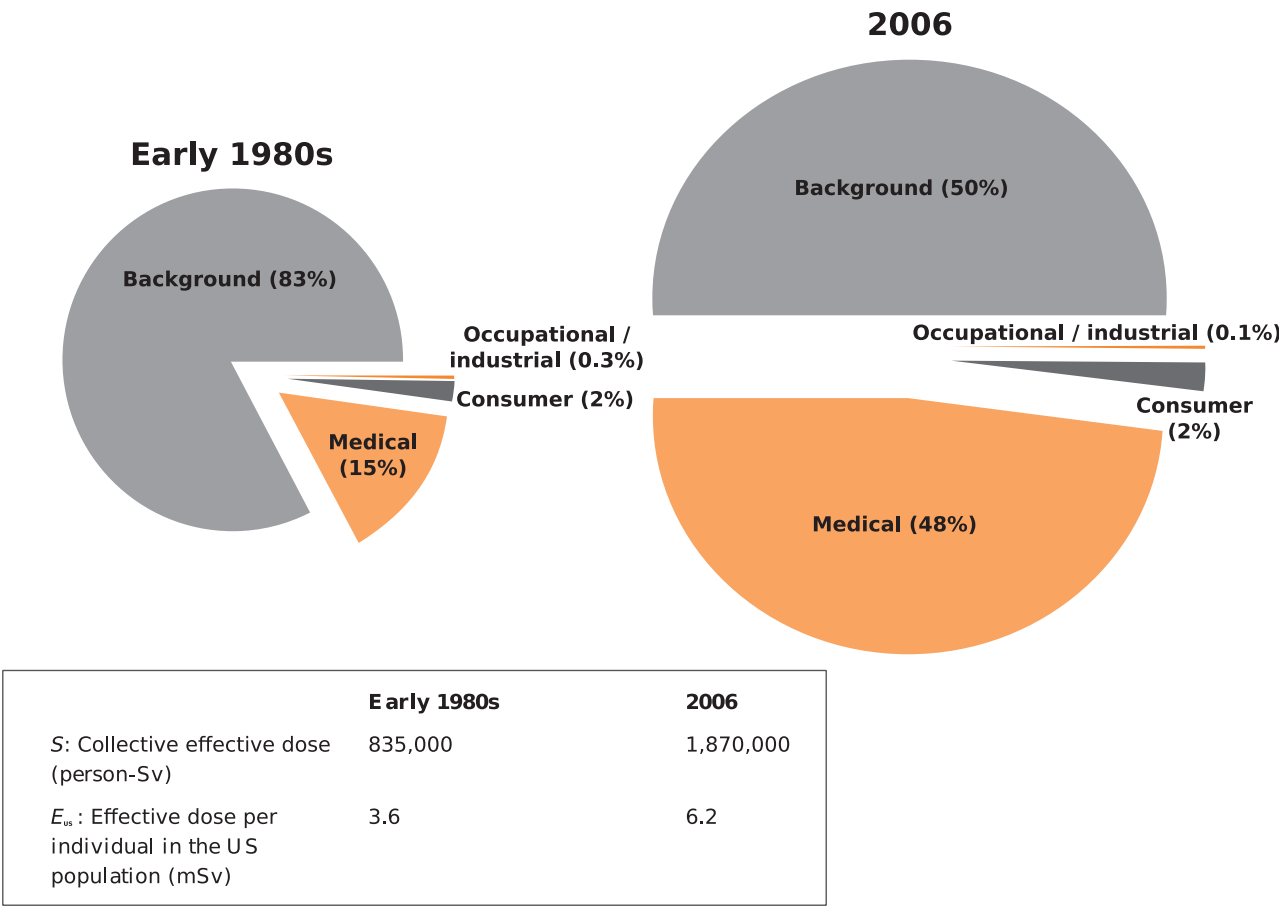
People living near the sites where nuclear weapons were tested received doses varying considerably in magnitude. Those near to the Nevada test site in the USA received an estimated average dose of about 3 mSv ([Anspaugh et al., 1990](#)). After a US test in 1954 at Bikini atoll in the Marshall Islands, the residents of Rongelap and Utirik atolls (230 persons) received high external exposures (1900 mSv), mainly from short-lived radionuclides, with 67 persons receiving doses of 1750 mSv on Rongelap ([Conard et al., 1980](#)). At Semipalatinsk in the former Soviet Union, atmospheric tests between 1949 and 1963, exposed 10000 people in settlements bordering the test site with doses ranging up to several Gy ([Tsyb et al., 1990](#)).

**Fig. 1.4** Temporal trends in global practice with medical X-ray examinations: average frequencies and doses for 1991–96 relative to previous estimates for 1985–90



Adapted from [UNSCEAR \(2000a\)](#)

**Fig. 1.5 Comparison of distribution of collective dose values (S) or effective dose (E<sub>us</sub>) for the categories of exposure as reported for the early 1980s and for 2006**



Adapted from [NCRP \(1987, 2009\)](#)

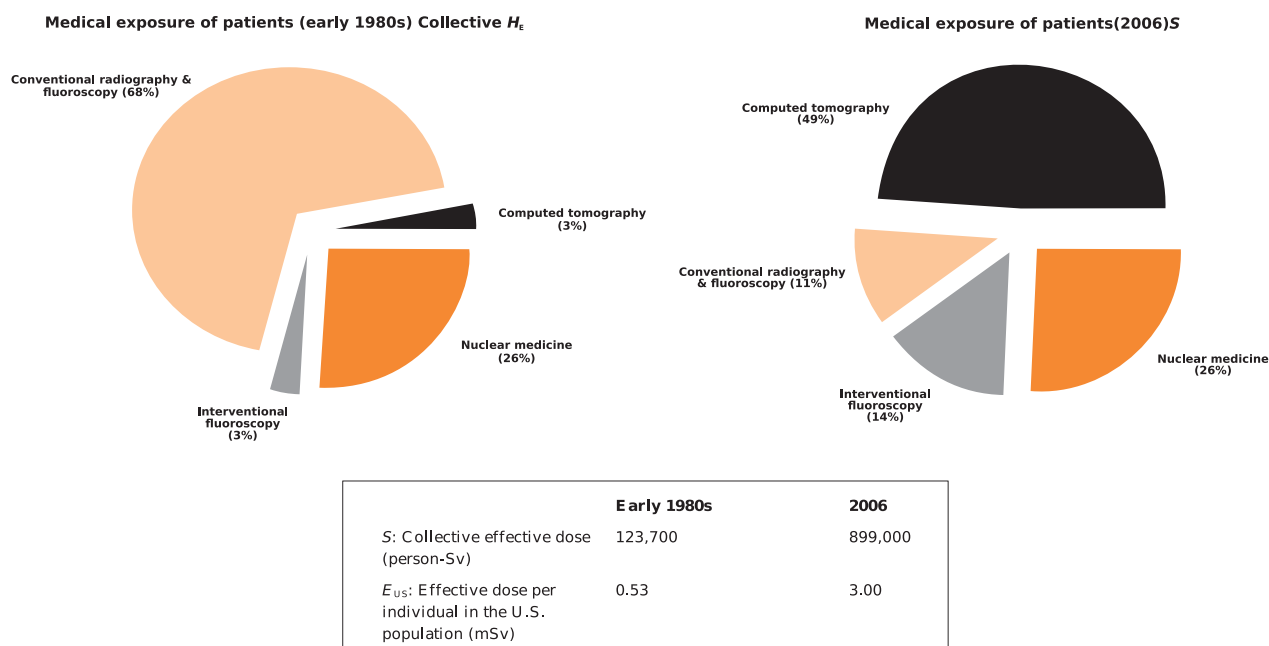
γ-ray exposures to the local population resulting from the production of weapons material and chemical separation can be considerable. For example, the release of nuclear wastes from the Mayak complex into the Techa River from a military plant of the former Soviet Union, resulted in organ doses up to 5.2 Gy at bone surfaces (median 0.37 Gy), mainly from internal radionuclides, with half of the much lower external doses lying between 0.0017 and 0.0062 Gy ([Degteva et al., 2006](#)).

*(v) Nuclear power production*

Assuming that the generation of electrical energy by nuclear power reactors lasts for 100 years, the maximum collective dose for the

entire fuel cycle (mining and milling, enrichment and fuel fabrication, reactor operation, fuel processing, waste disposal, transport of radioactive materials) has been estimated by [UNSCEAR \(2000a\)](#). If the present annual generation of 250 gigawatt continues for 100 years, the internal plus external dose to an individual of the general population would be less than 0.2 μSv per year. Evrard *et al.* reported an estimated dose of 0.17 μSv per year due to gaseous discharge in 2107 “communes” located in the vicinity of 23 French nuclear facilities, including all power plants ([Evrard et al., 2006](#)). Most of the exposure is due to internal irradiation.

**Fig. 1.6 Comparison of collective dose values for CT, conventional radiography and fluoroscopy, interventional fluoroscopy, and nuclear medicine (as % of total collective dose) as reported for the early 1980s (123700 person-Sv) (left: [NCRP, 1989](#)), and for 2006 (899000 person-Sv) (right: [NCRP, 2009](#)). For  $E_{US}$ , the same percentages apply. Collective dose quantities are S for 2006 and collective effective dose equivalent  $H_E$  for [NCRP \(1989\)](#).**



Adapted from [NCRP \(2009\)](#)

#### (vi) Accidents

For the Mayak, Windscale, and Chernobyl accidents, see Section 1.3.1 above.

Sealed sources used for industrial and medical purposes have occasionally been lost, stolen or damaged, resulting in exposure of members of the public to these materials. Examples include the sale of a Cobalt-60 ( $^{60}\text{Co}$ ) source as scrap metal in the city of Juarez, Mexico, in 1983 ([Marshall, 1984](#)); the theft and breaking up of a  $^{137}\text{Cs}$  source in Goiânia, Brazil, in 1987 ([IAEA, 1988](#)); and the retrieval of a lost  $^{60}\text{Co}$  source in Shanxi Province, the People's Republic of China, in 1992 ([UNSCEAR, 1993](#)). IAEA publications contain information on accidental irradiation during medical procedures, in particular Safety Report Series No. 17 ([IAEA, 2000](#)). While these incidents result in significant individual doses

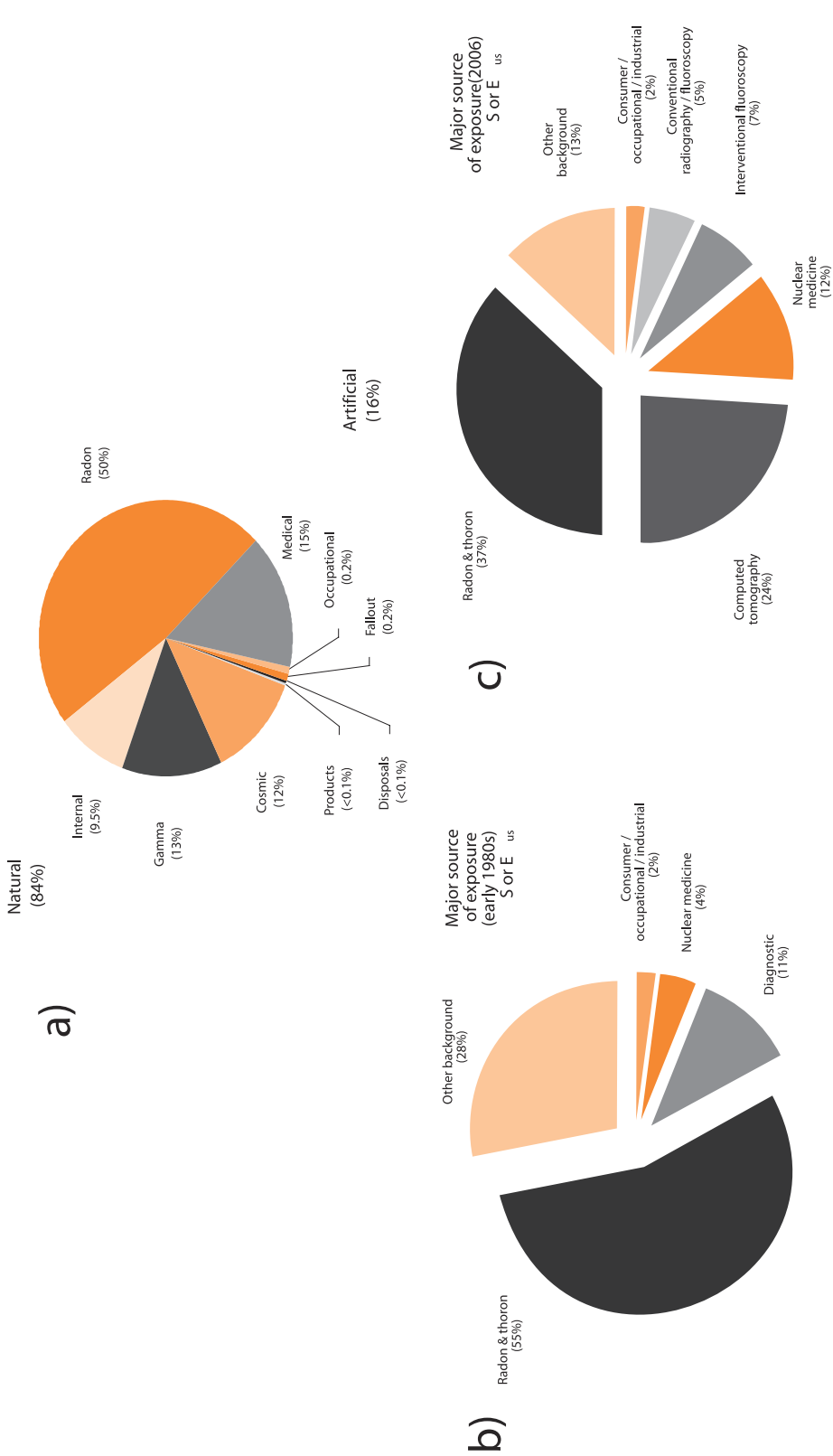
to a small number of people, the collective effective doses are not large. The steady increase in the use of sources of ionizing radiation has led to an increase in the number of fatalities, despite progress in radiation protection.

#### (vii) Occupational exposures

Occupational exposure to radiation occurs during nuclear power production and fuel recycling, military activities, industrial operations, flying and medical procedures (see above for details). Average annual effective doses are in [Table 1.3 \(UNSCEAR, 2000a\)](#). The average annual effective dose for occupational workers has reduced from 1.9 mSv in 1975–79 to 0.6 mSv in 1990–94.

Mean doses to medical radiation technologists in the US have reduced from 100 mSv per

Fig. 1.7 Percentage contribution of each natural and man-made radiation source



(a) UK population, average annual dose to the population = 2.7 mSv  
(b) Distribution of  $S$  or  $E_{US}$  for the major sources of exposure for the early 1980s (NCRP, 1987). The percent values have been rounded to the nearest 1%. The total for  $S$  is 835,000 person-Sv and the total for  $E_{US}$  is 3.6 mSv, using a U.S. population of 230 million for 1980.  
(c) Distribution of  $S$  or  $E_{US}$  for the major sources of exposure for 2006. The percent values have been rounded to the nearest 1%. The total for  $S$  is 1,870,000 person-Sv and the total for  $E_{US}$  is 6.2 mSv, using a U.S. population of 300 million for 2006. The other background category consists of the external (space and terrestrial) and internal subcategories. Adapted from Watson *et al.* (2005), NCRP (1987), NCRP (2009)

year before 1940 to 2.3 mSv per year during 1977–84 ([Simon et al., 2006](#)). In recent years, worldwide annual doses have also been reduced from 0.6 mSv in 1980–84 to 0.33 mSv in 1990–94 ([UNSCEAR, 1993, 2000a](#)).

Occupational exposure to neutrons constitutes a small fraction of the total effective dose and occurs mainly in the nuclear industry. In a United Kingdom compilation of dose to nuclear workers ([Carpenter et al., 1994](#)), the upper limit of the neutron component was estimated to be 3% of the total exposure. In the USA, more than 10000 nuclear workers per year receive measurable neutron doses ([NCRP, 1987](#)).

Neutron sources are used to chart progress in the search for gas and oil resources. For oil-well loggers, doses of 1–2 mSv per year were reported in one study ([Fujimoto et al., 1985](#)), and in another ([Inskip et al., 1991](#)), only seven of 1344 workers received above-threshold (0.02 mGy) doses.

The exposure of commercial aircraft crews to neutrons depends on the flight route and on the number of flight hours with secondary neutrons from galactic cosmic rays contributing about 10–15% of the dose at an altitude of 10 km. [Watson et al. \(2005\)](#) reviewed United Kingdom data by summarizing findings of [Warner Jones et al. \(2003\)](#) and [Irvine & Flower \(2005\)](#) and estimated overall average annual doses for all aircrew as 2 mSv from natural radiation and 19  $\mu$ Sv from the transport of radioactive material.

Staff involved in radiotherapy with neutrons are exposed mainly to  $\gamma$ - and  $\beta$ -rays due to activation of the room and equipment. The dose rates are well below 1  $\mu$ Gy/h and are not detectable by personal dosimetry ([Smathers et al., 1978](#); [Finch & Bonnett, 1992](#); [Howard & Yanch, 1995](#)). Individuals are exposed to neutrons largely through the use of high-energy photon beams (> 15 MeV), which produce photo-neutrons ([Hall et al., 1995](#); [Ongaro et al., 2000](#)), and also through the use of high-energy proton-therapy beams, which produce secondary neutrons ([Brenner & Hall, 2008](#)).

**Table 1.3 Occupational radiation exposures**

| Source/practice                           | Number of monitored workers (thousands) | Average annual effective dose (mSv) |
|-------------------------------------------|-----------------------------------------|-------------------------------------|
| <b>Man-made sources</b>                   |                                         |                                     |
| Nuclear fuel cycle (incl. uranium mining) | 800                                     | 1.8                                 |
| Industrial uses of radiation              | 700                                     | 0.5                                 |
| Defence activities                        | 420                                     | 0.2                                 |
| Medical uses of radiation                 | 2320                                    | 0.3                                 |
| Education/veterinary                      | 360                                     | 0.1                                 |
| <b>Enhanced natural sources</b>           |                                         |                                     |
| Air travel (crew)                         | 250                                     | 3.0                                 |
| Mining (other than coal)                  | 760                                     | 2.7                                 |
| Coal mining                               | 3910                                    | 0.7                                 |
| Mineral processing                        | 300                                     | 1.0                                 |
| Above-ground workplaces (radon)           | 1250                                    | 4.8                                 |

Adapted from [UNSCEAR \(2000a\)](#)

The neutron energy spectrum to which individuals may be exposed varies widely, depending on the neutron source and the degree of moderation undergone by the neutrons. In most occupational settings, the neutron spectrum will be a degraded fission spectrum. For example, for workers occupationally exposed to low neutron doses from nuclear reactors or similar settings, the important neutron energy range in terms of dose deposition is, on average, from about 10–100 keV ([Worgul et al., 1996](#)). Doses from radiotherapy-related photoneutrons are dominated by somewhat higher neutron energies (100–1000 keV) ([Ongaro et al., 2000](#)), while the dose from secondary neutrons from galactic cosmic rays ([De Angelis et al., 2003](#)), or from proton radiotherapy ([Zheng et al., 2007](#)), will generally be dominated by higher-energy neutrons.

Astronauts are exposed to high doses of space radiation, which consists of protons, heavy ions

and secondary neutrons produced by galactic cosmic ray interactions, particularly if they go beyond low earth orbits. Based on data from a human phantom torso, the organ dose rates outside the International Space Station have been derived by [Reitz \*et al.\* \(2009\)](#) and are in the range of ~0.2–1.0 mGy/day. Data for average personnel badge doses for previous space missions give similar figures ([Cucinotta \*et al.\*, 2008](#)). The estimated dose ([Cucinotta & Durante, 2006](#)) for a lunar mission of 180 days is 60 mGy, and for a Mars exploration of 1000 days it is 420 mGy. The relative biological effectiveness for these heavy ions may be as high as 40.

### 1.3.2 $\alpha$ - and $\beta$ -emitting radionuclides, internally deposited

#### (a) Tritium

##### (i) Nuclear weapons production

Because the amount of  $^3\text{H}$  needed for nuclear weapons purposes is relatively small, the facilities used to produce it tend to be much smaller than those used to produce plutonium, consequently the number of workers exposed to  $^3\text{H}$  also tends to be small. The secrecy often associated with military  $^3\text{H}$  production means that there are also relatively few  $^3\text{H}$  worker cohorts identified from this activity. Relaxation of secrecy associated with military  $^3\text{H}$  production in the United Kingdom in the last 10 years has meant that several hundred workers are now known to have potentially been exposed to  $^3\text{H}$  at the Capenhurst and Chapelcross sites ([HPA, 2007](#)).

##### (ii) Nuclear power production

With heavy-water moderated reactors, such as the CANDU design,  $^3\text{H}$  exposures normally account for the majority of the workers' dose.

##### (iii) Occupational exposure

$^3\text{H}$  has also been used to produce self-illuminating devices (the  $\beta$ -particle emissions are used to stimulate light production in a suitable

phosphorescent material) used in various applications including watches, gun sights, and signs. For example, about 100000 self-illuminating exit signs were produced per year in the USA during 1983–2002 ([PSI, 2003](#)), containing a total of approximately 100 PBq (petabecquerel,  $10^{15}$  becquerel) of  $^3\text{H}$ .

#### (b) Phosphorus-32

##### (i) Medical use

$^{32}\text{P}$ , in the form  $^{32}\text{PO}_4$ , has been used in the treatment of *polycythaemia vera* since 1939. This has been the primary medical use for this radionuclide, representing ~5% of all therapeutic use of radionuclides in a survey of 17 European countries ([Hoefnagel \*et al.\*, 1999](#)) but only ~1% worldwide ([UNSCEAR, 2000a](#)). Individual treatments typically involve the use of 150–170 MBq of  $^{32}\text{PO}_4$  ([UNSCEAR, 2000a](#)) administered orally or intravenously.

$^{32}\text{P}$  has also been used as a radioactive tracer, for purposes such as identifying tumours as an aid in surgical removal. Historically,  $^{32}\text{P}$  was also used in the treatment of leukaemia (both chronic myelocytic leukaemia and chronic lymphocytic leukaemia).

#### (c) Strontium-90

As exposure to  $^{90}\text{Sr}$  is mostly in conjunction with other fission products, further information on exposures is given in the mixed fission products section below.

#### (d) Iodine-131

As exposure to  $^{131}\text{I}$  can often be in conjunction with other fission products, further information on exposures is also given in the mixed fission products section below.

##### (i) Medical use

Radioiodine has been used in the treatment of hyperthyroidism and cancer of the thyroid for more than 50 years, and is by far the most common internal emitter used for therapeutic

purposes. It should also be noted that radioiodine treatment can be a source of external exposure to other people, and it is the main source of exposure to the public and relatives from patients who have received unsealed radionuclides ([ICRP, 2004](#)).

#### (ii) Accidents

### Windscale fire

The Windscale fire in 1957, in the United Kingdom, resulted in the release of a total of  $1.5 \times 10^{15}$  Bq of radioisotopes. Because of the design of this reactor, which incorporated the filtration of exhausted coolant air, mainly gaseous and volatile radioisotopes escaped ( $^{133}\text{Xe}$  ( $14 \times 10^{15}$  Bq),  $^{210}\text{Po}$  ( $0.09 \times 10^{15}$  Bq)) including  $1.4 \times 10^{15}$  Bq of  $^{131}\text{I}$ . Prompt action to limit exposure to  $^{131}\text{I}$  resulted in low doses being released to the general public; however, workers at the plant involved in efforts to extinguish the fire did receive larger than normal exposures ([UNSCEAR, 1993](#); [IARC, 2001](#)).

### Three Mile Island

Initially, the activity released during the Three Mile Island reactor accident in the USA was largely contained within the primary containment building but gaseous and volatile radionuclides including  $^{133}\text{Xe}$  ( $370 \times 10^{15}$  Bq) and  $^{131}\text{I}$  ( $550 \times 10^9$  Bq) were subsequently released into the environment ([UNSCEAR 1993](#); [IARC, 2001](#)).

### Chernobyl

Following the Chernobyl accident, reported individual thyroid doses ranged up to several tens of Gy, while average doses range from a few tens of mGy to several Gy ([UNSCEAR, 2000b](#); [Cardis et al., 2006a, b](#)).

#### (e) Caesium-137

As exposure to  $^{137}\text{Cs}$  is mostly in conjunction with other fission products, further information on exposures is given in the mixed fission products section below.

#### (f) Radon

##### (i) Natural sources

Internal exposures from Naturally Occurring Radioactive Materials (NORM) are generally dominated by the isotopes in the  $^{232}\text{Th}$  and  $^{238}\text{U}$  decay chains, particularly  $^{222}\text{Rn}$  and its progeny.  $^{222}\text{Rn}$  makes by far the largest contribution to average individual internal exposures to the public from natural sources (see [Table 1.1](#)).  $^{222}\text{Rn}$  concentration in buildings varies greatly, typically from less than  $10 \text{ Bq/m}^3$  to more than  $100 \text{ Bq/m}^3$  ([UNSCEAR, 2006](#)), depending on factors such as local geology and air movement (restricted ventilation in places such as caves can lead to much greater  $^{222}\text{Rn}$  concentrations).

Residential  $^{222}\text{Rn}$  concentrations can vary appreciably in different parts of the home, with basement  $^{222}\text{Rn}$  concentrations typically 50% higher than on the ground floor ([Field et al., 2000, 2006](#)).  $^{222}\text{Rn}$  concentrations within homes in the same neighbourhood can also vary appreciably due to subtle aspects of building construction, such as cracks and fissures in the foundation, and ventilation of the home ([Radford, 1985](#)). Residential  $^{222}\text{Rn}$  concentrations also exhibit seasonal variation, both within and between years ([Pinel et al., 1995](#); [Krewski et al., 2005](#)). One other source of  $^{222}\text{Rn}$  can be from domestic water supplies.

##### (ii) Occupational exposure

Because  $^{222}\text{Rn}$  is formed from the radioactive decay of  $^{238}\text{U}$  which is ubiquitous in the Earth's crust, high levels of  $^{222}\text{Rn}$  gas have historically been found in underground mines (Committee on Health Risks of Exposure to Radon ([BEIR VI, 1999](#))). Since the discovery of lung disease in underground miners exposed to high levels of  $^{222}\text{Rn}$  in the 19<sup>th</sup> century, subsequently confirmed to be lung cancer in the 20<sup>th</sup> century,  $^{222}\text{Rn}$  concentrations in mines were greatly reduced in the interest of industrial hygiene. Currently,  $^{222}\text{Rn}$  concentrations in underground mines are

generally well below the current occupational exposure guideline of 2 working-level month/year (WLM/yr) in ventilated mines (1 WLM is exposure for 1 month (170 h) at 1 WL (working-level) corresponding to 130000 MeV of potential  $\alpha$  energy released by the short-lived progeny in equilibrium with 100 pCi of  $^{222}\text{Rn}$  in one litre of air ( $3.7 \text{ kBq/m}^3$ )). Assuming a breathing rate of  $1.2 \text{ m}^3/\text{h}$ , the cumulative intake of 1 WLM is 0.755 MBq. Although historical exposures in underground mines have exceeded residential exposures by a factor up to a 1000-fold or more, this difference has been much reduced by a factor of 20–30-fold in recent years.

(g) *Radium*

(i) *Occupational exposure*

The practice of painting clock dials with radium-based paint to make them luminous was introduced just before the First World War. The production and application of luminous paint soon became an industry, particularly in the USA. Because of the precision required in applying these radium-based paints, ‘Dial painters’ or ‘Luminisers’ (as they were commonly known) frequently ‘tipped’ their brushes (i.e. brought the bristles to a point) using their mouths, and as a result would ingest some of the paint and the radium it contained. The use of radium-based paints has also occurred in Germany, the United Kingdom, and many other countries throughout the world ([IARC, 2001](#)).

(h) *Thorium-232*

(i) *Medical use*

Thorium dioxide ( $\text{ThO}_2$ ) was first used as an X-ray contrast medium for splenography in the 1920s, and from 1931, a commercial preparation containing it, under the trade name ‘Thorotrast’, was marketed as a general vascular contrast medium. Thorotrast was administered by instillation or injection and was widely used throughout the world. It has been estimated that

as many as 2.5 million individuals may have been exposed to it, before it was replaced by other contrast media in the 1950s ([IARC, 2001](#)).

(i) *Uranium*

(i) *Natural source*

Uranium is naturally present in small amounts almost everywhere in soil, rock including well water, and groundwater. Higher levels are present in natural uranium ores.

(ii) *Occupational exposure*

As it is the raw material for most nuclear power generation, uranium is ubiquitous in the nuclear fuel cycle: from mining and initial processing to enrichment and/or fuel manufacturing, power production, and reprocessing.

Exposure can involve natural, depleted and/or enriched uranium, in a wide variety of chemical forms ([IARC, 2001](#)).

(j) *Plutonium*

(i) *Nuclear weapons production and testing*

The USA was the first nation to pursue plutonium production as a means to construct a nuclear weapon, but the populations of exposed individuals tend to be compartmentalised and/or widely dispersed. The two largest continuous populations of workers exposed to plutonium are those at the Mayak Production Association in the southern urals, the Russian Federation, and those at the Sellafield (formerly Windscale) plant in the United Kingdom. Both of these facilities have plutonium worker cohorts of over 10000 individuals, with exposures starting in the late 1940s (Mayak) and early 1950s (Sellafield).

Political pressure to develop nuclear weapons as rapidly as possible both during and in the decade after the Second World War resulted in considerable internal exposure, primarily to plutonium. Unfortunately this tends to be the period in which monitoring data is most lacking, particularly for Mayak, where exposures were

the largest, with many individuals having no monitoring information at all.

(ii) *Occupational exposure*

The reprocessing of irradiated nuclear fuel, and to a lesser extent the production of mixed oxide 'MOX' fuel assemblies, can result in exposure to plutonium.

(k) *Mixed fission products*

Information on some major individual fission products ( $^{90}\text{Sr}$ ,  $^{131}\text{I}$ ,  $^{137}\text{Cs}$ ) is given above. However, because of the stochastic nature of fission-product production, fission products are always produced in mixtures; and consequently, exposures are often to mixtures of fission products. Assessment of doses from mixed fission products that have been released into the environment are frequently dependent on environmental transport models.

(i) *Southern urals*

As stated previously, Mayak, the former Soviet Union's main production facility for weapons-grade plutonium was built near the town of Ozersk in the southern urals, the Russian Federation, in the 1940s. Operations at this facility resulted in several major, and persistent minor, releases of activity into the surrounding environment, particularly the Techa river and the surrounding area ([IARC, 2001](#)).

(ii) *Techa river*

During 1949–56, 100 PBq ( $100 \times 10^{15}$  Bq) of activity were released into the Techa–Isset–Tobol river system. Of the approximately 28000 people living in settlements near the Techa river during this period, around 7500 were relocated during 1953–60 because of their exposure to radionuclides ([UNSCEAR, 2000a](#)).

(iii) *Kyshtym accident*

The Kyshtym accident released 74 PBq of radionuclides. The region contaminated by this accident had a population of approximately

273000 people and around 11000 of these had to be relocated, including 1500 that had previously been resettled from the Techa River area ([UNSCEAR, 2000a](#)).

(iv) *Karachay lake*

The Karachay lake accident released 0.022 PBq of radionuclides into the environment and distributed them over a wide area ([UNSCEAR, 2000a](#)).

(v) *Chernobyl*

The Chernobyl accident released substantial amounts of radionuclides into the environment including  $^{131}\text{I}$  (1760 PBq) and  $^{137}\text{Cs}$  (85 PBq), and these radionuclides were dispersed over an enormous area. The two main groups exposed were individuals working on recovery operations (so called liquidators) at the reactor site and members of the general population living in the vicinity of the site. A total of 116000 members of the public were evacuated from a 30-km area around the Chernobyl site following the accident, and 226000 recovery operators worked at the site or within this evacuated zone during the following year.

## 2. Cancer in Humans

X-radiation and  $\gamma$ -radiation were previously classified as Group 1 carcinogens by a previous *IARC Monograph* ([IARC, 2000](#)). This classification was based on increased risk of several cancers associated with X- and  $\gamma$ -rays, including leukaemia (excluding chronic lymphocytic leukaemia), breast cancer in women exposed before the menopause, cancer of the thyroid gland among people exposed during childhood, non-melanoma skin cancer, and cancer of the stomach, colon, and lung.

Epidemiological information on the carcinogenic effects of X- and  $\gamma$ -rays comes from studies of people exposed to radiation from the

detonations of atomic weapons, from medical procedures, and in occupational or environmental settings. The epidemiological findings that have been reported since the previous *IARC Monograph* (IARC, 2000) have been reviewed, with an emphasis on large, well designed studies with adequate assessment of radiation doses. Major reviews of the literature and risk estimates provided by UNSCEAR (UNSCEAR, 2008b) and the US National Academy of Sciences Council Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation (National Research Council, 2006) on radiation risks by cancer sites were also reviewed. The recent evidence is summarized by sources of exposure first, and then both earlier and more recent evidence is reviewed by cancer site. Cohort and case-control studies of cancer following X-ray exposure are summarized in Table 2.1 available at <http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-02-Table2.1.pdf> and Table 2.2 available at <http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-02-Table2.2.pdf>, and following  $\gamma$ -ray exposure in Table 2.3 available at <http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-02-Table2.3.pdf> and Table 2.4 available at <http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-02-Table2.4.pdf>.

## 2.1 Detonation of atomic bombs

The study of Japanese atomic bomb (A-bomb) survivors holds an important place in the literature on radiation epidemiology. Atomic bombs were dropped on Hiroshima and Nagasaki in August 1945. Survivors' external radiation doses were primarily from exposure to  $\gamma$ -radiation, although there was also a neutron contribution. Several years after the bombings, the Atomic Bomb Casualty Commission initiated a large population-based study of mortality and disease risk in relation to survivors' distance from the hypocentres of the atomic bombings (Francis *et al.*, 1955; Ishida & Beebe, 1959). That study,

known as the Life Span Study (LSS), became the foundation for much of the ongoing research on mortality and cancer incidence among the Japanese A-bomb survivors (Shimizu *et al.*, 1990; Preston, *et al.*, 1994). The experiences of the Japanese A-bomb survivors have shown that the effect of exposure to detonation of atomic weapons persists for decades, and has an impact on the development of a wide range of malignant diseases.

The LSS provides an extremely important source of information about radiation health effects. The study cohort encompasses a large number of people, including men and women, exposed to a wide range of doses at all ages. An important development since of the previous *IARC Monograph* has been the introduction of revised radiation dose estimates for the A-bomb survivors: the Reassessment of the Atomic Bomb Radiation Dosimetry for Hiroshima and Nagasaki Dosimetry System 2002 (DS02) (Young & Kerr, 2005). Individual dose estimates for survivors within 2 km of the bombings are based on estimates of penetrating radiation emitted by the bombs and the location and shielding of survivors derived from interviews conducted in the late 1950s and early 1960s. Dose estimates for other survivors are based on less detailed information on shielding provided during interviews.

The LSS study does not provide information on the impact of radiation on cancer risk during the years immediately after the bombings. Follow-up for mortality started in 1950, and follow-up for cancer incidence in 1958. Furthermore, inclusion in the LSS cohort required people to have survived for at least 5 years after the bombings. Questions have been raised about potential biases associated with the impacts of early mortality on subsequent radiation risks, and about potential differences between survivors as a function of age at the time of the bombings and distance from the hypocentres (Cologne & Preston, 2000; Pierce *et al.*, 2007). Due to potential "healthy survivor effect," selection bias might be expected

to attenuate risk estimates or obscure evidence of associations rather than to induce spurious positive associations in the LSS; values for the magnitude of dose-related selective survival assumed in a recent study suggested a modest potential for bias in dose–response estimates ([Pierce et al., 2007](#)). The DS02 system focuses on the prompt  $\gamma$  and neutron doses from the bomb detonations, but survivors could have also received doses from fallout and neutron activation of soil and other materials ([Imanaka et al., 2008](#); [Tanaka et al., 2008](#)), which are not accounted for in current epidemiological analyses of the LSS data. Assumptions about the relative biological effectiveness of the neutron component of survivors' doses may have a substantial impact on quantitative estimates of  $\gamma$ -radiation dose effects ([Walsh et al., 2004](#)).

Since the previous *IARC Monograph*, reports on the associations between the DS02-estimated dose and mortality due to leukaemia and solid cancers ([Preston et al., 2004](#)) and solid cancer incidence ([Preston et al., 2007](#)) have been published. The extension of follow-up of these cohorts, and the resultant increase in the number of cancer cases ascertained, has increased the ability to conduct site-specific analyses of cancer risks as well as permitted analyses that can characterize the risk of cancer in this population more than five decades after the bombings. Some recent analyses suggest a U-shaped pattern of association of the excess relative risk per Sievert (ERR/Sv) with age at exposure for solid cancers ([Preston et al., 2007](#); [Little, 2009](#)). Results of these analyses are discussed below along with results from a recent analysis examining cancer risks following in-utero exposure to radiation from the atomic bombings.

### 2.1.1 Leukaemia

[Preston et al. \(2004\)](#) analysed the association between leukaemia mortality during 1950–2000 and DS02 estimates of bone-marrow dose. There

was clear evidence of excess risk of leukaemia among the A-bomb survivors, which increased with increasing magnitude of estimated dose, as illustrated by the ratio of the fitted excess to the expected background number of cases by category of dose ([Table 2.5](#)). The largest excess risks were observed for those exposed at younger ages, the excess tended to diminish in magnitude with time since exposure, and the exposure–response relationship appeared to be linear-quadratic. UNSCEAR ([UNSCEAR, 2008b](#)) and the US National Academy of Sciences Council Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation ([National Research Council, 2006](#)) have also reported analyses of leukaemia mortality in the LSS using the DS02 dose estimates and mortality data through 2000; both have shown the association between leukaemia mortality and the exposure.

Analyses of mortality by type of leukaemia among the Japanese A-bomb survivors during 1950–2000 have found that the ERR/Gy for acute myeloid leukaemia was best described by a quadratic dose–response function that peaked approximately 10 years after exposure. Mortality associated with acute lymphocytic leukaemia or chronic myeloid leukaemia was best described by a linear dose–response function that did not vary with time since exposure, while adult T-cell leukaemia was not associated with estimated bone-marrow dose ([Richardson et al., 2009](#)).

No updates of analyses of leukaemia incidence in the LSS have been reported since the previous *IARC Monograph*.

### 2.1.2 Solid cancers

[Preston et al. \(2004\)](#) reported an analysis of all solid cancer mortality using DS02 dose estimates and mortality follow-up information for the period of 1950–2000. The ratio of the fitted excess to the expected background number of cases increased with dose ([Table 2.6](#)). The excess

**Table 2.5 Association between leukaemia mortality during the period 1950–2000 and DS02 estimates of bone-marrow dose among A-bomb survivors in Japan**

| Weighted marrow dose category (Sv) | Subjects     | Person-years   | Leukaemia death | Expected background | Fitted excess |
|------------------------------------|--------------|----------------|-----------------|---------------------|---------------|
| < 0.005                            | 37407        | 1376521        | 92              | 84.9                | 0.1           |
| 0.005–0.1                          | 30387        | 1125891        | 69              | 72.1                | 4.0           |
| 0.1–0.2                            | 5841         | 208445         | 14              | 14.5                | 4.7           |
| 0.2–0.5                            | 6304         | 231149         | 27              | 15.6                | 10.4          |
| 0.5–1                              | 3963         | 144276         | 30              | 9.5                 | 18.9          |
| 1–2                                | 1972         | 71485          | 39              | 4.9                 | 27.7          |
| 2+                                 | 737          | 26589          | 25              | 1.6                 | 28.2          |
| <b>Total</b>                       | <b>86955</b> | <b>3184256</b> | <b>296</b>      | <b>203.0</b>        | <b>93.0</b>   |

risk of solid cancer appeared to be linear in dose, with modifying effects of gender, age at exposure, and attained age.

Unlike recent analyses of mortality in the LSS, which included 86611 people, recent analyses of cancer incidence in the LSS also include the Hiroshima or Nagasaki residents who were temporarily not in either Hiroshima or Nagasaki or were more than 10 km from the hypocentre in either city at the time of the bombings. [Preston et al. \(2007\)](#) reported analyses of incidence data during 1958–98 from 105427 people who had DS02 dose estimates and who were alive, and had not been diagnosed with cancer as of 1958. The data for solid cancer incidence were consistent with a linear dose–response over a range of 0–2 Gy. Approximately 850 (about 11%) of the cases among cohort members with doses to the colon in excess of 0.005 Gy were estimated to be associated with A-bomb radiation exposure. Significant radiation-associated increases in incidence were reported for cancer of the oral cavity, oesophagus, stomach, colon, liver, lung, non-melanoma skin, breast, ovary, bladder, nervous system, and thyroid. Although there was no indication of a statistically significant dose–response for cancer of the pancreas, prostate, and kidney, the excess relative risks for these sites

were also consistent with that for all solid cancers as a group. Elevated risks were seen for the five broadly classified histological groups considered, including squamous cell carcinoma, adenocarcinoma, other epithelial cancers, sarcomas, and other non-epithelial cancers. While the ERR/Gy was modelled with a linear term, the fit suggested departures at older ages, driven in part by the lung cancer risk.

Although the previous *IARC Monograph* noted that there was no association between radiation dose and thyroid cancer incidence among those over the age of 14 years when exposed, more recent analyses have shown positive associations between radiation dose and thyroid cancer incidence among adult female A-bomb survivors (ERR/Gy = 0.70; 95%CI: 0.20–1.46) ([Richardson, 2009a](#)). The ERR/Gy among men was –0.25 (90%CI: < 0–0.35). In that study, the number of thyroid cancer cases among women ( $n = 241$ ) was nearly 5-fold the number of cases among men ( $n = 55$ ).

Results for site-specific solid cancers in the LLS are discussed later in this section.

**Table 2.6 Association between mortality from solid cancers during the period 1950–2000 and DS02 estimates of bone-marrow dose among A-bomb survivors in Japan**

| Weighted marrow dose category (Sv) | Subjects     | Person-years   | Solid cancer death | Expected background | Fitted excess |
|------------------------------------|--------------|----------------|--------------------|---------------------|---------------|
| < 0.005                            | 38507        | 1415830        | 4270               | 4282                | 2             |
| 0.005–0.1                          | 29960        | 1105215        | 3387               | 3313                | 44            |
| 0.1–0.2                            | 5949         | 218670         | 732                | 691                 | 41            |
| 0.2–0.5                            | 6380         | 232407         | 815                | 736                 | 99            |
| 0.5–1                              | 3426         | 125243         | 483                | 378                 | 116           |
| 1–2                                | 1764         | 64689          | 326                | 191                 | 113           |
| 2+                                 | 625          | 22302          | 114                | 56                  | 64            |
| <b>Total</b>                       | <b>86611</b> | <b>3184356</b> | <b>10127</b>       | <b>9647</b>         | <b>479</b>    |

### 2.1.3 Cancers after irradiation in utero, and pre-conception exposure

[Preston \*et al.\* \(2008\)](#) reported on cancer incidence during the period 1958–2000 among A-bomb survivors exposed to radiation *in utero*. While prior work had focused on the excess risk of cancer in the first years of life following in-utero irradiation, Preston *et al.* found evidence of an association between in-utero irradiation and excess solid cancer risk in the period starting approximately 13 years after the atomic bombings in Japan. The optimal model indicated relationships between radiation dose in both in-utero and childhood exposures and risk of solid cancers, with modifications by a (negative) power of attained age. The ERR/Sv at age 50 years was 1.0 (95%CI: 0.2–2.3) for the in-utero cohort, slightly lower but not significantly different from the ERR in the early childhood-exposed cohort at this age (ERR/Sv, 1.7; 95%CI: 1.1–2.5). Excess absolute rates (EAR) at age 50 years increased markedly with attained age among those exposed in early childhood (EAR/10<sup>4</sup> person-year Sv, 56; 95%CI: 36–79) but exhibited little change in the in utero group (EAR/10<sup>4</sup> person-year Sv, 6.8; 95%CI: < 0–49) ([Preston \*et al.\*, 2008](#)).

There have been updated analyses of cancer incidence ([Izumi \*et al.\*, 2003a](#)) and cancer

mortality ([Izumi \*et al.\*, 2003b](#)) with regard to pre-conception exposure in the F<sub>1</sub> cohort of the Japanese A-bomb survivors. The study participants were conceived between 1 month and 38 years after the atomic bombings, and one or both parents were in either the cities of Hiroshima or Nagasaki at the time of the bombing and for childbirth. During the 40-year period of follow-up, 575 solid cancer cases and 68 haemopoietic neoplasms were recorded, and no associations were found with either paternal or maternal pre-conception dose ( $P > 0.1$ ) ([Izumi \*et al.\*, 2003b](#)). During the 1946–99 period of follow-up, 314 solid cancer deaths were recorded, and no associations were found with either paternal or maternal pre-conception dose ( $P > 0.1$ ) ([Izumi \*et al.\*, 2003a](#)).

## 2.2 Fallout from nuclear weapons testing

### 2.2.1 Semipalatinsk

Several hundred nuclear weapons tests, including above-ground tests, occurred at Semipalatinsk, Kazakhstan, then part of the former Soviet Union. Nearby residents were exposed to external doses of γ-radiation and internal doses due to the inhalation and ingestion of radioactive fallout from these nuclear

weapons tests (including  $^{131}\text{I}$ ,  $^{137}\text{Cs}$ , and  $^{90}\text{Sr}$ ). Estimating dose for these residents has shown to be difficult, and there are conflicting estimates of the magnitude of the doses received by individuals living in villages in the vicinity of Semipalatinsk ([Simon et al., 2003](#)). The study was comprised of two groups: 9850 permanent inhabitants of rural areas of the Semipalatinsk region and 9604 permanent inhabitants of villages located several hundred kilometres east of the test site. For the first group, individual internal and external doses were available, and a collective estimate of 20 mSv due to fallout from multiple atmospheric nuclear testing was used for the second group. Risk estimates were found to differ depending on whether they were based on the total cohort (including the comparison villages) or on the exposed villages only. The estimate of the ERR/Sv for all solid tumours was 1.77 (95%CI: 1.35–2.27) based on the data for the total cohort. A significant trend with dose was observed for cancer of the stomach (ERR/Sv, 1.68; 95%CI: 0.83–2.99), lung (ERR/Sv, 2.60; 95%CI: 1.38–4.63), and of the female breast (ERR/Sv, 1.28; 95%CI: 0.27–3.28). However, selection bias regarding the comparison group could not be ruled out. Based on the data for the exposed group only, the estimate of the ERR/Sv for all solid tumours was 0.81 (95%CI: 0.46–1.33); for cancer of the stomach, 0.95 (95%CI: 0.17–3.49); lung, 1.76 (95%CI: 0.48–8.83), and of the female breast, 1.09 (95%CI: –0.05–15.8) ([Bauer et al., 2005](#)).

## 2.3 Medical exposures

The previous *IARC Monograph* ([IARC, 2000](#)) reviewed several studies of second cancer risk following X- or  $\gamma$ -radiation therapy for a first cancer. Since then, several reports have been published on second cancers following radiotherapy; in these studies patients were treated primarily, or solely, with X-rays. However, studies of cancers following radiation therapy pose

several challenges: (i) the doses may be so high that cell-killing (the objective of the treatment) overwhelms cancer initiation, (ii) radiotherapy is often coupled with chemotherapy and their separate impacts may be difficult to distinguish, and (iii) patients with existing cancers may differ from the general population (raising questions about making generalisations of radiation risk estimates derived from studies of cancer survivors). In this *Monograph*, the risk of the second cancer following radiation therapy reported by recent X-ray studies is reviewed.

### 2.3.1 Cancer of the lung

The only major X-ray study with good quality radiation dosimetry and follow-up is an international Hodgkin disease study ([Gilbert et al., 2003](#)). This resulted in an ERR/Gy of 0.15 (95%CI: 0.06–0.39) after adjusting for chemotherapy and smoking. As with all studies considered, a potential problem with this study is ascertainment and adjustment for cigarette smoking. Although the methods used in this study are thorough, they are based on data abstracted from medical records, in which assessment of smoking before the primary cancer was mainly retrospective, so recall bias cannot be excluded. This study demonstrated that the interaction of radiation and chemotherapy risk was consistent with an additive relationship on the logistic scale, and a multiplicative relationship could be rejected ( $P = 0.017$ ). Conversely, the interaction of radiation and smoking was consistent with a multiplicative relationship, but not with an additive relationship ( $P < 0.001$ ). There was little indication of modification of ERR by age at exposure, years since exposure (after a 5-year minimum latent period) or attained age ([Gilbert et al., 2003](#)).

### 2.3.2 Cancer of the female breast

The major X-ray studies with good quality radiation dosimetry and follow-up are nested case-control studies in an international Hodgkin disease study ([Travis \*et al.\*, 2003](#)) and the Netherlands Hodgkin disease study ([van Leeuwen \*et al.\*, 2003](#)), as well as the French-United Kingdom childhood cancer ([Guibout \*et al.\*, 2005](#)) and the US scoliosis ([Ronckers \*et al.\*, 2008](#)) cohorts. The excess risk in the first three of these studies are reasonably consistent, at least for those women not treated with chemotherapy: the ERR/Gy was 0.15 (95%CI: 0.04–0.73) in [Travis \*et al.\* \(2003\)](#), 0.06 (95%CI: 0.01–0.13) in [van Leeuwen \*et al.\* \(2003\)](#), and 0.13 (95%CI: < 0.0–0.75) in [Guibout \*et al.\* \(2005\)](#). A higher point estimate of risk (ERR/Gy, 2.86; 95%CI: –0.07–8.62) was observed in the US scoliosis study ([Ronckers \*et al.\*, 2008](#)), but in view of the wide confidence interval this can be considered as consistent with the other three studies. A complication in some of these radiotherapy studies is radiation dose to the ovaries; the analyses of [van Leeuwen \*et al.\* \(2003\)](#) and [Travis \*et al.\* \(2003\)](#) suggested that women receiving large ovarian doses (> 5 Gy) were at lower risk of radiation-induced breast cancer, presumably because of ovarian ablation and induced menopause.

[Ronckers \*et al.\* \(2008\)](#) reported a significantly greater dose-response ( $P = 0.03$ ) for women who reported a family history of breast cancer in first- or second-degree relatives (ERR/Gy, 8.37; 95%CI: 1.50–28.16) compared with those without affected relatives (ERR/Gy, –0.16; 95%CI: < 0–4.41). Susceptibility alleles of single genes that confer a high risk of breast cancer are rare in the general population, but some studies have shown modification of breast cancer risk by family history ([Easton, 1999](#)). Recent genome-wide association studies (GWAS) have established several new breast cancer susceptibility loci ([Pharoah \*et al.\*, 2008](#)). The study of [Millikan \*et al.\* \(2005\)](#) suggests that other common polymorphisms

in DNA-repair genes may modify the effects of low-dose radiation exposure from medical sources. They reported a stronger trend of breast cancer risk with the number of diagnostic X-rays among women with 2–4 variant codons in *XRCC3*, *NBS1*, *XRCC2*, *BRCA2* genes than in women with only 0 or 1 variant codons in those genes. [The Working Group noted, however, that the results were inconclusive, being based only on self-reported exposure to ionizing radiation from medical sources, which may therefore be subject to recall bias. The particular genes used, and the gene “dose” cut-off points ( $\geq 2$  versus  $< 2$  codons), both presumably chosen *a posteriori*, may imply uncertainties regarding the statistical significance in this study].

### 2.3.3 Cancer of the brain/central nervous system

The major X-ray studies with good quality radiation dosimetry and follow-up are the Israeli tinea capitis study and the International Childhood Cancer Study. The ERR/Gy in the first of these, a cohort study of survivors of tinea capitis (a fungal infection of the scalp) treated with radiation in childhood, was 4.63 (95%CI: 2.43–9.12) for benign meningioma and 1.98 (95%CI: 0.73–4.69) for malignant brain tumour ([Sadetzki \*et al.\*, 2005](#)). In the second study ([Neglia \*et al.\*, 2006](#)), the ERR/Gy was 0.33 (95%CI: 0.07–1.71) for gliomas, 1.06 (95%CI: 0.21–8.15) for meningiomas, and 0.69 (95%CI: 0.25–2.23) for all central nervous system tumours. Therefore, in both studies, there is a pattern of increased relative risk per unit dose for benign brain tumours compared with malignant brain tumours, a pattern also observed in some other earlier studies ([Little \*et al.\*, 1998](#)).

### 2.3.4 Leukaemia

Modern classifications of leukaemia and other lymphatic and haematopoietic malignancies (e.g. [Swerdlow \*et al.\*, 2008](#)) are based on cytogenetic and

molecular principles that do not always coincide with the International Classification of Diseases. There are generally considered to be three main radiogenic subtypes: acute lymphocytic leukaemia, which is a leukaemia of precursor cells of either B-cell or T-cell origin; acute myeloid leukaemia, whose lineage and subtype are generally defined according to the French-American-British (FAB) system ([Bennett et al., 1982](#); [Harris et al., 1999](#)); and chronic myeloid leukaemia, whose predominant haematological feature is an elevated white-cell count in the peripheral blood, and which is characterized cytogenetically by the Philadelphia chromosome ([Linnet & Cartwright, 1996](#)).

The major X-ray studies with good quality radiation dosimetry and follow-up are an international nested case-control study on testicular cancer survivors and the New York tinea capitis cohort. The ERR at 10 Gy in the first of these ([Travis et al., 2000](#)) was 3.27 (95%CI: 1.2–13). In the New York tinea capitis study ([Shore et al., 2003](#)), the standardized incidence ratio (SIR) for leukaemia (following an average dose of about 4 Gy to cranial marrow) was 3.2 (95%CI: 1.5–6.1). No dose-response analysis was reported [possibly as a consequence of the small number of cases (eight leukaemias, of which six were non-chronic lymphocytic leukaemia in the exposed group versus one chronic lymphocytic leukaemia in the control group)].

For the risk of leukaemia associated with prenatal exposures, see Section 2.1.3 and Section 2.6.19.

## 2.4 Occupational studies

### 2.4.1 IARC 15-country study

IARC conducted a collaborative study of cancer risk among workers in the nuclear industry. Analyses include 407391 nuclear industry workers who were individually monitored for external irradiation (primarily  $\gamma$ -rays),

and were employed in the industry for at least 1 year ([Cardis et al., 2007](#)). Workers with potential for substantial doses from other radiation types and workers with potential for high-dose-rate exposure were excluded from the main study population. [The Working Group noted that strengths of the study include a common core study protocol and quantitative radiation dose estimates based upon personal dosimetry. Although it was a large study, the 15-country study's statistical power was limited by small numbers of workers with higher doses. As is common in occupational cohort mortality studies, there was limited information available on confounders, such as cigarette smoking.] Concerns about confounding by smoking were addressed indirectly by the examination of associations between radiation dose and non-malignant respiratory disease. Smoking-related and non-smoking-related solid cancers were also analysed separately. No statistically significant association was seen between radiation dose and any of the groups of non-malignant respiratory diseases examined. Risk estimates for mortality from all non-malignant respiratory disease and for chronic bronchitis and emphysema combined were positive but not significantly different from zero, and risk estimates for chronic pulmonary disease not otherwise specified and for emphysema were negative, but not significantly different from zero.

Among the cancer categories examined, a significant positive dose-response association was reported for lung cancer mortality; no other specific cancer category exhibited a statistically significant dose-response trend. The ERR/Sv was 1.86 (90%CI: 0.49–3.63) for cancer of the lung, 1.93 (90%CI: < 0–7.14) for leukaemia (excluding chronic lymphocytic leukaemia), 0.97 (90%CI: 0.27–1.80) for all cancers excluding leukaemia, 0.59 (90%CI: –0.16–1.51) for all cancers excluding leukaemia, lung and pleura, and 0.87 (90%CI: 0.16–1.71) for all solid cancers ([Cardis et al., 2007](#)). Risk estimates for all

cancers excluding leukaemia and for all cancers excluding leukaemia, lung and pleural cancers were very similar and above 200 mSv. [The Working Group noted that, therefore, although confounding by smoking might be present, it is unlikely to explain all of the increased risk for all cancers excluding leukaemia in that study.] Results by country show that, for all cancers excluding leukaemia, the ERR/Sv estimate for Canadian workers (6.65; 90%CI: 2.56–13.0) was larger than for workers from most other countries with sizable numbers of deaths, statistically significant, and exerted a substantial influence on the overall pooled analysis.

The ERR/Sv was greater for those exposed at ages over 50 years than for those exposed at younger ages. With regard to all cancers excluding leukaemia, ERR/Sv by age at exposure was 1.74 (90%CI: 0.24–3.58) for age > 50 years, 1.32 (90%CI: 0.12–2.71) for age 35–50 years, and –1.07 (90%CI: < 0–1.24) for age < 35 years. The respective values were 3.87 (90%CI: 0.92–7.93), 1.52 (90%CI: –0.71–4.36) and 2.51 (90%CI: –1.96–8.89) for cancer of the lung, and 5.01 (90%CI: < 0–14.7), –1.59 (90%CI: < 0–3.02) and 1.51 (90%CI: < 0–11.6) for leukaemia excluding chronic lymphocytic leukaemia.

An analysis examined the association between radiation dose and chronic lymphocytic leukaemia mortality among 295963 workers in the seven countries with chronic lymphocytic leukaemia deaths; there were 65 chronic lymphocytic leukaemia deaths in this cohort ([Vrijheid et al., 2008](#)). The relative risk (RR) at an occupational dose of 100 mSv compared to 0 mSv was 0.84 (95%CI: 0.39–1.48) under the assumption of a 10-year exposure lag. [The Working Group noted that this study had little power due to low doses (average cumulative bone marrow dose, 15 mSv), short follow-up periods, and uncertainties in chronic lymphocytic leukaemia ascertainment from death certificates.]

#### 2.4.2 United Kingdom radiation workers

Although many workers included in the United Kingdom National Registry for Radiation Workers (NRRW) were included in the IARC 15-country study, [Muirhead et al. \(2009\)](#) reported on an updated and expanded study of mortality and cancer incidence through December 2001 among 174541 people occupationally exposed to ionizing radiation, based on the NRRW. Doses from the internal deposition of radionuclides were not generally available and were not used in the analysis, nor was individual information available on smoking history. The analyses focused on doses from penetrating radiation at the surface of the body, estimated using personal dosimeters. Mortality and cancer incidence were studied in relation to dose after adjusting – through stratification – for age, gender, calendar period, industrial classification (industrial/non-industrial/unknown), and first employer. Within each stratum, the number of deaths or cases expected in each category for cumulative external dose (0–, 10–, 20–, 50–, 100–, 200–, 400+ mSv) was calculated, conditional on the total overall dose categories, and presuming no effect of dose. There was a highly significant negative association observed between mortality from bronchitis, emphysema and chronic obstructive disease and dose (ERR/Sv, –1.04; 90%CI: –1.35, –0.59) [The Working Group noted that this would be consistent with lower smoking prevalence among workers who accrued higher radiation doses and suggests potential negative confounding in analyses of radiation dose–response associations for smoking-related cancers]. There was a positive association between radiation dose and mortality due to leukaemia excluding chronic lymphocytic leukaemia (ERR/Sv, 1.71; 90%CI: 0.06–4.29), and also between radiation dose and mortality due to all malignant neoplasms excluding leukaemia (ERR/Sv, 0.28; 90%CI: 0.02–0.56). In analyses of cancer incidence, positive associations were also seen with leukaemia

excluding chronic lymphocytic leukaemia (ERR/Sv, 1.78; 90%CI: 0.17–4.36), and all malignant neoplasms excluding leukaemia (ERR/Sv, 0.27; 90%CI: 0.04–0.51). Among the leukaemia subtypes, the strongest evidence of association, from both analyses of mortality and incidence data, was for chronic myeloid leukaemia; there was no evidence of an association between chronic lymphocytic leukaemia (mortality or incidence) and radiation.

### 2.4.3 US radiation workers

The results of several epidemiological studies of US radiation workers have been reported, providing results that extend those encompassed by the US workers included in the 15-country study. An analysis of leukaemia mortality among workers employed at the Savannah River site, a large cohort of US nuclear weapons workers that is independent of the 15-country study, reported a positive association between leukaemia mortality and radiation dose under a 3-year lag assumption (ERR/Sv, 4; 90%CI: –0–12). The association was of larger magnitude for leukaemia excluding chronic lymphocytic leukaemia (ERR/Sv, 8; 90%CI: 1–20) and for myeloid leukaemia (ERR/Sv, 12; 90%CI: 2–35), and these associations tended to diminish in magnitude with time since exposure to radiation ([Richardson & Wing, 2007](#)). A positive association was also observed between lymphoma mortality and radiation dose under a 5- and 10-year lag (ERR/Sv, 6.99; 90%CI: 0.96–18.39 and ERR/Sv, 8.18; 90%CI: 1.44–21.16, respectively; [Richardson et al., 2009](#)). A nested case–control study of leukaemia among workers at four US nuclear weapons facilities and the Portsmouth naval shipyard reported a positive [but highly imprecise] association between leukaemia mortality and radiation dose (ERR/Sv, 1.44; 90%CI: <–1.03–7.59; [Schubauer-Berigan et al., 2007](#)). A case–control study of lung cancer among workers at Portsmouth Naval shipyard reported some evidence of a positive association

with lung cancer, which was substantially attenuated after adjusting for medical X-ray exposures ([Yiin et al., 2007](#)). [Matanoski et al. \(2008\)](#) reported the results of analyses of leukaemia, lymphohaematopoietic cancers, lung cancer, and mesothelioma among workers from shipyards involved in nuclear powered ship overhauls. The study included 28000 workers with cumulative doses of 5 mSv or more, 10462 workers with cumulative doses less than 5 mSv, and 33353 non-nuclear workers. Exposures were almost exclusively due to  $\gamma$ -radiation. There was evidence of dose-related increases in leukaemia, lung cancer, and lymphohaematopoietic cancers. In an internal comparison of workers with 50.0 mSv exposures to workers with exposures of 5.0–9.9 mSv, the relative risk was 2.41 (95%CI: 0.5–23.8) for leukaemia, 1.26 (95%CI: 0.9–1.9) for lung cancer, and 2.94 (95%CI: 1.0–12.0) for lymphohaematopoietic cancers.

### 2.4.4 Mayak

Since the previous *IARC Monograph* ([IARC, 2000](#)), updated reports have been published on cancer risk among workers at the Mayak nuclear complex in the Russian Federation, another large cohort of nuclear workers not included in the IARC study. Exposures at Mayak included external  $\gamma$ -radiation exposure as well as internal  $\alpha$ -particle exposure. A large number of workers, particularly those employed in the radiochemical and plutonium production facilities, had significant potential for plutonium exposures. [Gilbert et al. \(2004\)](#) investigated lung cancer mortality over the period 1955–2000 in a cohort of 21790 Mayak workers. The average cumulative external radiation dose among those monitored for radiation was 0.8 Gy. For external doses, the ERR/Gy was 0.17 (95%CI: 0.052–0.32) among men and 0.32 (95%CI: < 0–1.3) among women. [The Working Group noted that uncertainties in plutonium exposure assessment could lead to inadequate adjustment for the effects of internal exposures.]

Analyses restricted to Mayak workers who were monitored for plutonium or worked only in the reactor or auxiliary plants led to smaller estimates of ERR/Gy of external dose (ERR/Gy, 0.065; 95%CI:  $< 0-0.25$ ) than obtained via the analysis of the full cohort (ERR/Gy, 0.10; 95%CI:  $< 0-0.29$ ). The potential confounding by smoking was investigated in a subset of the cohort, and in that subcohort there was sparse data with which to evaluate the effects of external dose but the ERR/Gy was smaller when adjusted for smoking status (ERR/Gy, 0.027; 95%CI:  $< 0-0.18$ ; [Gilbert et al., 2004](#)). [Shilnikova et al. \(2003\)](#) reported that solid cancer and leukaemia death rates increased significantly with increasing  $\gamma$ -ray dose. For external doses, the ERR/Sv (adjusted for plutonium exposure) was 0.15 (90%CI: 0.09–0.20) for solid tumours and 0.99 (90%CI: 0.45–2.12) for leukaemia excluding chronic lymphocytic leukaemia.

#### 2.4.5 Chernobyl clean-up workers

[Kesminiene et al. \(2008\)](#) reported the results of a case-control study of leukaemia and lymphoma incidence among Chernobyl liquidators from Belarus, the Russian Federation, and Baltic countries. The main analyses included 70 cases (40 leukaemia, 20 non-Hodgkin lymphoma, and ten other types) and 287 age-matched controls. Bone-marrow doses were estimated by the “RADRUE” (realistic analytical dose reconstruction with uncertainty estimation) individual reconstruction methods ([Kryuchkov et al., 2009](#)). The overall ERR/Gy was 6.0 (90%CI:  $-0.2, 23.5$ ; [Kesminiene et al., 2008](#)). The dose-response relationship was of larger magnitude for non-Hodgkin lymphoma (ERR/Gy, 28.1; 90%CI: 0.9–243.0) than for leukaemia (ERR/Gy, 4.8; 90%CI:  $< 0, 33.1$ ), although the confidence intervals were wide for both outcomes. The ERR/Gy for leukaemia excluding chronic lymphocytic leukaemia was 5.0 (90%CI:  $-0.38, 5.7$ ) based on 19 cases and 83 controls; the risk estimate for

chronic lymphocytic leukaemia (ERR/Gy, 4.7; 90%CI:  $-\infty, 76.1$ ) was similar to the estimate for all leukaemia combined (ERR/Gy, 4.8; 90%CI:  $-\infty, 33.1$ ).

[Romanenko et al. \(2008\)](#) reported results from a nested case-control study of leukaemia in a cohort of clean-up workers identified from the Chernobyl State Registry of Ukraine. The study included 71 cases of leukaemia diagnosed during 1986–2000, and 501 age- and residence-matched controls; bone-marrow doses were estimated by the RADRUE reconstruction method. The ERR/Gy of total leukaemia was 3.44 (95%CI: 0.47–9.78). Overall, the dose-response relationship for both chronic (ERR/Gy, 4.09; 95%CI:  $< 0-14.41$ ) and non-chronic lymphocytic leukaemia (ERR/Gy, 2.73; 95%CI:  $< 0-13.50$ ) was comparable.

While leukaemia and lymphoma incidence among Chernobyl liquidators from the Russian Federation were examined in the study by [Kesminiene et al. \(2008\)](#), analyses of mortality and cancer incidence among Russian liquidators were also reported by [Ivanov \(2007\)](#). In 1991–98, the ERR/Gy of death from malignant neoplasm was 2.11 (95%CI: 1.31–2.92). In 1991–2001, the ERR estimation for incident solid cancers was positive [but imprecise] (ERR/Gy, 0.34; 95%CI:  $-0.39-1.22$ ; [Ivanov, 2007](#)).

## 2.5 Environmental studies

### 2.5.1 Techa River

Studies of environmental exposures to  $\gamma$ -radiation also provide insights into the carcinogenic effects of protracted exposures. A notable investigation of the effects of environmental exposures to  $\gamma$ -radiation concerns releases of radioactive materials into the Techa River in the southern urals, the Russian Federation, as a result of operations at the Mayak production facility. External exposures were primarily due to  $\gamma$ -radiation from contamination of the river shoreline and floodplains; in addition, internal

exposures resulted from the consumption of food and drink contaminated with radionuclides. Fission products were the largest component of the internal dose, and residents thus received internal  $\gamma$ - and  $\beta$ -radiation exposures. The ratio of external/internal radiation varied according to the site.

Since the previous *IARC Monograph*, several reports have been published on associations between radiation exposure and cancer among residents of villages along the Techa river. [Krestinina et al. \(2007\)](#) reported results on solid cancer incidence in a cohort of 17433 people who resided in villages along the Techa river, with follow-up from 1956–2002, in relation to the estimated cumulative stomach dose (approximately half from internal dose). There was a highly significant linear dose–response relationship between cumulative stomach dose and incidence of solid tumours ( $P = 0.004$ ). [Ostroumova et al. \(2008\)](#) reported results on breast cancer incidence in a cohort of 9908 women with follow-up from 1956–2004. A significant dose–response relationship ( $P = 0.01$ ) was reported between cumulative stomach dose and breast cancer incidence, with an estimated ERR/Gy of 5.00 (95%CI: 0.80–12.76). [Ostroumova et al. \(2006\)](#) reported results from a nested case–control study of leukaemia among residents near the Techa river. The study included 83 cases ascertained over a 47-year period of follow-up and 415 controls; in analyses of leukaemia excluding chronic lymphocytic leukaemia, the odds ratio at 1 Gy, estimated via a log-linear model, was 4.6 (95%CI: 1.7–12.3), 7.2 (95%CI: 1.7–30.0), and 5.4 (95%CI: 1.1–27.2) for total, external and internal red bone-marrow doses, respectively.

### 2.5.2 High-background radiation areas

[Hwang et al. \(2008\)](#) reported results on cancer risks in a cohort of Chinese residents in Taiwan, China, who received protracted low-dose-rate  $\gamma$ -radiation exposures from  $^{60}\text{Co}$ -contaminated

reinforcing steel used to build their apartments. The study included 117 cancer cases diagnosed during 1983–2005 among 6242 people with an average excess cumulative exposure estimate of about 48 mGy. There was a significant association between the estimated radiation dose and leukaemia excluding chronic lymphocytic leukaemia (hazard ratio (HR)/100 mGy, 1.19; 90%CI: 1.01–1.31); the HR/100 mGy estimated for breast cancer was 1.12 (90%CI: 0.99–1.21).

[Nair et al. \(2009\)](#) reported results on cancer incidence in Kerala, India, in an area known for high-background radiation from thorium-containing monazite sand. Cancer incidence in a cohort of 69958 residents aged 30–84 years was ascertained through to 2005 (average duration of follow-up, 10.5 years); the cumulative radiation dose for each individual was estimated based on outdoor and indoor dosimetry of each household. The median outdoor radiation levels were approximately 4 mGy per year; median indoor radiation levels were somewhat lower. The analysis, which included 1379 cancer cases and 30 leukaemia cases, found no cancer site was significantly related to cumulative radiation dose. The estimated ERR/Gy of cancer excluding leukaemia was  $-0.13$  (95%CI:  $-0.58$ – $0.46$ ).

## 2.6 Synthesis

The previous *IARC Monograph* ([IARC, 2000](#)) states there is strong evidence for causal associations between X- and  $\gamma$ -radiation and several cancer sites, including those listed in [Table 2.7](#). In this current *Monograph*, the Working Group re-evaluated the evidence (the earlier evidence and that published after the previous *IARC Monograph*) for those cancer sites, and similarly, found strong evidence of causation. The major publications on which the above conclusion is based are also listed in [Table 2.7](#). The United States [National Research Council \(2006\)](#) and [UNSCEAR \(2008b\)](#) have also made similar conclusions for the cancer sites listed in [Table 2.7](#).

**Table 2.7 Cancer sites and tumours judged to have sufficient evidence for a causal association with X-ray and γ-ray exposure**

| Organ site                              | Selected key studies                                                                                                                                                                                   |
|-----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Stomach                                 | <a href="#">Boice et al. (1988)</a> , <a href="#">Mattsson et al. (1997)</a> , <a href="#">Carr et al. (2002)</a> , <a href="#">Preston et al. (2003, 2007)</a>                                        |
| Colon                                   | <a href="#">Darby et al. (1994)</a> , <a href="#">Preston et al. (2003, 2007)</a>                                                                                                                      |
| Lung                                    | <a href="#">Weiss et al. (1994)</a> , <a href="#">Carr et al. (2002)</a> , <a href="#">Gilbert et al. (2003)</a> , <a href="#">Preston et al. (2003, 2007)</a>                                         |
| Basal cell skin carcinoma               | <a href="#">Schneider et al. (1985)</a> , <a href="#">Ron et al. (1991, 1998)</a> , <a href="#">Little et al. (1997)</a> , <a href="#">Shore et al. (2002)</a> , <a href="#">Preston et al. (2007)</a> |
| Female breast                           | <a href="#">Howe &amp; McLaughlin (1996)</a> , <a href="#">Preston et al. (2002, 2003, 2007)</a>                                                                                                       |
| Thyroid                                 | <a href="#">Lundell et al. (1994)</a> , <a href="#">Lindberg et al. (1995)</a> , <a href="#">Ron et al. (1995)</a> , <a href="#">Preston et al. (2007)</a>                                             |
| Leukaemia excluding chronic lymphocytic | <a href="#">Little et al. (1999)</a> , <a href="#">Travis et al. (2000)</a> , <a href="#">Preston et al. (2003, 2004)</a> , <a href="#">Muirhead et al. (2009)</a>                                     |

The evidence for the other individual cancer sites is shown in [Table 2.8](#). The focus has been on relatively large studies of good design, where good quality dosimetry has been carried out, and where the magnitude of the doses is generally substantial. Wherever possible, risk estimates from several studies were provided including the latest LSS incidence analysis ([Preston et al., 2007](#)) and in some cases the latest LSS mortality data ([Preston et al., 2003](#)), the International Radiation Study of Cervical Cancer Patients (IRSCCP; [Boice et al. 1988](#)), the United Kingdom ankylosing spondylitis data ([Weiss et al., 1994](#)), the United Kingdom metropathia haemorrhagica study ([Darby et al., 1994](#)), the NRRW ([Muirhead et al., 2009](#)), and the IARC 15-country study ([Cardis et al., 2007](#)). For certain cancer sites, some of these studies are largely uninformative (e.g. only standardized mortality ratios (SMRs) are given for various cancer sites in the metropathia haemorrhagica study), which were therefore omitted from [Table 2.8](#).

### 2.6.1 Cancer of the salivary gland

This is a rare cancer site and has not been much studied in most of the major radiation-exposed cohorts (e.g. [Boice et al., 1988](#); [Weiss et al., 1994](#); [Cardis et al., 2007](#), [Muirhead et al., 2009](#)). Nevertheless, there is a statistically

significant positive dose–response relationship in the Japanese A-bomb survivor incidence data ([Land et al., 1996](#)), and in the study of patients who received radiation therapy during childhood for benign conditions in the head and neck area ([Schneider et al., 1998](#)). The estimated ERR/Sv for the incidence data of the Japanese A-bomb survivors was 4.47 (90%CI: 2.45–8.46) for malignant tumours, based on 31 cases, and for benign tumours the risk estimate was 1.71 (90%CI: 1.13–2.71), based on 64 cases ([Land et al., 1996](#)). The ERR/Gy in the [Schneider et al. \(1998\)](#) study was –0.06 (95%CI: –∞–4.0) for malignant tumours, based on 22 cases, and 19.6 (95%CI: 0.16–∞) for benign tumours, based on 66 cases. Although data on dose–response are lacking, there are also indications of significant excess risk in the Israeli tinea capitis study ([Modan et al., 1998](#)), and in the Rochester thymus irradiation study ([Hildreth et al., 1985](#); [Table 2.8](#)). In the Israeli study as in the LSS, risks for malignant tumours (RR, 4.49; 95%CI: 1.45–13.9) were greater than benign tumours (RR, 2.62; 95%CI: 1.10–6.25), in contrast to the pattern in the study of [Schneider et al. \(1998\)](#). In the Rochester study, there were eight benign tumours (RR, 4.4; 95%CI: 1.2–16.7), but no malignant tumour in the irradiated group. A non-significant excess risk (RR, 1.8; 95%CI: 0.4–8.9) for salivary gland tumours (two

malignant and four benign) was reported in the New York tinea capitis study ([Shore et al., 2003](#)).

[Preston et al. \(2007\)](#) did not analyse this tumour in the most recent analysis of cancer incidence among the Japanese A-bomb survivors. [The Working Group analysed the publicly available data set using a linear relative risk model in which the expected number of cases in stratum  $i$  and dose group  $d$  is assumed to be given by  $PY_{id}\lambda_d [1 + \alpha D_{id}]$  fitted by Poisson maximum likelihood, and profile-likelihood bounds derived ([McCullagh & Nelder, 1989](#)) using EPICURE ([Preston et al., 1998](#)).

Here,  $PY_{id}$  is the number of (migration-adjusted) person-years of follow-up,  $\lambda_d$  is the (semi-parametric) background hazard rate (estimated separately for each stratum), and  $D_{id}$  is the DS02 organ dose in Sv (brain dose is used as a surrogate), using the neutron quality factor of 10 recommended by the [ICRP \(1991\)](#). The estimate of the ERR coefficient  $\alpha$  is given in [Table 2.8](#), and is seen to be statistically significant (2.42 per Sv; 95%CI: 0.48–6.70).]

In summary, although this is a rare cancer site, there are strong and highly statistically significant trends in the LSS data ([Land et al., 1996](#); [Preston et al., 2007](#)), and trends of similar magnitude in the study of [Schneider et al. \(1998\)](#). There are indications of excess risk in several other radiotherapeutically exposed groups.

### 2.6.2 Cancer of the oesophagus

Cancer incidence data from the latest LSS data show a significant excess risk of oesophageal cancer ([Preston et al., 2007](#)), as do the latest site-specific mortality data ([Preston et al., 2003](#)), as reported in [Table 2.8](#). The estimate of the ERR/Sv coefficient for the incidence data is 0.52 (90%CI: 0.15–1.0), based on 352 cases. For the LSS mortality data the ERR/Sv was broadly similar with 0.61 (90%CI: 0.15–1.2) for men, based on 224 deaths; and, 1.7 (90%CI: 0.46–3.8) for women, based on 67 deaths. There was also a

statistically significant excess risk reported in the United Kingdom ankylosing spondylitis study ([Weiss et al., 1994](#)); the ERR/Gy was 0.17 (95%CI: 0.09–0.25), based on 74 deaths.

In summary, there are strong and highly statistically significant trends in the LSS incidence and mortality data ([Preston et al., 2003, 2007](#)), as is the case in the United Kingdom ankylosing spondylitis data ([Weiss et al., 1994](#)). There are (statistically non-significant) indications of excess in several other studies (e.g. [Boice et al. 1985](#); [Muirhead et al. 2009](#); [Table 2.8](#)).

### 2.6.3 Cancer of the small intestine, including the duodenum

This is a rare cancer site and has not been much studied in most of the major radiation-exposed cohorts (e.g. [Weiss et al., 1994](#); [Cardis et al., 2007](#); [Muirhead et al., 2009](#)). There was no significant excess risk and no evidence of a positive dose-response in the IRSCCP ([Boice et al., 1988](#)): the odds ratio was 1.0 (90%CI: 0.3–2.9), based on 22 cases, despite the very high doses received (estimated to be several hundred Gy on average). [Preston et al. \(2007\)](#) did not analyse this tumour among A-bomb survivors. [The Working Group analysed the publicly available LSS incidence data set using a linear relative risk model (*Formula 1*) and obtained an ERR, given in [Table 2.8](#), which is not statistically significant (ERR/Sv, 0.65; 95%CI: –0.32–4.89), based on 16 cases.]

In summary, for this rare cancer, there are essentially only two informative studies, the LSS incidence data ([Preston et al., 2007](#)) and the IRSCCP ([Boice et al., 1988](#)), but neither of which reports a statistically significant excess risk.

### 2.6.4 Cancer of the rectum

Among the survivors of the atomic bombings, mortality from cancer of the rectum was not clearly associated with radiation dose

**Table 2.8 Summary of evidence for organ sites initially deemed to be potentially having limited evidence of carcinogenicity or inadequate evidence of carcinogenicity**

| Organ site                         | Study                              | Target                                                                                        | Dose range (mean)(Gy)          | Reference                                                               | ERR/EOR per Gy/ Sv unless otherwise stated (95%CI) (A-bomb, IARC 15-country and NRRW are Sv <sup>-1</sup> , all others Gy <sup>-1</sup> ) | Mortality/ incidence | Cases/ deaths | Other comments                                                                 |
|------------------------------------|------------------------------------|-----------------------------------------------------------------------------------------------|--------------------------------|-------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|----------------------|---------------|--------------------------------------------------------------------------------|
| Salivary gland                     | A-bomb                             | Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons | 0–4 (0.1)                      | <a href="#">Land <i>et al.</i> (1996)</a>                               | All malignant: 4.47 (2.45–8.46) <sup>a</sup><br>All benign: 1.71 (1.13–2.71) <sup>a</sup>                                                 | Incidence            | 31            |                                                                                |
|                                    | A-bomb                             | Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons | 0–4 (0.1)                      | <a href="#">Preston <i>et al.</i> (2007)</a>                            | All malignant: 2.42 (0.48–6.70)                                                                                                           | Incidence            | 64            | Stratified linear RR model fitted to publicly available data, using brain dose |
| Benign head & neck RT in childhood | Benign head & neck RT in childhood | 200 KeV X-rays to head and neck                                                               | 0.01–15.8 (4.2)                | <a href="#">Schneider <i>et al.</i> (1998)</a>                          | All malignant: –0.06 (–∞–4.0)<br>All benign: 19.6 (0.16–+∞)                                                                               | Incidence            | 22            |                                                                                |
|                                    | Thymic enlargement                 | Thymus 250 kVp X-rays                                                                         | Breast dose 0.01–19.51 (0.69)  | <a href="#">Hildreth <i>et al.</i> (1985)</a>                           | All malignant: RR, 0.0 (0.0–34.6)<br>All benign: RR, 4.4 (1.2–16.7)                                                                       | Incidence            | 66            | Women only                                                                     |
| New York tinea capitis             | New York tinea capitis             | X-rays to scalp                                                                               | (0.39 per treatment)           | <a href="#">Shore <i>et al.</i> (2003), Harley <i>et al.</i> (1976)</a> | RR, 1.8 (0.4–13)                                                                                                                          | Incidence            | 11            | 6 exposed, 2 unexposed cases                                                   |
| Israeli tinea capitis: malignant   | Israeli tinea capitis: malignant   | X-rays to scalp                                                                               | 0.63–2.86 (0.78) per treatment | <a href="#">Modan <i>et al.</i> (1998)</a>                              | Malignant: RR, 4.49 (1.45–13.9)                                                                                                           | Incidence            | 16            | 12 exposed, 4 controls                                                         |
|                                    |                                    |                                                                                               |                                |                                                                         | Benign: RR, 2.62 (1.10–6.25)                                                                                                              |                      | 22            | 14 exposed, 8 controls                                                         |

**Table 2.8 (continued)**

| Organ site                                                         | Study                                 | Target                                                                                                         | Dose range<br>(mean)(Gy)          | Reference                                        | ERR/EOR per Gy/<br>Sv unless otherwise<br>stated (95%CI)<br>(A-bomb, IARC<br>15-country and<br>NRRW are Sv <sup>-1</sup> , all<br>others Gy <sup>-1</sup> ) | Mortality/<br>incidence | Cases/<br>deaths | Other<br>comments                                       |
|--------------------------------------------------------------------|---------------------------------------|----------------------------------------------------------------------------------------------------------------|-----------------------------------|--------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|------------------|---------------------------------------------------------|
| Oesophagus                                                         | A-bomb                                | Uniform whole<br>body, mostly high-<br>energy (2–5 MeV)<br>gamma + small<br>amount of high-<br>energy neutrons | 0–4 (0.1)                         | <a href="#">Preston <i>et al.</i><br/>(2007)</a> | 0.52 (0.15–1.0) <sup>a</sup>                                                                                                                                | Incidence               | 352              | 80% of cases<br>confirmed<br>histologically             |
|                                                                    | A-bomb                                | Uniform whole<br>body, mostly high-<br>energy (2–5 MeV)<br>gamma + small<br>amount of high-<br>energy neutrons | 0–4 (0.1)                         | <a href="#">Preston <i>et al.</i><br/>(2003)</a> | Men: 0.61 (0.15–1.2) <sup>a</sup><br>Women:<br>1.7 (0.46–3.8) <sup>a</sup>                                                                                  | Mortality               | 224<br>67        |                                                         |
| Ankylosing<br>spondylitis                                          |                                       | X-rays to spinal                                                                                               | 90% range<br>0.48–10.16<br>(5.55) | <a href="#">Weiss <i>et al.</i><br/>(1994)</a>   | 0.17 (0.09–0.25)                                                                                                                                            | Mortality               | 74               |                                                         |
|                                                                    | Metropathia<br>haemorrhagica          | X-rays to ovaries                                                                                              | 90% range<br>0.02–0.11<br>(0.05)  | <a href="#">Darby <i>et al.</i><br/>(1994)</a>   | SMR, 0.97 (0.44–1.84)                                                                                                                                       | Mortality               | 9                |                                                         |
| International<br>Radiation Study<br>of Cervical<br>Cancer Patients |                                       | Mostly 200–<br>400 kVp X-ray<br>+radium +gamma<br>to cervix                                                    | (0.35)                            | <a href="#">Boice <i>et al.</i><br/>(1985)</a>   | 0.26 (–1.1–1.3) <sup>b</sup>                                                                                                                                | Incidence               | 12               | 10-year<br>survivors<br>following the<br>primary cancer |
|                                                                    | IARC<br>15-country<br>nuclear workers | Uniform whole<br>body                                                                                          | 0–> 0.5 Sv<br>(0.0194)            | <a href="#">Cardis <i>et al.</i><br/>(2007)</a>  | –1.6 (–4.3–1.5) <sup>a,d</sup>                                                                                                                              | Mortality               | 144              |                                                         |
| United Kingdom<br>NRRW                                             |                                       | Uniform whole<br>body                                                                                          | 0–> 0.1 Sv<br>(0.0249)            | <a href="#">Muirhead <i>et al.</i> (2009)</a>    | 0.15 (–0.84–1.72)<br>0.15 (–0.91–2.06)                                                                                                                      | Mortality<br>Incidence  | 341<br>300       |                                                         |

Table 2.8 (continued)

| Organ site                   | Study                                                              | Target                                                                                                         | Dose range<br>(mean)(Gy)                       | Reference                                        | ERR/EOR per Gy/<br>Sv unless otherwise<br>stated (95%CI)<br>(A-bomb, IARC<br>I5-country and<br>NRRW are Sv <sup>-1</sup> , all<br>others Gy <sup>-1</sup> ) | Mortality/<br>incidence | Cases/<br>deaths | Other<br>comments                                                                          |
|------------------------------|--------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|------------------------------------------------|--------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|------------------|--------------------------------------------------------------------------------------------|
| Small<br>intestine           | A-bomb                                                             | Uniform whole<br>body, mostly high-<br>energy (2–5 MeV)<br>gamma + small<br>amount of high-<br>energy neutrons | 0–4 (0.1)                                      | <a href="#">Preston <i>et al.</i><br/>(2007)</a> | 0.65 (–0.32–4.89)                                                                                                                                           | Incidence               | 16               | Stratified linear<br>RR model fitted<br>to publicly<br>available data,<br>using colon dose |
|                              |                                                                    | Mostly 200–<br>400 kVp X-ray<br>+radium +gamma<br>to cervix                                                    | 10–20                                          | <a href="#">Boice <i>et al.</i><br/>(1988)</a>   | OR, 1.0 (0.3–2.9) <sup>a</sup>                                                                                                                              | Incidence               | 22               | RR trend not<br>computed<br>because of small<br>number of non-<br>exposed cases            |
| Cervical<br>cancer           | A-bomb                                                             | Uniform whole<br>body, mostly high-<br>energy (2–5 MeV)<br>gamma + small<br>amount of high-<br>energy neutrons | 0–4 Sv (0.1)                                   | <a href="#">Preston <i>et al.</i><br/>(2007)</a> | 0.19 (–0.04–0.47) <sup>a</sup>                                                                                                                              | Incidence               | 838              | 90% of cases<br>confirmed<br>histologically                                                |
| Rectum                       | A-bomb                                                             | Uniform whole<br>body, mostly high-<br>energy (2–5 MeV)<br>gamma + small<br>amount of high-<br>energy neutrons | 0–4 (0.1)                                      | <a href="#">Preston <i>et al.</i><br/>(2003)</a> | Men: –0.25<br>(< –0.3–0.15) <sup>a</sup><br>Women:<br>0.75 (0.16–1.6) <sup>a</sup>                                                                          | Mortality               | 172              |                                                                                            |
|                              |                                                                    | Uniform whole<br>body, mostly high-<br>energy (2–5 MeV)<br>gamma + small<br>amount of high-<br>energy neutrons | 0–4 (0.1)                                      | <a href="#">Preston <i>et al.</i><br/>(2003)</a> | Men: –0.25<br>(< –0.3–0.15) <sup>a</sup><br>Women:<br>0.75 (0.16–1.6) <sup>a</sup>                                                                          | Mortality               | 198              |                                                                                            |
| Ankylosing<br>spondylitis    | Ankylosing<br>spondylitis                                          | X-rays to spine                                                                                                | 90% range<br>0.53–10.20<br>(4.12) <sup>c</sup> | <a href="#">Weiss <i>et al.</i><br/>(1994)</a>   | 0.03 (–0.03–0.10) <sup>c</sup>                                                                                                                              | Mortality               | 62               |                                                                                            |
|                              |                                                                    | X-rays to ovaries                                                                                              | 90% range<br>3.4–6.3 (4.9)                     | <a href="#">Darby <i>et al.</i><br/>(1994)</a>   | 0.04 (–0.09–0.16)                                                                                                                                           | Mortality               | 14               |                                                                                            |
| Metropathia<br>haemorrhagica | International<br>Radiation Study<br>of Cervical<br>Cancer Patients | Mostly 200–<br>400 kVp X-ray<br>+radium +gamma<br>to cervix                                                    | 30–60                                          | <a href="#">Boice <i>et al.</i><br/>(1988)</a>   | 0.02 (0.00–0.04) <sup>a</sup>                                                                                                                               | Incidence               | 488              |                                                                                            |

**Table 2.8 (continued)**

| Organ site                                     | Study                                   | Target                                                                                                         | Dose range<br>(mean)(Gy)         | Reference                                         | ERR/EOR per Gy/<br>Sv unless otherwise<br>stated (95%CI)<br>(A-bomb, IARC<br>15-country and<br>NRRW are Sv <sup>-1</sup> , all<br>others Gy <sup>-1</sup> ) | Mortality/<br>incidence | Cases/<br>deaths | Other<br>comments                           |
|------------------------------------------------|-----------------------------------------|----------------------------------------------------------------------------------------------------------------|----------------------------------|---------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|------------------|---------------------------------------------|
| <b>Rectum<br/>(contd.)</b>                     | IARC<br>15-country<br>nuclear workers   | Uniform whole<br>body                                                                                          | 0–> 0.5 Sv<br>(0.0194)           | <a href="#">Cardis <i>et al.</i><br/>(2007)</a>   | 1.27 (< 0–7.62) <sup>a</sup>                                                                                                                                | Mortality               | 185              |                                             |
|                                                | United Kingdom<br>NRRW                  | Uniform whole<br>body                                                                                          | 0–> 0.1 Sv<br>(0.0249)           | <a href="#">Muirhead <i>et al.</i><br/>(2009)</a> | 1.69 (–0.02–4.73)<br>1.31 (0.04–3.2)                                                                                                                        | Mortality<br>Incidence  | 303<br>586       |                                             |
|                                                | A-bomb                                  | Uniform whole<br>body, mostly high-<br>energy (2–5 MeV)<br>gamma + small<br>amount of high-<br>energy neutrons | 0–4 (0.1)                        | <a href="#">Preston <i>et al.</i><br/>(2007)</a>  | 0.30 (0.11–0.55) <sup>a,e</sup>                                                                                                                             | Incidence               | 1494             | 41% of cases<br>histologically<br>confirmed |
| <b>Liver</b>                                   | A-bomb                                  | Uniform whole<br>body, mostly high-<br>energy (2–5 MeV)<br>gamma + small<br>amount of high-<br>energy neutrons | 0–4 (0.1)                        | <a href="#">Preston <i>et al.</i><br/>(2003)</a>  | Men: 0.39 (0.11–0.68) <sup>a</sup><br>Females: 0.35 (0.07,<br>0.72) <sup>a</sup>                                                                            | Mortality<br>Mortality  | 722<br>514       |                                             |
|                                                | Ankylosing<br>spondylitis               | X-rays to spine                                                                                                | 90% range<br>0.31–3.83<br>(2.13) | <a href="#">Weiss <i>et al.</i><br/>(1994)</a>    | RR, 0.81 (0.40–1.44)                                                                                                                                        | Mortality               | 11               | Dose–response<br>not calculated             |
|                                                | Metropathia<br>haemorrhagica            | X-rays to ovaries                                                                                              | 90% range<br>0.12–0.55<br>(0.27) | <a href="#">Darby <i>et al.</i><br/>(1994)</a>    | SMR, 0.33 (0.04, 1.21)                                                                                                                                      | Mortality               | 2                | Dose–response<br>not calculated             |
| <b>IARC<br/>15-country<br/>nuclear workers</b> | IARC<br>15-country<br>nuclear workers   | Uniform whole<br>body                                                                                          | 0–> 0.5 Sv<br>(0.0194)           | <a href="#">Cardis <i>et al.</i><br/>(2007)</a>   | 6.47 (< 0–27.0) <sup>a</sup>                                                                                                                                | Mortality               | 62               |                                             |
|                                                | United Kingdom<br>NRRW primary<br>liver | Uniform whole<br>body                                                                                          | 0–> 0.1 Sv<br>(0.0249)           | <a href="#">Muirhead <i>et al.</i><br/>(2009)</a> | –1.50 (< –1.93–8.56)<br>–0.65 (< –1.93–7.73)                                                                                                                | Mortality<br>Incidence  | 40<br>56         |                                             |

Table 2.8 (continued)

| Organ site                                                         | Study               | Target                                                                                                         | Dose range<br>(mean)(Gy)         | Reference                                        | ERR/EOR per Gy/<br>Sv unless otherwise<br>stated (95%CI)<br>(A-bomb, IARC<br>15-country and<br>NRRW are Sv <sup>-1</sup> , all<br>others Gy <sup>-1</sup> ) | Mortality/<br>incidence | Cases/<br>deaths | Other<br>comments                           |
|--------------------------------------------------------------------|---------------------|----------------------------------------------------------------------------------------------------------------|----------------------------------|--------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|------------------|---------------------------------------------|
| Pancreas                                                           | A-bomb              | Uniform whole<br>body, mostly high-<br>energy (2–5 MeV)<br>gamma + small<br>amount of high-<br>energy neutrons | 0–4 (0.1)                        | <a href="#">Preston <i>et al.</i><br/>(2007)</a> | 0.26 (< –0.07–0.68) <sup>a</sup>                                                                                                                            | Incidence               | 512              | 52% of cases<br>confirmed<br>histologically |
|                                                                    | A-bomb              | Uniform whole<br>body, mostly high-<br>energy (2–5 MeV)<br>gamma + small<br>amount of high-<br>energy neutrons | 0–4 (0.1)                        | <a href="#">Preston <i>et al.</i><br/>(2003)</a> | Men: –0.11<br>(< –0.3–0.44) <sup>a</sup><br>Females: –0.01 (–0.28-<br>0.45) <sup>a</sup>                                                                    | Mortality               | 163<br><br>244   |                                             |
| Peptic ulcer                                                       |                     | 250 kVp X-ray                                                                                                  | 0.9–> 16 (13.5)                  | <a href="#">Carr <i>et al.</i><br/>(2002)</a>    | Irradiated + not:<br>0.04 (0.00–0.08)<br>Irradiated only: –0.03<br>(–0.10–0.05)                                                                             | Mortality               | 59               |                                             |
|                                                                    | Skin<br>haemangioma | Radium-226<br>applicators                                                                                      | < 0.01–> 1.0<br>(0.09)           | <a href="#">Lundell &amp;<br/>Holm (1995)</a>    | 25.1 (5.5–57.7)                                                                                                                                             | Incidence               | 9                |                                             |
| Ankylosing<br>spondylitis                                          |                     | X-rays to spine                                                                                                | 90% range<br>0.53–8.24<br>(4.52) | <a href="#">Weiss <i>et al.</i><br/>(1994)</a>   | 0.12 (0.05–0.20)                                                                                                                                            | Mortality               | 84               |                                             |
| Metropathia<br>haemorrhagica                                       |                     | X-rays to ovaries                                                                                              | 90% range<br>0.12–0.61<br>(0.29) | <a href="#">Darby <i>et al.</i><br/>(1994)</a>   | SMR, 0.66 (0.30–1.26)                                                                                                                                       | Mortality               | 9                | Dose–response<br>not calculated             |
| International<br>Radiation Study<br>of Cervical<br>Cancer Patients |                     | Cervix                                                                                                         | 0–> 3 (1.9)                      | <a href="#">Boice <i>et al.</i><br/>(1988)</a>   | 0.00 (–0.28–0.62) <sup>a</sup>                                                                                                                              | Incidence               | 221              |                                             |
| IARC<br>15-country<br>nuclear workers                              |                     | Uniform whole<br>body                                                                                          | 0–> 0.5 Sv<br>(0.0194)           | <a href="#">Cardis <i>et al.</i><br/>(2007)</a>  | 2.10 (–0.59–6.77) <sup>a</sup>                                                                                                                              | Mortality               | 272              |                                             |
| United Kingdom<br>NRRW                                             |                     | Uniform whole<br>body                                                                                          | 0–> 0.1 Sv<br>(0.0249)           | <a href="#">Muirhead <i>et al.</i> (2009)</a>    | –0.05 (–1.11–2.07)<br>0.08 (–1.07–2.51)                                                                                                                     | Mortality<br>Incidence  | 330<br>320       |                                             |

**Table 2.8 (continued)**

| Organ site                     | Study                                                                       | Target                                                                                                         | Dose range<br>(mean)(Gy)                | Reference                                        | ERR/EOR per Gy/<br>Sv unless otherwise<br>stated (95%CI)<br>(A-bomb, IARC<br>15-country and<br>NRRW are Sv <sup>-1</sup> , all<br>others Gy <sup>-1</sup> ) | Mortality/<br>incidence | Cases/<br>deaths | Other<br>comments                                                                                |
|--------------------------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|-----------------------------------------|--------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|------------------|--------------------------------------------------------------------------------------------------|
| Bone &<br>connective<br>tissue | A-bomb                                                                      | Uniform whole<br>body, mostly high-<br>energy (2–5 MeV)<br>gamma + small<br>amount of high-<br>energy neutrons | 0–4 (0.1)                               | <a href="#">Preston <i>et al.</i><br/>(2007)</a> | Bone: 1.01 (< 0–4.38)<br>Connective tissue:<br>1.76 (< 0–6.41)<br>Bone+connective<br>tissue: 1.34 (0.14–3.74)                                               | Incidence               | 18<br>23<br>41   | Stratified linear<br>RR model fitted<br>to publicly<br>available data,<br>using skeletal<br>dose |
|                                | Retinoblastoma<br>patients                                                  |                                                                                                                | (0.0)                                   | <a href="#">Wong <i>et al.</i><br/>(1997)</a>    | 0.19 (0.14–0.32) <sup>b</sup>                                                                                                                               | Incidence               | 81               |                                                                                                  |
|                                | Childhood<br>radiotherapy<br>(international)                                |                                                                                                                | (27)                                    | <a href="#">Tucker <i>et al.</i><br/>(1987)</a>  | 0.06 (0.01–0.2) <sup>a,b</sup>                                                                                                                              | Incidence               | 54               |                                                                                                  |
|                                | United Kingdom<br>childhood<br>cancer: bone                                 |                                                                                                                | 0–> 50 (10)                             | <a href="#">Hawkins <i>et al.</i><br/>(1996)</a> | 0.16 (0.07–0.37) <sup>b</sup>                                                                                                                               | Incidence               | 49               |                                                                                                  |
|                                | Ankylosing<br>spondylitis                                                   | X-rays to spine                                                                                                | 90% range<br>1.42–7.82<br>(4.54)        | <a href="#">Weiss <i>et al.</i><br/>(1994)</a>   | Bone: RR,<br>3.29 (1.58–5.92)<br>Connective tissue: RR,<br>2.83 (1.41–4.95)                                                                                 | Mortality               | 9<br>10          | Dose-response<br>not calculated                                                                  |
|                                | Metropathia<br>haemorrhagica:<br>bone                                       | X-rays to ovaries                                                                                              | 90% range<br>1.0–1.6 (1.3) <sup>g</sup> | <a href="#">Darby <i>et al.</i><br/>(1994)</a>   | SMR, 0.00 (0.00–4.01)                                                                                                                                       | Mortality               | 0                | Dose-response<br>not calculated                                                                  |
|                                | International<br>Radiation Study<br>of Cervical<br>Cancer Patients:<br>bone | Cervix                                                                                                         | 0–> 30 (22.0)                           | <a href="#">Boice <i>et al.</i><br/>(1988)</a>   | RR, 1.34 (0.3–5.6) <sup>a</sup>                                                                                                                             | Incidence               | 15               | RR trend not<br>computed<br>because of small<br>number of non-<br>exposed cases                  |
|                                |                                                                             |                                                                                                                |                                         |                                                  |                                                                                                                                                             |                         |                  |                                                                                                  |
|                                |                                                                             |                                                                                                                |                                         |                                                  |                                                                                                                                                             |                         |                  |                                                                                                  |
|                                |                                                                             |                                                                                                                |                                         |                                                  |                                                                                                                                                             |                         |                  |                                                                                                  |

Table 2.8 (continued)

| Organ site                                            | Study                                                                                    | Target                                                                                                         | Dose range<br>(mean)(Gy) | Reference                                         | ERR/EOR per Gy/<br>Sv unless otherwise<br>stated (95%CI)<br>(A-bomb, IARC<br>15-country and<br>NRRW are Sv <sup>-1</sup> , all<br>others Gy <sup>-1</sup> )       | Mortality/<br>incidence                          | Cases/<br>deaths    | Other<br>comments |
|-------------------------------------------------------|------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|--------------------------|---------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|---------------------|-------------------|
| Bone &<br>connective<br>tissue<br>(contd.)            | International<br>Radiation Study<br>of Cervical<br>Cancer Patients:<br>connective tissue | Cervix                                                                                                         | 0-> 20 (7.0)             | <a href="#">Boice <i>et al.</i><br/>(1988)</a>    | -0.05 (-0.11-0.13) <sup>a</sup>                                                                                                                                   | Incidence                                        | 46                  |                   |
|                                                       | IARC<br>15-country<br>nuclear workers                                                    | Uniform whole<br>body                                                                                          | 0-> 0.5 Sv<br>(0.0194)   | <a href="#">Cardis <i>et al.</i><br/>(2007)</a>   | Bone: -8.4<br>(-10.0-17.2) <sup>a,d</sup><br>Connective tissue:<br>0.32 (< 0-11.5) <sup>a</sup>                                                                   | Mortality                                        | 16                  |                   |
|                                                       | United Kingdom<br>NRRW                                                                   | Uniform whole<br>body                                                                                          | 0-> 0.1 Sv<br>(0.0249)   | <a href="#">Muirhead <i>et al.</i><br/>(2009)</a> | Bone: < -1.93<br>(< -1.93-28.51)<br>Bone: 1.18<br>(< -1.93-52.16)<br>Connective tissue:<br>< -1.93 (< -1.93-7.49)<br>Connective tissue:<br>< -1.93 (< -1.93-1.42) | Mortality<br>Incidence<br>Mortality<br>Incidence | 8<br>17<br>31<br>58 |                   |
| <b>Skin cancers other than basal cell skin cancer</b> |                                                                                          |                                                                                                                |                          |                                                   |                                                                                                                                                                   |                                                  |                     |                   |
| <i>Squamous<br/>cell<br/>carcinoma</i>                | A-bomb                                                                                   | Uniform whole<br>body, mostly high-<br>energy (2-5 MeV)<br>gamma + small<br>amount of high-<br>energy neutrons | 0-4 (0.1)                | <a href="#">Ron <i>et al.</i><br/>(1998)</a>      | < -0.1 (< -0.1-0.10) <sup>a</sup>                                                                                                                                 | Incidence                                        | 69                  |                   |
| New York tinea<br>capitis                             | X-rays to scalp                                                                          | 3.3-6 scalp<br>dose (4.75)                                                                                     |                          | <a href="#">Shore <i>et al.</i><br/>(2002)</a>    | Irradiated 7 cases vs<br>unirradiated 0 cases                                                                                                                     | Incidence                                        | 7                   |                   |
| Israeli tinea<br>capitis                              | X-rays to scalp                                                                          | 5.5-24.4 scalp<br>dose (6.8)                                                                                   |                          | <a href="#">Ron <i>et al.</i><br/>(1991)</a>      | Irradiated 0 cases vs<br>unirradiated 2 cases                                                                                                                     | Incidence                                        | 2                   |                   |

**Table 2.8 (continued)**

| Organ site      | Study                                           | Target                                                                                                         | Dose range<br>(mean)(Gy) | Reference                                     | ERR/EOR per Gy/<br>Sv unless otherwise<br>stated (95%CI)<br>(A-bomb, IARC<br>15-country and<br>NRRW are Sv <sup>-1</sup> , all<br>others Gy <sup>-1</sup> )                              | Mortality/<br>incidence | Cases/<br>deaths   | Other<br>comments                                                                                                                                                 |
|-----------------|-------------------------------------------------|----------------------------------------------------------------------------------------------------------------|--------------------------|-----------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Melanoma</i> | A-bomb                                          | Uniform whole<br>body, mostly high-<br>energy (2–5 MeV)<br>gamma + small<br>amount of high-<br>energy neutrons | 0–4 (0.1)                | <a href="#">Thompson <i>et al.</i> (1994)</a> | 0.22 (< 0–4.14)                                                                                                                                                                          | Incidence               | 13                 | Stratified linear<br>RR model fitted<br>to publicly<br>available data,<br>using skeletal<br>dose                                                                  |
|                 | France-United<br>Kingdom<br>childhood<br>cancer | Treatment at<br>various sites                                                                                  | 0–51 (3.1)               | <a href="#">Guérin <i>et al.</i> (2003)</a>   | 0.07 (0.00–0.15)                                                                                                                                                                         | Incidence               | 16                 |                                                                                                                                                                   |
|                 | IARC<br>15-country<br>nuclear workers<br>(bone) | Uniform whole<br>body                                                                                          | 0–> 0.5 Sv<br>(0.0194)   | <a href="#">Cardis <i>et al.</i> (2007)</a>   | 0.15 (< 0–5.44) <sup>a</sup>                                                                                                                                                             | Mortality               | 87                 |                                                                                                                                                                   |
|                 | United Kingdom<br>NRRW                          | Uniform whole<br>body                                                                                          | 0–> 0.1 Sv<br>(0.0249)   | <a href="#">Muirhead <i>et al.</i> (2009)</a> | 1.39 (–0.65–5.6)                                                                                                                                                                         | Incidence               | 261                |                                                                                                                                                                   |
| <b>Uterus</b>   | A-bomb: uterine<br>corpus                       | Uniform whole<br>body, mostly high-<br>energy (2–5 MeV)<br>gamma + small<br>amount of high-<br>energy neutrons | 0–4 (0.1)                | <a href="#">Preston <i>et al.</i> (2007)</a>  | Uterine corpus: 0.29<br>(–0.14–0.95) <sup>a</sup><br>Uterine cervix + NOS:<br>0.06 (–0.14–0.31) <sup>a</sup><br>Uterine corpus,<br>uterine NOS+cervix:<br>0.10 (–0.09–0.33) <sup>a</sup> | Incidence               | 184<br>978<br>1162 | 97% of cases<br>confirmed<br>histologically<br>Cervix: 97% of<br>cases confirmed<br>histologically<br>Uterine NOS:<br>55% of cases<br>confirmed<br>histologically |

Table 2.8 (continued)

| Organ site         | Study                                                                                 | Target                                                                                                         | Dose range<br>(mean)(Gy)          | Reference                                         | ERR/EOR per Gy/<br>Sv unless otherwise<br>stated (95%CI)                                                                                           | Mortality/<br>incidence | Cases/<br>deaths | Other<br>comments                                                               |
|--------------------|---------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|-----------------------------------|---------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|------------------|---------------------------------------------------------------------------------|
| Uterus<br>(contd.) | A-bomb                                                                                | Uniform whole<br>body, mostly high-<br>energy (2–5 MeV)<br>gamma + small<br>amount of high-<br>energy neutrons | 0–4 (0.1)                         | <a href="#">Preston <i>et al.</i><br/>(2003)</a>  | 0.17 (–0.10–0.52) <sup>a</sup>                                                                                                                     | Mortality               | 518              |                                                                                 |
|                    | Ankylosing<br>spondylitis                                                             | X-rays to spine                                                                                                | 90% range<br>0.14–10.35<br>(4.94) | <a href="#">Weiss <i>et al.</i><br/>(1994)</a>    | Uterus including<br>cervix: ERR/Gy 0.09<br>(–0.02–0.19)<br>Uterus apart<br>from cervix: RR,<br>1.91 (0.92–3.51)<br>Cervix: RR,<br>0.36 (0.07–1.04) | Mortality               | 10               |                                                                                 |
|                    | Metropathia<br>haemorrhagica:<br>uterine corpus<br>+cervix                            | X-rays to ovaries                                                                                              | 90% range<br>4.3–6.4 (5.2)        | <a href="#">Darby <i>et al.</i><br/>(1994)</a>    | 0.09 (–0.02–0.19)                                                                                                                                  | Mortality               | 25               |                                                                                 |
|                    | International<br>Radiation Study<br>of Cervical<br>Cancer Patients:<br>uterine corpus | Mostly 200 –<br>400 kVp X-ray<br>+radium +gamma<br>to cervix                                                   | (165)                             | <a href="#">Boice <i>et al.</i><br/>(1988)</a>    | OR, 1.34 (0.8–2.3) <sup>a,h</sup>                                                                                                                  | Incidence               | 313              | RR trend not<br>computed<br>because of small<br>number of non-<br>exposed cases |
|                    | IARC<br>15-country<br>nuclear workers:<br>uterus apart<br>from cervix:                | Uniform whole<br>body                                                                                          | 0–> 0.5 Sv<br>(0.0194)            | <a href="#">Cardis <i>et al.</i><br/>(2007)</a>   | Uterus apart from<br>cervix 0.16 (< 0–94.1) <sup>a,i</sup>                                                                                         | Mortality               | 13               |                                                                                 |
|                    | United Kingdom<br>NRRW: uterine<br>corpus +cervix                                     | Uniform whole<br>body                                                                                          | 0–> 0.1 Sv<br>(0.0249)            | <a href="#">Muirhead <i>et al.</i><br/>(2009)</a> | Cervix –0.11 (< 0,<br>131) <sup>a</sup><br>17.81 (< –1.93–91.96)<br>10.52 (–0.50–48.02)                                                            | Mortality<br>Incidence  | 19<br>58         |                                                                                 |

**Table 2.8 (continued)**

| Organ site | Study                                                              | Target                                                                                                         | Dose range<br>(mean)(Gy)          | Reference                                        | ERR/EOR per Gy/<br>Sv unless otherwise<br>stated (95%CI)<br>(A-bomb, IARC<br>15-country and<br>NRRW are Sv <sup>-1</sup> , all<br>others Gy <sup>-1</sup> ) | Mortality/<br>incidence | Cases/<br>deaths | Other<br>comments                           |
|------------|--------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|-----------------------------------|--------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|------------------|---------------------------------------------|
| Ovary      | A-bomb                                                             | Uniform whole<br>body, mostly high-<br>energy (2–5 MeV)<br>gamma + small<br>amount of high-<br>energy neutrons | 0–4 (0.1)                         | <a href="#">Preston <i>et al.</i><br/>(2007)</a> | 0.61 (0.00–1.5) <sup>a</sup>                                                                                                                                | Incidence               | 245              | 88% of cases<br>confirmed<br>histologically |
|            | A-bomb                                                             | Uniform whole<br>body, mostly high-<br>energy (2–5 MeV)<br>gamma + small<br>amount of high-<br>energy neutrons | 0–4 (0.1)                         | <a href="#">Preston <i>et al.</i><br/>(2003)</a> | 0.94 (0.07–2.0) <sup>a</sup>                                                                                                                                | Mortality               | 136              |                                             |
|            | Ankylosing<br>spondylitis                                          | X-rays to spine                                                                                                | 90% range<br>0.12–12.28<br>(5.53) | <a href="#">Weiss <i>et al.</i><br/>(1994)</a>   | RR, 0.97 (0.52–1.67)                                                                                                                                        | Mortality               | 13               |                                             |
|            | Metropathia<br>haemorrhagica                                       | X-rays to ovaries                                                                                              | < 4.8–> 6.0<br>(5.3)              | <a href="#">Darby <i>et al.</i><br/>(1994)</a>   | 0.02 (–0.08–0.12)                                                                                                                                           | Mortality               | 18               |                                             |
|            | International<br>Radiation Study<br>of Cervical<br>Cancer Patients | Mostly 200 –<br>400 kVp X-ray<br>+radium +gamma<br>to cervix                                                   | 0–> 50 (32.1)                     | <a href="#">Boice <i>et al.</i><br/>(1988)</a>   | 0.01 (–0.02–0.14) <sup>a</sup>                                                                                                                              | Incidence               | 309              |                                             |
|            | IARC<br>15-country<br>nuclear workers                              | Uniform whole<br>body                                                                                          | 0–> 0.5 Sv<br>(0.0194)            | <a href="#">Cardis <i>et al.</i><br/>(2007)</a>  | –9.1 (–10.0–15.8) <sup>a,d</sup>                                                                                                                            | Mortality               | 35               |                                             |
|            | United Kingdom<br>NRRW                                             | Uniform whole<br>body                                                                                          | 0–> 0.1 Sv<br>(0.0249)            | <a href="#">Muirhead <i>et al.</i> (2009)</a>    | < –1.93<br>(< –1.93–121.76)                                                                                                                                 | Mortality               | 18               |                                             |
|            |                                                                    |                                                                                                                |                                   |                                                  | < –1.93<br>(< –1.93–88.75)                                                                                                                                  | Incidence               | 15               |                                             |

Table 2.8 (continued)

| Organ site      | Study                                 | Target                                                                                                         | Dose range<br>(mean)(Gy)                      | Reference                                         | ERR/EOR per Gy/<br>Sv unless otherwise<br>stated (95%CI)<br>(A-bomb, IARC<br>15-country and<br>NRRW are Sv <sup>-1</sup> , all<br>others Gy <sup>-1</sup> ) | Mortality/<br>incidence | Cases/<br>deaths | Other<br>comments                           |
|-----------------|---------------------------------------|----------------------------------------------------------------------------------------------------------------|-----------------------------------------------|---------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|------------------|---------------------------------------------|
| <b>Prostate</b> | A-bomb                                | Uniform whole<br>body, mostly high-<br>energy (2–5 MeV)<br>gamma + small<br>amount of high-<br>energy neutrons | 0–4 (0.1)                                     | <a href="#">Preston <i>et al.</i><br/>(2007)</a>  | 0.11 (–0.10–0.54) <sup>a</sup>                                                                                                                              | Incidence               | 387              | 88% of cases<br>confirmed<br>histologically |
|                 | A-bomb                                | Uniform whole<br>body, mostly high-<br>energy (2–5 MeV)<br>gamma + small<br>amount of high-<br>energy neutrons | 0–4 (0.1)                                     | <a href="#">Preston <i>et al.</i><br/>(2003)</a>  | 0.21 (< –0.3–0.96) <sup>a</sup>                                                                                                                             | Mortality               | 104              |                                             |
| <b>Bladder</b>  | Ankylosing<br>spondylitis             | X-rays to spine                                                                                                | 90% range<br>0.18–0.71<br>(0.36) <sup>i</sup> | <a href="#">Weiss <i>et al.</i><br/>(1994)</a>    | 0.14 (0.02–0.28)                                                                                                                                            | Mortality               | 88               |                                             |
|                 | IARC<br>15-country<br>nuclear workers | Uniform whole<br>body                                                                                          | 0–> 0.5 Sv<br>(0.0194)                        | <a href="#">Cardis <i>et al.</i><br/>(2007)</a>   | 0.77 (< 0–4.58) <sup>a</sup>                                                                                                                                | Mortality               | 301              |                                             |
| <b>Bladder</b>  | United Kingdom<br>NRRW                | Uniform whole<br>body                                                                                          | 0–> 0.1 Sv<br>(0.0249)                        | <a href="#">Muirhead <i>et al.</i><br/>(2009)</a> | 0.42 (–0.42–1.64)<br>–0.18 (–0.73–0.57)                                                                                                                     | Mortality<br>Incidence  | 702<br>1516      |                                             |
|                 | A-bomb                                | Uniform whole<br>body, mostly high-<br>energy (2–5 MeV)<br>gamma + small<br>amount of high-<br>energy neutrons | 0–4 (0.1)                                     | <a href="#">Preston <i>et al.</i><br/>(2007)</a>  | 1.23 (0.59–2.1) <sup>a,c</sup>                                                                                                                              | Incidence               | 469              | 88% of cases<br>confirmed<br>histologically |
| <b>Bladder</b>  | A-bomb                                | Uniform whole<br>body, mostly high-<br>energy (2–5 MeV)<br>gamma + small<br>amount of high-<br>energy neutrons | 0–4 (0.1)                                     | <a href="#">Preston <i>et al.</i><br/>(2003)</a>  | Men: 1.1 (0.2–2.5) <sup>a</sup><br>Women: 1.2 (0.10–3.1) <sup>a</sup>                                                                                       | Mortality               | 83<br>67         |                                             |

**Table 2.8 (continued)**

| Organ site                  | Study                                                              | Target                                                                                                         | Dose range<br>(mean)(Gy)          | Reference                                         | ERR/EOR per Gy/<br>Sv unless otherwise<br>stated (95%CI)<br>(A-bomb, IARC<br>15-country and<br>NRRW are Sv <sup>-1</sup> , all<br>others Gy <sup>-1</sup> ) | Mortality/<br>incidence | Cases/<br>deaths | Other<br>comments                           |
|-----------------------------|--------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|-----------------------------------|---------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|------------------|---------------------------------------------|
| <b>Bladder<br/>(contd.)</b> | Ankylosing<br>spondylitis                                          | X-rays to spine                                                                                                | 90% range<br>0.20–4.85<br>(2.18)  | <a href="#">Weiss <i>et al.</i><br/>(1994)</a>    | 0.24 (0.09–0.41)                                                                                                                                            | Mortality               | 71               |                                             |
|                             | Metropathia<br>haemorrhagica                                       | X-rays to ovaries                                                                                              | 90% range<br>4.3–6.4 (5.2)        | <a href="#">Darby <i>et al.</i><br/>(1994)</a>    | 0.40 (0.15–0.66)<br>SMR, 3.01 (1.84–4.64)                                                                                                                   | Mortality               | 20               |                                             |
|                             | International<br>Radiation Study<br>of Cervical<br>Cancer Patients | Mostly 200 –<br>400 kVp X-ray<br>+radium +gamma<br>to cervix                                                   | 30–60 Gy                          | <a href="#">Boice <i>et al.</i><br/>(1988)</a>    | 0.07 (0.02–0.17) <sup>a</sup>                                                                                                                               | Incidence               | 273              |                                             |
|                             | IARC<br>15-country<br>nuclear workers                              | Uniform whole<br>body                                                                                          | 0–> 0.5 Sv<br>(0.0194)            | <a href="#">Cardis <i>et al.</i><br/>(2007)</a>   | –2.2 (–5.0–1.0) <sup>a,d</sup>                                                                                                                              | Mortality               | 145              |                                             |
| <b>Kidney</b>               | United Kingdom<br>NRRW                                             | Uniform whole<br>body                                                                                          | 0–> 0.1 Sv<br>(0.0249)            | <a href="#">Muirhead <i>et al.</i><br/>(2009)</a> | 0.40 (–0.78–2.48)<br>0.65 (–0.28–1.96)                                                                                                                      | Mortality<br>Incidence  | 301<br>748       |                                             |
|                             | A-bomb                                                             | Uniform whole<br>body, mostly high-<br>energy (2–5 MeV)<br>gamma + small<br>amount of high-<br>energy neutrons | 0–4 (0.1)                         | <a href="#">Preston <i>et al.</i><br/>(2007)</a>  | 0.13 (–0.25–0.75) <sup>a</sup><br>EAR, 0.25 × 10 <sup>-4</sup> /PY/<br>Sv (0.07–0.53) <sup>a</sup>                                                          | Incidence               | 167              | 82% of cases<br>confirmed<br>histologically |
|                             | A-bomb                                                             | Uniform whole<br>body, mostly high-<br>energy (2–5 MeV)<br>gamma + small<br>amount of high-<br>energy neutrons | 0–4 (0.1)                         | <a href="#">Preston <i>et al.</i><br/>(2003)</a>  | Men: –0.02<br>(< –0.3–1.1) <sup>a</sup><br>Women: 0.97<br>(< –0.3–3.8) <sup>a</sup>                                                                         | Mortality               | 36<br>31         |                                             |
|                             | Ankylosing<br>spondylitis                                          | X-rays to spine                                                                                                | 90% range<br>0.71–11.74<br>(6.08) | <a href="#">Weiss <i>et al.</i><br/>(1994)</a>    | 0.10 (0.02–0.20)                                                                                                                                            | Mortality               | 35               |                                             |

Table 2.8 (continued)

| Organ site         | Study                                                              | Target                                                                                                         | Dose range<br>(mean)(Gy)         | Reference                                         | ERR/EOR per Gy/<br>Sv unless otherwise<br>stated (95%CI)<br>(A-bomb, IARC<br>I5-country and<br>NRRW are Sv <sup>-1</sup> , all<br>others Gy <sup>-1</sup> ) | Mortality/<br>incidence | Cases/<br>deaths       | Other<br>comments                                                                                          |
|--------------------|--------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|----------------------------------|---------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|------------------------|------------------------------------------------------------------------------------------------------------|
| Kidney<br>(contd.) | Metropathia<br>haemorrhagica                                       | X-rays to ovaries                                                                                              | 90% range<br>0.17–0.79<br>(0.40) | <a href="#">Darby <i>et al.</i><br/>(1994)</a>    | SMR, 1.19 (0.39–2.78)                                                                                                                                       | Mortality               | 5                      | Dose-response<br>not calculated                                                                            |
|                    | International<br>Radiation Study<br>of Cervical<br>Cancer Patients | Mostly 200–<br>400 kVp X-ray<br>+radium +gamma<br>to cervix                                                    | 0–> 3 (2.0)                      | <a href="#">Boice <i>et al.</i><br/>(1988)</a>    | 0.71 (0.03–2.24) <sup>a</sup>                                                                                                                               | Incidence               | 148                    |                                                                                                            |
|                    | IARC<br>15-country<br>nuclear workers                              | Uniform whole<br>body                                                                                          | 0–> 0.5 Sv<br>(0.0194)           | <a href="#">Cardis <i>et al.</i><br/>(2007)</a>   | 2.26 (< 0–14.9) <sup>a</sup>                                                                                                                                | Mortality               | 127                    |                                                                                                            |
| Brain &<br>CNS     | United Kingdom<br>NRRW                                             | Uniform whole<br>body                                                                                          | 0–> 0.1 Sv<br>(0.0249)           | <a href="#">Muirhead <i>et al.</i><br/>(2009)</a> | –1.03 (–1.57–0.39)<br>–0.41 (–1.32–1.48)                                                                                                                    | Mortality<br>Incidence  | 187<br>296             |                                                                                                            |
|                    | A-bomb                                                             | Uniform whole<br>body, mostly high-<br>energy (2–5 MeV)<br>gamma + small<br>amount of high-<br>energy neutrons | 0–4 (0.1)                        | <a href="#">Preston <i>et al.</i><br/>(2007)</a>  | All brain & CNS:<br>0.62 (0.21–1.2) <sup>a</sup><br>Glioma: 0.56<br>(–0.2–2.0)<br>Meningioma: 0.64<br>(–0.01–1.8)<br>Schwannoma:<br>4.50 (1.9–9.2)          | Incidence               | 281<br>56<br>110<br>64 | 81% of cases<br>confirmed<br>histologically                                                                |
|                    | A-bomb                                                             | Uniform whole<br>body, mostly high-<br>energy (2–5 MeV)<br>gamma + small<br>amount of high-<br>energy neutrons | 0–4 (0.1)                        | <a href="#">Preston <i>et al.</i><br/>(2003)</a>  | Men: 5.3 (1.4–16) <sup>a</sup><br>Women: 0.51<br>(< –0.3–3.9) <sup>a</sup>                                                                                  | Mortality               | 14<br>17               |                                                                                                            |
|                    | New York tinea<br>capitis                                          | Scalp irradiation                                                                                              | 0.75–1.7 (1.4)                   | <a href="#">Shore <i>et al.</i><br/>(2003)</a>    | 1.1 (0.1–2.8)<br>RR (treated:control),<br>+∞ (1.2–+ ∞)                                                                                                      | Incidence               | 7                      | SIR for brain<br>cancer,<br>3.0 (1.3–5.9). No<br>brain cancers<br>were observed<br>in the control<br>group |
|                    |                                                                    |                                                                                                                |                                  |                                                   |                                                                                                                                                             |                         |                        |                                                                                                            |

**Table 2.8 (continued)**

| Organ site                              | Study                                           | Target                                                                                                         | Dose range<br>(mean)(Gy)                  | Reference                                       | ERR/EOR per Gy/<br>Sv unless otherwise<br>stated (95%CI)<br>(A-bomb, IARC<br>15-country and<br>NRRW are Sv <sup>-1</sup> , all<br>others Gy <sup>-1</sup> )       | Mortality/<br>incidence | Cases/<br>deaths | Other<br>comments                                                                                    |
|-----------------------------------------|-------------------------------------------------|----------------------------------------------------------------------------------------------------------------|-------------------------------------------|-------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|------------------|------------------------------------------------------------------------------------------------------|
| <b>Brain &amp;<br/>CNS<br/>(contd.)</b> | Israeli tinea<br>capitis                        | X-rays to scalp                                                                                                | 1.0–6.0 (1.5)                             | <a href="#">Sadetzki <i>et al.</i> (2005)</a>   | All malignant:<br>1.98 (0.73–4.69)<br>All benign:<br>4.63 (2.43–9.12)                                                                                             | Incidence               | 44               |                                                                                                      |
|                                         |                                                 |                                                                                                                |                                           |                                                 |                                                                                                                                                                   |                         | 81               |                                                                                                      |
|                                         | France-United<br>Kingdom<br>childhood<br>cancer | Exposure of<br>various sites                                                                                   | 0–82.7 (6.2)                              | <a href="#">Little <i>et al.</i> (1998)</a>     | All malignant: 0.07<br>( $< 0-0.62$ )<br>All benign: $> 1000$<br>(0.25– $> 1\ 000$ )                                                                              | Incidence               | 12               |                                                                                                      |
|                                         |                                                 |                                                                                                                |                                           |                                                 |                                                                                                                                                                   |                         | 10               |                                                                                                      |
|                                         | Ankylosing<br>spondylitis<br>(spinal cord)      | X-rays to spine                                                                                                | Brain 90%<br>range<br>0.03–0.40<br>(0.20) | <a href="#">Weiss <i>et al.</i> (1994)</a>      | Spinal cord death<br>3.33 (0.08–18.6)                                                                                                                             | Mortality               | 1                |                                                                                                      |
|                                         | Metropathia<br>haemorrhagica                    | X-rays to ovaries                                                                                              | 90% range<br>0.001–0.004<br>(0.002)       | <a href="#">Darby <i>et al.</i> (1994)</a>      | SMR, 1.84 (0.84–3.49)                                                                                                                                             | Mortality               | 9                | Dose-response<br>not calculated                                                                      |
| <b>Non-<br/>Hodgkin<br/>lymphoma</b>    | IARC<br>15-country<br>nuclear workers           | Uniform whole<br>body                                                                                          | 0– $> 0.5$ Sv<br>(0.0194)                 | <a href="#">Cardis <i>et al.</i> (2007)</a>     | –1.8 (–4.7–1.7) <sup>a,d</sup>                                                                                                                                    | Mortality               | 235              |                                                                                                      |
|                                         | United Kingdom<br>NRRW                          | Uniform whole<br>body                                                                                          | 0– $> 0.1$ Sv<br>(0.0249)                 | <a href="#">Muirhead <i>et al.</i> (2009)</a>   | –1.36 (–1.85–0.55)<br>–0.88 (–1.56–0.69)                                                                                                                          | Mortality<br>Incidence  | 278<br>337       |                                                                                                      |
|                                         | A-bomb                                          | Uniform whole<br>body, mostly high-<br>energy (2–5 MeV)<br>gamma + small<br>amount of high-<br>energy neutrons | 0–4 (0.1)                                 | <a href="#">Richardson <i>et al.</i> (2009)</a> | 1.12 (0.26–2.51) <sup>a</sup>                                                                                                                                     | Mortality               | 84               | Men, aged 15–64<br>yr at exposure                                                                    |
|                                         | A-bomb                                          | Uniform whole<br>body, mostly high-<br>energy (2–5 MeV)<br>gamma + small<br>amount of high-<br>energy neutrons | 0–4 Sv (0.1)                              | <a href="#">Preston <i>et al.</i> (1994)</a>    | Combined ERR/Sv,<br>0.05 ( $< 0-0.70$ )<br>Men EAR, $0.56 \times 10^{-4}/$<br>PY/Sv (0.08–1.39)<br>Women EAR, $0 \times$<br>$10^{-4}/\text{PY/Sv}$ ( $< 0-0.28$ ) | Incidence               | 170              | Stratified linear<br>RR model fitted<br>to publicly<br>available data,<br>using bone-<br>marrow dose |

Table 2.8 (continued)

| Organ site                      | Study                                                     | Target                                            | Dose range<br>(mean)(Gy)                      | Reference                                       | ERR/EOR per Gy/<br>Sv unless otherwise<br>stated (95%CI)<br>(A-bomb, IARC<br>I5-country and<br>NRRW are Sv <sup>-1</sup> , all<br>others Gy <sup>-1</sup> ) | Mortality/<br>incidence | Cases/<br>deaths | Other<br>comments                                                              |
|---------------------------------|-----------------------------------------------------------|---------------------------------------------------|-----------------------------------------------|-------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|------------------|--------------------------------------------------------------------------------|
| Non-Hodgkin lymphoma (contd.)   | Ankylosing spondylitis                                    | X-rays to spine                                   | 90% range<br>1.65–8.41<br>(5.10) <sup>k</sup> | <a href="#">Weiss <i>et al.</i> (1994)</a>      | RR, 1.74 (1.23–2.36)                                                                                                                                        | Mortality               | 37               | Dose-response not calculated because there was no clear appropriate organ dose |
|                                 | Metropathia haemorrhagica                                 | X-rays to ovaries                                 | 90% range<br>1.0–1.6 (1.3) <sup>g</sup>       | <a href="#">Darby <i>et al.</i> (1994)</a>      | SMR, 0.75 (0.20–1.93)                                                                                                                                       | Mortality               | 4                | Dose-response not calculated                                                   |
|                                 | Benign gynaecological disease                             | Exposure of pelvic area                           | (1.19)                                        | <a href="#">Inskip <i>et al.</i> (1993)</a>     | RR (exposed: not),<br>0.9 (0.6–1.6) <sup>a</sup>                                                                                                            | Mortality               | 53               | Dose-response not calculated                                                   |
|                                 | International Radiation Study of Cervical Cancer Patients | Mostly 200–400 kVp X-ray +radium +gamma to cervix | 0–> 12 (7.1)                                  | <a href="#">Boice <i>et al.</i> (1988)</a>      | OR, 2.51 (0.8–7.6) <sup>a</sup>                                                                                                                             | Incidence               | 94               | RR trend not computed because of small number of non-exposed cases             |
|                                 | Savannah river site workers                               | Uniform whole body                                | 0–> 0.3 Sv                                    | <a href="#">Richardson <i>et al.</i> (2009)</a> | 7.62 (0.93–20.77) <sup>a</sup>                                                                                                                              | Mortality               | 51               |                                                                                |
| IARC I5-country nuclear workers | Chernobyl liquidator study                                | Work in aftermath of Chernobyl accident           | 0–> 0.5 (0.013)                               | <a href="#">Kesminiene <i>et al.</i> (2008)</a> | 28.1 (0.9–243) <sup>a</sup>                                                                                                                                 | Incidence               | 20               |                                                                                |
|                                 | IARC I5-country nuclear workers                           | Uniform whole body                                | 0–> 0.5 Sv<br>(0.0194)                        | <a href="#">Cardis <i>et al.</i> (2007)</a>     | 0.44 (< 0–4.78) <sup>a</sup>                                                                                                                                | Mortality               | 248              |                                                                                |
|                                 | United Kingdom NRRW                                       | Uniform whole body                                | 0–> 0.1 Sv<br>(0.0249)                        | <a href="#">Muirhead <i>et al.</i> (2009)</a>   | 0.78 (–0.66–3.4)<br>1.28 (–0.38–4.06)                                                                                                                       | Mortality<br>Incidence  | 237<br>305       |                                                                                |

**Table 2.8 (continued)**

| Organ site                            | Study                                                              | Target                                                                                                         | Dose range<br>(mean)(Gy)                      | Reference                                        | ERR/EOR per Gy/<br>Sv unless otherwise<br>stated (95%CI)<br>(A-bomb, IARC<br>15-country and<br>NRRW are Sv <sup>-1</sup> , all<br>others Gy <sup>-1</sup> ) | Mortality/<br>incidence | Cases/<br>deaths | Other<br>comments                                                                                    |
|---------------------------------------|--------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|-----------------------------------------------|--------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|------------------|------------------------------------------------------------------------------------------------------|
| <b>Hodgkin<br/>disease</b>            | A-bomb                                                             | Uniform whole<br>body, mostly high-<br>energy (2–5 MeV)<br>gamma + small<br>amount of high-<br>energy neutrons | 0–4 (0.1)                                     | <a href="#">Preston <i>et al.</i><br/>(1994)</a> | 0.48 (< 0–3.96)                                                                                                                                             | Incidence               | 21               | Stratified linear<br>RR model fitted<br>to publicly<br>available data,<br>using bone-<br>marrow dose |
|                                       | Ankylosing<br>spondylitis                                          | X-rays to spine                                                                                                | 90% range<br>1.65–8.41<br>(5.10) <sup>k</sup> | <a href="#">Weiss <i>et al.</i><br/>(1994)</a>   | RR, 1.65 (0.88–2.81)                                                                                                                                        | Mortality               | 13               | Dose–response<br>not calculated                                                                      |
|                                       | Metropathia<br>haemorrhagica                                       | X-rays to ovaries                                                                                              | 90% range<br>1.0–1.6 (1.3) <sup>k</sup>       | <a href="#">Darby <i>et al.</i><br/>(1994)</a>   | SMR, 3.30 (0.90–8.46)                                                                                                                                       | Mortality               | 4                | Dose–response<br>not calculated                                                                      |
|                                       | Benign<br>gynaecological<br>disease                                | Exposure of pelvic<br>area                                                                                     | (1.19)                                        | <a href="#">Inskip <i>et al.</i><br/>(1993)</a>  | RR (exposed: not),<br>0.9 (0.3–3.2) <sup>a</sup>                                                                                                            | Mortality               | 13               | Dose–response<br>not calculated                                                                      |
| IARC<br>15-country<br>nuclear workers | International<br>Radiation Study<br>of Cervical<br>Cancer Patients | Mostly 200–<br>400 kVp X-ray<br>+radium +gamma<br>to cervix                                                    | 0–> 12 (8.2)                                  | <a href="#">Boice <i>et al.</i><br/>(1988)</a>   | OR, 0.63 (0.2–2.6) <sup>a</sup>                                                                                                                             | Incidence               | 14               | RR trend not<br>computed<br>because of small<br>number of non-<br>exposed cases                      |
|                                       | IARC<br>15-country<br>nuclear workers                              | Uniform whole<br>body                                                                                          | 0–> 0.5 Sv<br>(0.0194)                        | <a href="#">Cardis <i>et al.</i><br/>(2007)</a>  | –0.18 (< –0.18–7.25) <sup>a</sup>                                                                                                                           | Mortality               | 44               |                                                                                                      |
| United Kingdom<br>NRRW                | Uniform whole<br>body                                              | Uniform whole<br>body                                                                                          | 0–> 0.1 Sv<br>(0.0249)                        | <a href="#">Muirhead <i>et al.</i> (2009)</a>    | < –1.93<br>(< –1.93–32.73)<br>< –1.93<br>(< –1.93–12.55)                                                                                                    | Mortality<br>Incidence  | 33<br>67         |                                                                                                      |

Table 2.8 (continued)

| Organ site                            | Study                                                              | Target                                                                                                         | Dose range<br>(mean)(Gy)                      | Reference                                        | ERR/EOR per Gy/<br>Sv unless otherwise<br>stated (95%CI)<br>(A-bomb, IARC<br>I5-country and<br>NRRW are Sv <sup>-1</sup> , all<br>others Gy <sup>-1</sup> ) | Mortality/<br>incidence | Cases/<br>deaths | Other<br>comments                                                                             |
|---------------------------------------|--------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|-----------------------------------------------|--------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|------------------|-----------------------------------------------------------------------------------------------|
| Multiple<br>myeloma                   | A-bomb                                                             | Uniform whole<br>body, mostly high-<br>energy (2–5 MeV)<br>gamma + small<br>amount of high-<br>energy neutrons | 0–4 (0.1)                                     | <a href="#">Preston <i>et al.</i><br/>(1994)</a> | EAR, $0.08 \times 10^{-4}$ /PY/<br>Sv (< 0–0.3)                                                                                                             | Incidence               | 59               |                                                                                               |
|                                       | Ankylosing<br>spondylitis                                          | X-rays to spine                                                                                                | 90% range<br>1.65–8.41<br>(5.10) <sup>k</sup> | <a href="#">Weiss <i>et al.</i><br/>(1994)</a>   | RR, 1.62 (1.07–2.46)                                                                                                                                        | Mortality               | 22               | Dose–response<br>not calculated<br>because there<br>was no clear<br>appropriate<br>organ dose |
|                                       | Metropathia<br>haemorrhagica                                       | X-rays to ovaries                                                                                              | 90% range<br>1.0–1.6 (1.3) <sup>g</sup>       | <a href="#">Darby <i>et al.</i><br/>(1994)</a>   | SMR, 2.59 (1.19–4.92)                                                                                                                                       | Mortality               | 9                | Dose–response<br>not calculated                                                               |
|                                       | Benign<br>gynaecological<br>disease                                | Exposure of pelvic<br>area                                                                                     | (1.19)                                        | <a href="#">Inskip <i>et al.</i><br/>(1993)</a>  | RR (exposed: not),<br>0.6 (0.3–1.4) <sup>a</sup>                                                                                                            | Mortality               | 21               | Dose–response<br>not calculated                                                               |
| IARC<br>I5-country<br>nuclear workers | International<br>Radiation Study<br>of Cervical<br>Cancer Patients | Mostly 200–<br>400 kVp X-ray<br>+radium +gamma<br>to cervix                                                    | 0–> 12 (7.1)                                  | <a href="#">Boice <i>et al.</i><br/>(1988)</a>   | RR, 0.26 (0.0–2.6) <sup>a</sup>                                                                                                                             | Incidence               | 49               | RR trend not<br>computed<br>because of small<br>number of non-<br>exposed cases               |
|                                       | IARC<br>I5-country<br>nuclear workers                              | Uniform whole<br>body                                                                                          | 0–> 0.5 Sv<br>(0.0194)                        | <a href="#">Cardis <i>et al.</i><br/>(2007)</a>  | 6.15 (< 0–20.6) <sup>a</sup>                                                                                                                                | Mortality               | 83               |                                                                                               |
|                                       | United Kingdom<br>NRRW                                             | Uniform whole<br>body                                                                                          | 0–> 0.1 Sv<br>(0.0249)                        | <a href="#">Muirhead <i>et al.</i> (2009)</a>    | 1.20 (–1.08–7.31)<br>3.60 (0.43–10.37)                                                                                                                      | Mortality<br>Incidence  | 113<br>149       |                                                                                               |

**Table 2.8 (continued)**

| Organ site                                                         | Study                               | Target                                                                         | Dose range<br>(mean)(Gy)                            | Reference                                       | ERR/EOR per Gy/<br>Sv unless otherwise<br>stated (95%CI)<br>(A-bomb, IARC<br>15-country and<br>NRRW are Sv <sup>-1</sup> , all<br>others Gy <sup>-1</sup> ) | Mortality/<br>incidence | Cases/<br>deaths | Other<br>comments               |
|--------------------------------------------------------------------|-------------------------------------|--------------------------------------------------------------------------------|-----------------------------------------------------|-------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|------------------|---------------------------------|
| Chronic<br>lymphocytic<br>leukaemia                                | Ankylosing<br>spondylitis           | X-rays to spine                                                                | 0-> 7.00 (4.38)                                     | <a href="#">Weiss <i>et al.</i><br/>(1995)</a>  | RR, 1.44 (0.62-2.79)                                                                                                                                        | Mortality               | 7                | Dose-response<br>not calculated |
|                                                                    | Benign<br>locomotor<br>lesions      | X-rays to spine<br>and joints                                                  | < 0.2-> 0.5                                         | <a href="#">Damber <i>et al.</i><br/>(1995)</a> | SIR, 1.07 (0.80-1.41)                                                                                                                                       | Mortality               | 50               | Dose-response<br>not calculated |
|                                                                    | Benign<br>gynaecological<br>disease | Exposure of pelvic<br>area                                                     | (1.19)                                              | <a href="#">Inskip <i>et al.</i><br/>(1993)</a> | RR (exposed: not),<br>1.1 (0.5-3.0) <sup>a1</sup>                                                                                                           | Mortality               | 21 <sup>1</sup>  | Dose-response<br>not calculated |
|                                                                    | Breast cancer                       | Radiation to chest,<br>supraclavicular<br>nodes, axilla, etc.                  | (5.3)                                               | <a href="#">Curtis <i>et al.</i><br/>(1989)</a> | RR (exposed: not),<br>1.84 (0.5-6.7) <sup>a</sup>                                                                                                           | Incidence               | 10               | Dose-response<br>not calculated |
| Uterine corpus<br>cancer                                           |                                     | Radiation to<br>vagina, pelvis and<br>regional lymph<br>nodes                  | Brachytherapy<br>90% range<br>0.7-2.7 (mean<br>1.7) | <a href="#">Curtis <i>et al.</i><br/>(1994)</a> | RR (exposed: not),<br>0.90 (0.4-1.9)                                                                                                                        | Incidence               | 54               | Dose-response<br>not calculated |
|                                                                    |                                     | External beam<br>90% range<br>6.4-14.0 (mean<br>9.7)<br>(overall mean<br>5.22) |                                                     |                                                 |                                                                                                                                                             |                         |                  |                                 |
| International<br>Radiation Study<br>of Cervical<br>Cancer Patients |                                     | Mostly 200 -<br>400 kVp X-ray<br>+radium +gamma<br>to cervix                   | 0-> 12 (7.1)                                        | <a href="#">Boice <i>et al.</i><br/>(1988)</a>  | OR, 1.03 (0.3-3.9) <sup>a</sup>                                                                                                                             | Incidence               | 52               | Dose-response<br>not calculated |

Table 2.8 (continued)

| Organ site                                      | Study                                 | Target                                        | Dose range<br>(mean)(Gy) | Reference                                | ERR/EOR per Gy/<br>Sv unless otherwise<br>stated (95%CI)<br>(A-bomb, IARC<br>15-country and<br>NRRW are Sv <sup>†</sup> , all<br>others Gy <sup>†</sup> ) | Mortality/<br>incidence | Cases/<br>deaths | Other<br>comments |
|-------------------------------------------------|---------------------------------------|-----------------------------------------------|--------------------------|------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|------------------|-------------------|
| Chronic<br>lymphocytic<br>leukaemia<br>(contd.) | Chernobyl<br>liquidator study         | Work in aftermath<br>of Chernobyl<br>accident | 0–3.22<br>(0.0764)       | <a href="#">Romanenko et al. (2008)</a>  | 4.09 (< 0–14.41)                                                                                                                                          | Incidence               | 39               |                   |
|                                                 | Chernobyl<br>liquidator study         | Work in aftermath<br>of Chernobyl<br>accident | 0–> 0.5 (0.013)          | <a href="#">Kesminiene et al. (2008)</a> | 4.7 (–∞–76.1) <sup>a,f</sup>                                                                                                                              | Incidence               | 21               |                   |
|                                                 | IARC<br>15-country<br>nuclear workers | Uniform whole<br>body                         | 0–> 0.5 Sv<br>(0.0194)   | <a href="#">Cardis et al. (2007)</a>     | –1.0 (–5.0–3.7) <sup>a,d</sup>                                                                                                                            | Mortality               | 47               |                   |
|                                                 | United Kingdom<br>NRRW                | Uniform whole<br>body                         | 0–> 0.1 Sv<br>(0.0249)   | <a href="#">Muirhead et al. (2009)</a>   | < –1.92 (< –1.92–1.23) <sup>a</sup><br>–0.12 (–1.42–2.71) <sup>a</sup>                                                                                    | Mortality<br>Incidence  | 69<br>128        |                   |

<sup>a</sup> 90%CI<sup>b</sup> Taken from [UNSCEAR \(2008b\)](#)<sup>c</sup> Based on descending & sigmoid colon dose<sup>d</sup> Computed using a log-linear model (central estimate and confidence bounds given as 10\*(RR-1) (RR estimated at 0.1 Sv))<sup>e</sup> Sex averaged<sup>f</sup> Lower confidence bound not determined<sup>g</sup> Based on total active red bone-marrow dose, using weights to 17 compartments defined by [Christy \(1981\)](#)<sup>h</sup> Patients receiving less than 100 Gy to uterus were designated as controls<sup>i</sup> Upper CI computed using a log-linear model<sup>j</sup> Based on dose on testes<sup>k</sup> Based on red bone-marrow dose<sup>†</sup> Chronic lymphocytic leukaemia and lymphocytic leukaemia not otherwise specified (NOS)

CNS, central nervous system; SMR, standardized mortality ratio

([Preston et al., 2003](#)). For men, there were 172 deaths yielding an ERR/Sv of  $-0.25$  (90%CI:  $< -0.3$ – $-0.15$ ), and for women, there were 198 deaths yielding an ERR/Sv of  $0.75$  (90%CI:  $0.16$ – $1.6$ ). In the analysis of incidence data, a borderline statistically significant dose–response was reported with an ERR/Sv of  $0.19$  (90%CI:  $-0.04$ – $0.47$ ), based on 838 cases of cancer of the rectum arising evenly between the genders ([Preston et al., 2007](#)). There was a highly significant excess of cancer of the rectum in the IRSCCP ( $P = 0.002$  for 10-year survivors), yielding an ERR/Gy of  $0.02$  (90%CI:  $0.00$ – $0.04$ ) ([Boice et al., 1988](#)). There was no statistically significant excess risk in the United Kingdom ankylosing spondylitis data ([Weiss et al., 1994](#)), nor in the IARC 15-country study ([Cardis et al., 2007](#)). In the latest NRRW analysis ([Muirhead et al., 2009](#)), there were borderline statistically significant elevations of ERR in the mortality data (ERR/Sv,  $1.69$ ; 95%CI:  $-0.02$ – $4.73$ ), based on 303 deaths, and in the incidence data (ERR/Sv,  $1.31$ ; 95%CI:  $0.04$ – $3.2$ ), based on 586 cases. Although the confidence intervals in the LSS, NRRW and IRSCCP overlap (as they also do with the other studies), the rather lower risks indicated in the LSS compared with the NRRW, and the even lower risks in the IRSCCP, might be explained by cell-sterilization effects.

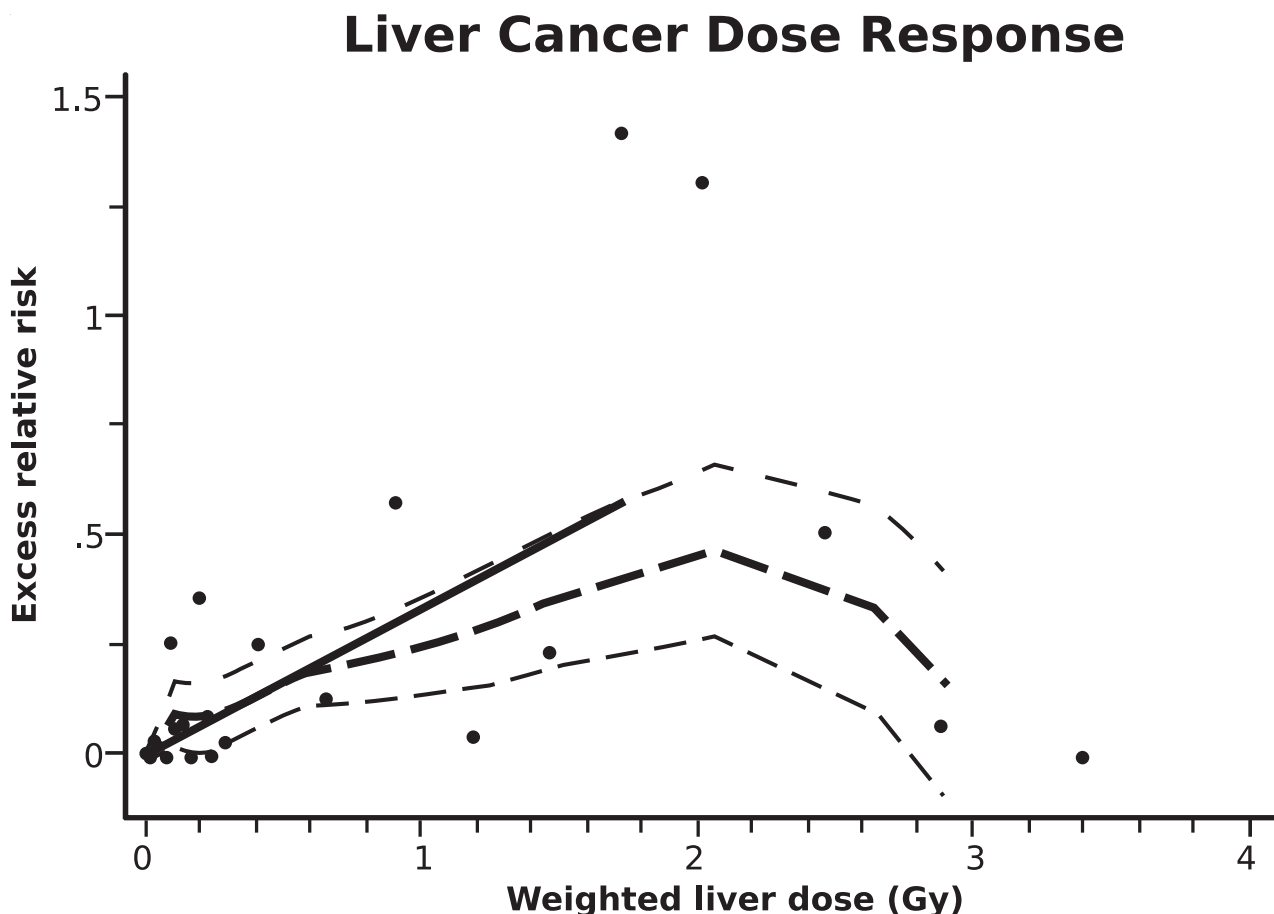
In summary, there are borderline statistically significant indications of excess risk for this cancer site in the LSS incidence data ([Preston et al., 2007](#)), and for women in the LSS mortality data ([Preston et al., 2003](#)). There is a significant excess risk in the IRSCCP ([Boice et al., 1988](#)), but not in other medically exposed groups ([Darby et al., 1994](#); [Weiss et al., 1994](#)). There are borderline statistically significant indications of excess in the NRRW ([Muirhead et al., 2009](#)), but not in the IARC 15-country study ([Cardis et al., 2007](#)). With only a single statistically significant positive study, chance cannot be entirely ruled out as an explanation for these results.

### 2.6.5 Cancer of the liver

Among the survivors of the atomic bombings, liver cancer mortality was clearly associated with radiation dose among men ([Preston et al., 2003](#)). For men, 722 deaths were reported yielding an ERR/Sv of  $0.39$  (90%CI:  $0.11$ – $0.68$ ); and for women, 514 deaths yielding an ERR/Sv of  $0.35$  (90%CI:  $0.07$ – $0.72$ ). In the analysis of cancer incidence in the LSS, there were 1494 cases yielding a (sex-averaged) ERR/Sv of  $0.30$  (90%CI:  $0.11$ – $0.55$ ; [Preston et al., 2007](#)). [The Working Group noted that histological confirmation rate of these cancers was low (41%), so it is possible that a substantial number were secondary tumours, and this might also explain the scatter observed in the dose–response.] The dose–response in the incidence data implies an increase in risk at lower dose, but a reduction above about 2 Sv, with a reasonable amount of scatter around the trend line ([Preston et al., 2007](#); Fig. 2.1). There was little or no evidence of excess in most radiotherapy studies, e.g. the United Kingdom ankylosing spondylitis study of [Weiss et al. \(1994\)](#), the metropathia haemorrhagica study ([Darby et al., 1994](#)), nor in any occupational studies, e.g. the IARC 15-country study ([Cardis et al., 2007](#)) or the NRRW ([Muirhead et al., 2009](#)). However, the numbers of cases or deaths in all these other studies is generally small.

In summary, there is strong and a statistically significant excess risk for this cancer site in the LSS incidence and mortality data ([Preston et al., 2003, 2007](#)). However, the shape of the dose–response is unusual, and there appears to be a lot of noise in those data. Possibly the comparatively low percentage of cases that were histologically confirmed in the incidence data might explain this, and is a cause for concern. There was no significant excess risk in any other studies ([Boice et al., 1988](#); [Darby et al., 1994](#); [Weiss et al., 1994](#); [Cardis et al., 2007](#); [Muirhead et al., 2009](#)), but the numbers of cases or deaths is small. With only a single statistically significant positive study,

Fig. 2.1 Liver cancer dose–response in the LSS incidence data



The thick solid line is the fitted linear gender-averaged excess relative risk (ERR) dose–response at age 70 after exposure at age 30 based on data in the 0–2-Gy dose range. The points are non-parametric estimates of the ERR in dose categories. The thick dashed line is a non-parametric smooth of the category-specific estimates, and the thin dashed lines are one standard error above and below this smooth.  
From [Preston \*et al.\* \(2007\)](#)

the LSS, chance cannot be entirely ruled out – it is also possible that there is contamination of the data for cancer of the liver by that for other cancer sites in the LSS.

#### 2.6.6 Cancer of the pancreas

Among the survivors of the atomic bombings, pancreatic cancer mortality was not clearly associated with radiation dose ([Preston \*et al.\*, 2003](#)). The ERR/Sv was  $-0.11$  (90%CI:  $< -0.3$ – $0.44$ ) for men, based on 163 deaths, and  $-0.01$  (90%:  $-0.28$ – $0.45$ ) for women, based on 244 deaths. The ERR/Sv for cancer incidence in the LSS was

$0.26$  (90%CI:  $< -0.07$ – $0.68$ ), based on 512 cases ([Preston \*et al.\*, 2007](#)). The histological confirmation rate of this cancer was low (52%). A statistically significant excess risk was reported (ERR/Gy,  $0.12$ ; 95%CI:  $0.05$ – $0.20$ , based on 84 cases) in the United Kingdom ankylosing spondylitis data ([Weiss \*et al.\*, 1994](#)). There was an indication of excess risk in the Stockholm skin haemangioma study, with nine cases yielding an ERR/Gy of  $25.1$  (95%CI:  $5.5$ – $57.7$ ; [Lundell & Holm, 1995](#)). The very large risk predicted by this study is statistically inconsistent with all the other studies, apart perhaps from the IARC 15-country study ([Cardis \*et al.\*, 2007](#)), with an ERR/Gy of  $2.10$  (95%CI:

–0.59–6.77), based on 272 cases. In the US peptic ulcer study of [Carr et al. \(2002\)](#), no excess risk was reported (ERR/Gy, –0.03; 95%CI: –0.10–0.05, based on 59 deaths). There was also no evidence of excess in the IRSCCP ([Boice et al., 1988](#)) and in the metropathia haemorrhagica study ([Darby et al., 1994](#)), nor in any occupational study, e.g. the IARC 15-country study ([Cardis et al., 2007](#)) or the NRRW ([Muirhead et al., 2009](#)).

In summary, there is evidence of an excess risk in the United Kingdom ankylosing spondylitis study ([Weiss et al., 1994](#)) and in the Stockholm haemangioma study ([Lundell & Holm, 1995](#)); the latter was very substantial but based on a small number of cases. However, there is no significant excess risk for this cancer in the LSS incidence and mortality data ([Preston et al., 2003, 2007](#)), nor in the other (radiotherapeutically or occupationally) exposed groups. With only two statistically significant positive studies, and one of these based on a small number of cases that is also inconsistent with most other studies, chance cannot be entirely ruled out, and coherence is also not well established.

#### 2.6.7 Cancers of the bone and connective tissue

This is a rare cancer site. In most studies, cancers of the bone and connective tissues are analysed together. In most of the cohorts that were considered, bone tumours were outnumbered by connective tissue tumours. For example, in the United Kingdom NRRW, there were 17 bone cancers against 58 connective tissue cancers ([Muirhead et al., 2009](#)). [The Working Group analysed the publicly available LSS incidence data set ([Preston et al., 2007](#)) using a linear relative risk model, and obtained for bone and connective tissues a statistically significant ERR/Sv of 1.34 (95%CI: 0.14–3.74), based on 41 cases. The ERR/Sv was 1.01 (95%CI: < 0–4.38) for bone tumours, based on 18 cases, and 1.76 (95%CI: < 0–6.41) for connective tissues, based on 23 cases ([Table 2.8](#)).]

Significant excess risks were also reported in a group treated for retinoblastoma (ERR/Gy, 0.19; 95%CI: 0.14–0.32), based on 81 cases ([Wong et al., 1997](#); risk estimate from [UNSCEAR, 2008b](#)); in two childhood cancer cohorts of [Tucker et al. \(1987\)](#) (ERR/Gy, 0.06; 95%CI: 0.01–0.2; risk estimate from [UNSCEAR, 2008b](#)), based on 54 cases; in [Hawkins et al. \(1996\)](#) (ERR/Gy, 0.16; 95%CI: 0.07–0.37; risk estimate from [UNSCEAR, 2008b](#)), based on 49 cases; and in the United Kingdom ankylosing spondylitis cohort (RR, 3.29; 95%CI: 1.58–5.92), based on nine deaths ([Weiss et al., 1994](#)). There was no significant excess risk in the IRSCCP ([Boice et al., 1988](#)), nor in various occupationally exposed groups ([Cardis et al., 2007](#); [Muirhead et al., 2009](#)). In these cohorts, where data were available ([Boice et al., 1988](#); [Weiss et al., 1994](#); [Cardis et al., 2007](#); [Muirhead et al., 2009](#)), the risks for bone and connective tissue tumours were not markedly different, similar to the findings from the cohort of Japanese A-bomb survivors.

In summary, there is evidence of an excess risk in the LSS incidence data ([Preston et al., 2007](#)) and in three other medical radiation cohorts ([Tucker et al., 1987](#); [Hawkins et al., 1996](#); [Wong et al., 1997](#)). The risks in all cohorts (those with statistically significant excess or not) are also reasonably consistent. There is no evidence that risks for bone and connective tissues are dissimilar.

#### 2.6.8 Skin cancers other than basal skin carcinoma

##### (a) Squamous cell carcinoma of the skin

[Ron et al. \(1998\)](#) analysed LSS incidence data and observed an ERR/Sv of –0.1 (90%CI: < –0.1–0.10), based on 69 cases ([Table 2.8](#)). Updated incidence data from LSS did not show any significant association ([Preston et al., 2007](#)). [Ron et al. \(1991\)](#) observed no cases of squamous cell carcinoma in the irradiated Israeli tinea capitis group, and two in the control group. [Shore et al. \(2002\)](#) observed seven cases of squamous cell carcinoma in the

irradiated New York tinea capitis group, and none in the control group.

In summary, for this rarely studied cancer, there is essentially only a single quantitatively informative study, the LSS incidence data ([Ron \*et al.\*, 1998](#)), which does not indicate an excess risk. Neither of the tinea capitis cohorts ([Ron \*et al.\*, 1991](#); [Shore \*et al.\*, 2002](#)) are quantitatively informative.

#### (b) *Melanoma*

This is a rare cancer site. In the latest analyses of A-bomb survivors' data, [Preston \*et al.\* \(2007\)](#) did not analyse this tumour, and the publicly available data were not provided. The much lower rates of this cancer in the Japanese population than observed in the western European population ([Parkin \*et al.\*, 2002](#)) imply that even quite large ERRs would fail to be statistically significant. [The Working Group analysed the older publicly available LSS data set (with follow-up to the end of 1987 rather than the end of 1998) of [Thompson \*et al.\* \(1994\)](#). Using a linear relative risk model, the ERR is not statistically significant (ERR/Sv, 0.22; 95%CI: < 0–4.14), based on 13 cases ([Table 2.8](#)).] There are few indications of excess risk in other groups, although a France–United Kingdom childhood cancer study yielded a statistically borderline association (excess odds ratio/Gy, 0.07; 95%CI: 0.00–0.14; [Guérin \*et al.\*, 2003](#)). There was no significant excess risk in the NRRW incidence data (ERR/Sv, 1.39; 95%CI: –0.65–5.6), based on 261 cases ([Muirhead \*et al.\*, 2009](#)), nor in the IARC 15-country study (ERR/Sv, 0.15; 90%CI: < 0–5.44), based on 87 deaths ([Cardis \*et al.\*, 2007](#)).

In summary, for this rarely studied cancer, there are essentially only four quantitatively informative studies, in none of which are there statistically significant excess risks. The lack of excess in the LSS is not surprising given the very low rates of this cancer in the Japanese population, even quite large ERRs would fail to be

statistically significant. That said, chance cannot be excluded as an explanation of what is reported.

#### 2.6.9 *Cancer of the uterus*

In the most recent analysis of cancer incidence in the LSS ([Preston \*et al.\*, 2007](#)), 1162 cases were reported yielding an ERR/Sv of 0.10 (90%CI: –0.09–0.33). There was a similar (non-significant) risk in the LSS mortality data (ERR/Sv, 0.17; 90%CI: –0.10–0.52), based on 518 deaths ([Preston \*et al.\*, 2003](#)). There are indications in the incidence data that the risks for uterine corpus cancer (ERR/Sv, 0.29; 90%CI: –0.14–0.95) is greater than for uterine cervix cancer (ERR/Sv, 0.06; 90%CI: –0.14–0.31) [although the uncertainties are consistent with risks being equal for these two cancer sites]. There was little or no evidence of an excess in risk of uterine cancer in most radiotherapy studies, e.g. the metropathia haemorrhagica ([Darby \*et al.\*, 1994](#)), the IRSCCP ([Boice \*et al.\*, 1988](#)) or the United Kingdom ankylosing spondylitis study ([Weiss \*et al.\*, 1994](#)), nor in any occupational studies, e.g. the IARC 15-country study ([Cardis \*et al.\*, 2007](#)) or the NRRW ([Muirhead \*et al.\*, 2009](#)). [The occupational studies ([Cardis \*et al.\*, 2007](#); [Muirhead \*et al.\*, 2009](#)) are particularly uninformative, for obvious reasons: there were few women in these cohorts, and women tended to have lower cumulative doses.] In the studies with subtype information, the indications, as with the LSS, are that ERRs for uterine corpus cancer are greater than for uterine cervix cancer ([Weiss \*et al.\*, 1994](#); [Cardis \*et al.\*, 2007](#)).

In summary, for no cohort are there significant excess risks of uterine cancer. In three cohorts with subtype information ([Weiss \*et al.\*, 1994](#); [Cardis \*et al.\*, 2007](#); [Preston \*et al.\*, 2007](#)), there were common patterns in risk across studies, with greater ERRs for uterine corpus cancer than for uterine cervix cancer. The lack of excess risks in the two occupational cohorts ([Cardis \*et al.\*, 2007](#); [Muirhead \*et al.\*, 2009](#)) is not

informative, as there were few women in those cohorts, and women tended to have lower cumulative doses.

### 2.6.10 Cancer of the ovary

A borderline significant excess in the incidence of cancer of the ovary (ERR/Sv, 0.61; 90%CI: 0.00–1.5), based on 245 cases ([Preston et al., 2007](#)), and a similar excess of mortality (ERR/Sv, 0.94; 90%CI: 0.07–2.0), based on 136 deaths ([Preston et al., 2003](#)), were reported in the LSS. There was little or no evidence of excess in most radiotherapy studies, e.g. the IRSCCP ([Boice et al., 1988](#)) or the United Kingdom ankylosing spondylitis study ([Weiss et al., 1994](#)), nor in any occupational studies, e.g. the IARC 15-country study ([Cardis et al., 2007](#)) or the NRRW ([Muirhead et al., 2009](#); [Table 2.8](#)). [The occupational studies ([Cardis et al., 2007](#); [Muirhead et al., 2009](#)) are particularly uninformative, because there were few women in those cohorts, and women tended to have lower cumulative doses. The lack of excess risk in the IRSCCP ([Boice et al., 1988](#)) and metropathia haemorrhagica ([Darby et al., 1994](#)) studies may partly be explained by very large doses to the ovaries, well into the range at which cell sterilization might occur.]

In summary, the only cohort with significant excess risks of ovarian cancer is the LSS. The lack of excess risks in the other studies, in particular the two occupational cohorts ([Cardis et al., 2007](#); [Muirhead et al., 2009](#)), and the IRSCCP ([Boice et al., 1988](#)) and metropathia haemorrhagica ([Darby et al., 1994](#)) studies may not be informative, because of the low number of women, who usually had low cumulative doses, in occupational cohorts and potential cell sterilization in medical radiation cohorts.

### 2.6.11 Cancer of the prostate

A non-significant excess of incidence of cancer of the prostate (ERR/Sv, 0.11; 90%CI: –0.10–0.54), based on 387 cases ([Preston et al., 2007](#)), and a similar excess (also lacking statistical significance) of mortality (ERR/Sv, 0.21; 90%CI: < –0.3–0.96), based on 104 deaths ([Preston et al., 2003](#)), were reported in the LSS. In the United Kingdom ankylosing spondylitis data, 88 deaths were reported yielding a significant ERR/Gy of 0.14 (95%CI: 0.02–0.28; [Weiss et al., 1994](#)). There was a non-significant excess of mortality from cancer of the prostate in occupational studies, e.g. the IARC 15-country study ([Cardis et al., 2007](#)) or the NRRW ([Muirhead et al., 2009](#); [Table 2.8](#)).

In summary, the only cohort with significant excess risks of cancer of the prostate is the ankylosing spondylitis cohort. The risks in the other studies, although not statistically significant, are not incompatible with those in this cohort.

### 2.6.12 Cancer of the urinary bladder

Significant excess risk for cancer of the urinary bladder in the LSS has been reported in the most recent analysis of cancer incidence (ERR/Sv, 1.23; 90%CI: 0.59–2.1; [Preston et al., 2007](#)) and of mortality with an ERR/Sv of 1.1 (90%CI: 0.2–2.5) for men and 1.2 (90%CI: 0.10–3.1) for women ([Preston et al., 2003](#)). Significant excess risks were also reported from the United Kingdom ankylosing spondylitis data (ERR/Gy, 0.24; 95%CI: 0.09–0.41), based on 71 deaths ([Weiss et al., 1994](#)), and the IRSCCP study (ERR/Gy, 0.07; 90%CI: 0.02–0.17), based on 273 cases ([Boice et al., 1988](#)). [The Working Group noted that although the risk estimated in the last two cohorts are lower than those in the LSS, cell sterilization resulting from the somewhat higher average doses might explain this difference.] The metropathia haemorrhagica study ([Darby et al., 1994](#)) suggests quite high risks (SMR, 3.01; 95%CI: 1.84–4.64) based on 20 deaths (average

dose, 5.2 Gy), and the ERR/Gy was 0.40 (95%CI: 0.15–0.66). There was no significant excess in any occupational study, e.g. the IARC 15-country study ([Cardis et al., 2007](#)) or the NRRW ([Muirhead et al., 2009; Table 2.8](#)).

In summary, there is strong evidence of excess risk in the LSS incidence and mortality data ([Preston et al., 2003, 2007](#)), and in three other medical radiation cohorts ([Boice et al., 1988; Darby et al., 1994; Weiss et al., 1994](#)). The risks in all cohorts (those with statistically significant excess or not) are all reasonably consistent.

### 2.6.13 Cancer of the kidney

[Preston et al. \(2007\)](#) analysed renal cell carcinomas (comprising 68% of the kidney cancers) in the LSS incidence data set, and obtained a non-significant ERR/Sv of 0.13 (90%CI: –0.25–0.75), based on 167 cases ([Table 2.8](#)). However, there were indications that ERR significantly decreased with either increasing age at exposure ( $P = 0.005$ ) or with increasing attained age ( $P < 0.001$ ). For this reason [Preston et al. \(2007\)](#) also fitted an absolute risk model, yielding a statistically significant dose–response EAR of  $0.25 \times 10^{-4}$  person–year Sv (90%CI: 0.07–0.53). There were similar, although non-significant, excess risks in the most recent LSS analysis of mortality ([Preston et al., 2003](#))—for men, there were 36 deaths resulting in an ERR/Sv of –0.02 (90%CI: < –0.3–1.1), and for women, there were 31 deaths and an ERR/Sv of 0.97 (90%CI: < –0.3–3.8). In the United Kingdom ankylosing spondylitis data, there were 35 deaths yielding a significant ERR/Gy of 0.10 (95%CI: 0.02–0.20) ([Weiss et al., 1994](#)). There is also a significant excess in the IRSCCP ([Boice et al., 1988](#)); 148 cases resulting in a significant ERR/Gy of 0.71 (90%CI: 0.03–2.24). There was no significant excess in any occupational study, e.g. the IARC 15-country study ([Cardis et al., 2007](#)) or the NRRW ([Muirhead et al., 2009; Table 2.8](#)).

In summary, there is evidence of excess risk in the LSS incidence data ([Preston et al., 2007](#))

and in two other medical radiation cohorts ([Boice et al., 1988; Weiss et al., 1994](#)). The risks in all cohorts (those with statistically significant excess or not) are all reasonably consistent.

### 2.6.14 Cancer of the brain and central nervous system

In the most recent analysis of cancer incidence in the LSS ([Preston et al., 2007](#)), there were 281 cases resulting in a significant ERR/Sv of 0.62 (90%CI: 0.21–1.2). In the LSS mortality analysis, there were very large and significant excess risks for men (ERR/Sv, 5.3; 90%CI: 1.4–16) based on 14 deaths ([Preston et al., 2003](#)). For women, there were 17 deaths yielding a more modest ERR/Sv of 0.51 (90%CI: < –0.3–3.9). In the New York tinea capitis study, there was also a significant association (ERR/Gy, 1.1; 95%CI: 0.1–2.8), based on seven cases ([Shore et al., 2003](#)). In the Israeli tinea capitis study, there were also significantly raised risks of both malignant brain tumours (ERR/Gy, 1.98; 95%CI: 0.73–4.69; based on 44 cases) and benign meningiomas (ERR/Gy, 4.63; 95%CI: 2.43–9.12; based on 81 cases), with a stronger increase in risk for benign brain tumours ([Sadetzki et al., 2005](#)). A similar pattern of risks was seen in the France–United Kingdom childhood cancer study; the ERR/Gy was 0.07 (95%CI: < 0–0.62) based on 12 cases for malignant lesions, and > 1000 (95%CI: 0.25–> 1000) based on ten cases for benign lesions; ([Little et al., 1998](#)). In the United Kingdom ankylosing spondylitis data, there was one spinal cord death resulting in a significant ERR/Gy of 3.33 (95%CI: 0.08–18.6; [Weiss et al., 1994](#)). There is no significant excess in any occupational study, e.g. the IARC 15-country study ([Cardis et al., 2007](#)) or the NRRW ([Muirhead et al., 2009; Table 2.8](#)).

In summary, there is evidence of significant excess brain and central nervous system tumour risk in the LSS incidence data ([Preston et al., 2007](#)), in two tinea capitis cohorts ([Shore et al., 2003; Sadetzki et al., 2005](#)), in an ankylosing

spondylitis cohort ([Weiss et al., 1994](#)) and in the France–United Kingdom childhood cancer study ([Weiss et al., 1994](#)). A similar pattern of excess risk being higher for benign tumours than for malignant is in the Israeli tinea capitis and France–United Kingdom cohorts. The risks in all cohorts (those with statistically significant excess or not) are all reasonably consistent.

### 2.6.15 Non-Hodgkin lymphoma

In the analysis of haematological malignancy incidence in the LSS cohort ([Preston et al., 1994](#)), there was a borderline significant EAR of  $0.56 \times 10^{-4}$  /person–years /Sv (90%CI: 0.08–1.39) for men, but this was not true for women (EAR  $\times 10^{-4}$ /person–year /Sv, 0; 90%CI: < 0–0.28). [Fitting a simple linear relative risk model, overall there was no significant excess risk (ERR/Sv, 0.05; 90%CI: < 0–0.70).] These incident findings are consistent with the analysis of male adult LSS mortality data, with a reported ERR/Sv of 1.12 (90%CI: 0.26–2.51) based on 84 cases ([Richardson et al., 2009](#)). In the United Kingdom ankylosing spondylitis cohort, there were 37 deaths yielding a significant relative risk of 1.74 (95%CI: 1.23–2.36; [Weiss et al., 1994](#)); there was no dose–response analysis in this cohort. There was no significant excess risk in the IRSCCP ([Boice et al., 1988](#)), in the metropathia haemorrhagica cohort ([Darby et al., 1994](#)), or in a group treated for benign gynaecological disease ([Inskip et al., 1993](#); [Table 2.8](#)). Among occupational studies, there was a very large excess risk in a cohort of Chernobyl liquidators (ERR/Gy, 28.1; 90%CI: 0.9–243) based on 20 cases ([Kesminiene et al., 2008](#)), and in the cohort of Savannah River Site workers (ERR/Gy, 7.62; 90%CI: 0.93–20.77) based on 51 cases ([Richardson et al., 2009](#)). However, there was no significant excess risk in the IARC 15-country study (ERR/Sv, 0.44; 90%CI: < 0–4.78) based on 248 deaths ([Cardis et al., 2007](#)), or in the NRRW cohort (ERR/Sv,

1.28; 95%CI: –0.38–4.06) based on 305 cases ([Muirhead et al., 2009](#)).

In summary, there is evidence of a significant excess risk of non-Hodgkin lymphoma in men (but not women) in the LSS mortality and incidence data ([Preston et al., 2003, 2007](#)), in a cohort of Chernobyl liquidators ([Kesminiene et al., 2008](#)) and in the Savannah River Site workers ([Richardson et al., 2009](#)).

### 2.6.16 Hodgkin disease

[Preston et al. \(1994\)](#) in the LSS did not analyse this tumour. [The Working Group analysed the publicly available data set using a linear relative risk model, and obtained a non-significant ERR/Sv of 0.48 (95%CI: < 0–3.96), based on 21 cases ([Table 2.8](#)).] In the United Kingdom ankylosing spondylitis data, there were 13 deaths yielding a non-significant relative risk of 1.65 (95%CI: 0.88–2.81; [Weiss et al., 1994](#)); no dose–response analysis was reported. There was no significant excess in the IRSCCP ([Boice et al., 1988](#)), in the metropathia haemorrhagica cohort ([Darby et al., 1994](#)), in a group treated for benign gynaecological disease ([Inskip et al., 1993](#)), in the IARC 15-country study ([Cardis et al., 2007](#)), or in the NRRW ([Muirhead et al., 2009](#); [Table 2.8](#)). [The Working Group noted that a common feature of all the cohorts is the small number of cases, so that large ERRs would be required to detect a significant excess in these groups.]

In summary, there are no cohorts with significant excess risks for Hodgkin disease. However, the small number of cases in all groups mean that a large ERR would be required to detect significant excess risks.

### 2.6.17 Multiple myeloma

In the most recent analysis of haematological malignancy incidence in the LSS, [Preston et al. \(1994\)](#) used an absolute risk model and obtained a non-significant EAR (EAR/ $10^4$  person–year

Sv, 0.08; 95%CI: < 0–0.3), based on 59 cases (Table 2.8). In the United Kingdom ankylosing spondylitis data, there were 22 deaths yielding a borderline significant relative risk of 1.62 (95%CI: 1.07–2.46; Weiss *et al.*, 1994); there was no dose–response analysis in this cohort due to a lack of appropriate organ dose. There was a significant excess risk in the metropathia haemorrhagica cohort with an SMR of 2.59 (95%CI: 1.19–4.92), based on nine deaths (Darby *et al.*, 1994). There was no significant excess risk in the IRSCCP (Boice *et al.*, 1988), and in a group treated for benign gynaecological disease (Inskip *et al.*, 1993). There was also no excess risk in the IARC 15-country study (Cardis *et al.*, 2007). There was a highly significant excess in the incidence of multiple myeloma in the NRRW (ERR/Sv, 3.60; 95%CI: 0.43–10.37), based on 149 cases; and there was an excess of much smaller size (which was non-significant) for mortality in that cohort (ERR/Sv, 1.20; 95%CI: –1.08–7.31), based on 113 deaths (Muirhead *et al.*, 2009; Table 2.8).

In summary, there is no evidence of an excess risk of multiple myeloma in the LSS incidence data (Preston *et al.*, 1994), although an excess risk has been reported from the NRRW study (only incidence and not mortality; Muirhead *et al.*, 2009), and also from the ankylosing spondylitis study (Weiss *et al.*, 1994) and from the metropathia haemorrhagica study (though based only on analysis of SMR) (Darby *et al.*, 1994).

### 2.6.18 Chronic lymphocytic leukaemia

Most of the information on this tumour comes from occupationally and medically exposed groups. There are very few chronic lymphocytic leukaemias in the LSS cohort – only four were documented in the latest reported analysis of haematological malignancy incidence (Preston *et al.*, 1994). In general, this is a much less common tumour in the Japanese population than in the European population. In all occupational cohorts, there were no significant excess.

For example, the ERR/Sv for the incidence of chronic lymphocytic leukaemia in the NRRW was –0.12 (90%CI: –1.42–2.71), based on 128 cases (Muirhead *et al.*, 2009; Table 2.8). In the IARC 15-country study, there was an ERR/Sv of –1.0 (95%CI: –5.0–3.7), based on 47 deaths (Cardis *et al.*, 2007). In the two Chernobyl liquidator studies (Kesminiene *et al.*, 2008; Romanenko *et al.*, 2008), the risks are both large and positive, although in neither case conventionally statistically significant. For example, the ERR/Gy in the study by Kesminiene *et al.* (2008) was 4.7 (90%CI: – $\infty$ –76.1), based on 21 cases (Table 2.8). In medically exposed groups, there was no indication of excess risk in the benign gynaecological disease cohort of Inskip *et al.* (1993) (RR, 1.1; 90%CI: 0.5–3.0; based on 21 deaths), in a group irradiated for benign locomotor lesions (SIR, 1.07, 90%CI: 0.80–1.41; based on 50 deaths; Damber *et al.*, 1995), in the IRSCCP (OR, 1.03, 90%CI: 0.3–3.9; based on 52 cases; Boice *et al.*, 1988), and in many other medically irradiated groups (Curtis *et al.*, 1989, 1994; Weiss *et al.*, 1994).

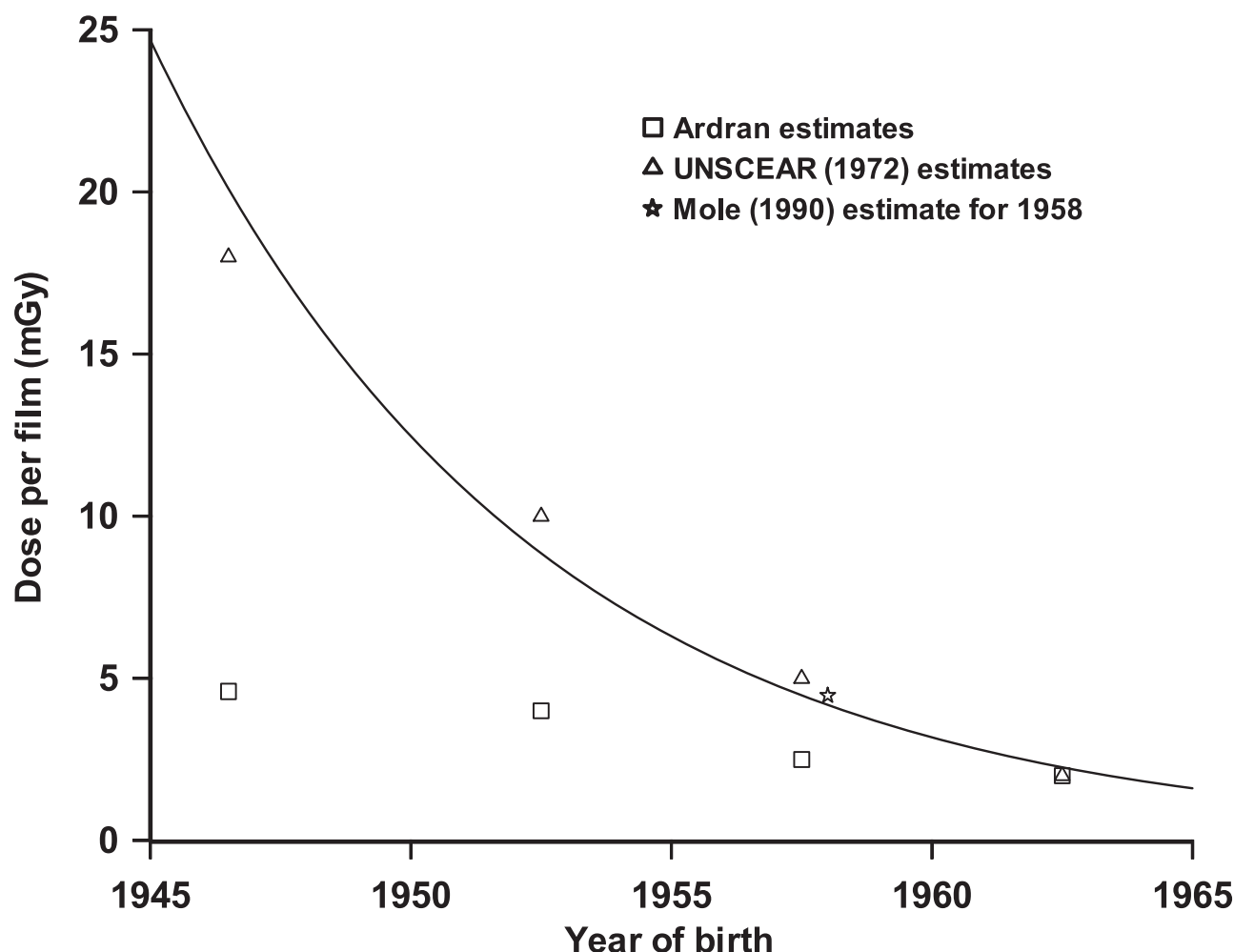
In summary, there is remarkably little evidence of a significant excess risk of chronic lymphocytic leukaemia in a large number of studies.

### 2.6.19 Exposure in utero

Preston *et al.* (2008) reported statistically significant dose-related increases in incidence rates of solid cancers among A-bomb survivors exposed to radiation *in utero* (see Section 2.1.3).

Excess cancer risk associated with diagnostic X-ray exposure was reported in the Oxford Survey of Childhood Cancers (Bithell & Stewart, 1975), and in various other groups exposed *in utero* (Stewart *et al.*, 1958; Monson & MacMahon, 1984; Harvey *et al.*, 1985). However, the interpretation of these in-utero studies remains controversial (Boice & Miller, 1999; ICRP, 2003), in particular because the risk for most childhood solid tumour types is increased, at about 40%, by the

Fig. 2.2 Estimates of average fetal dose per film exposed in an obstetric X-ray examination



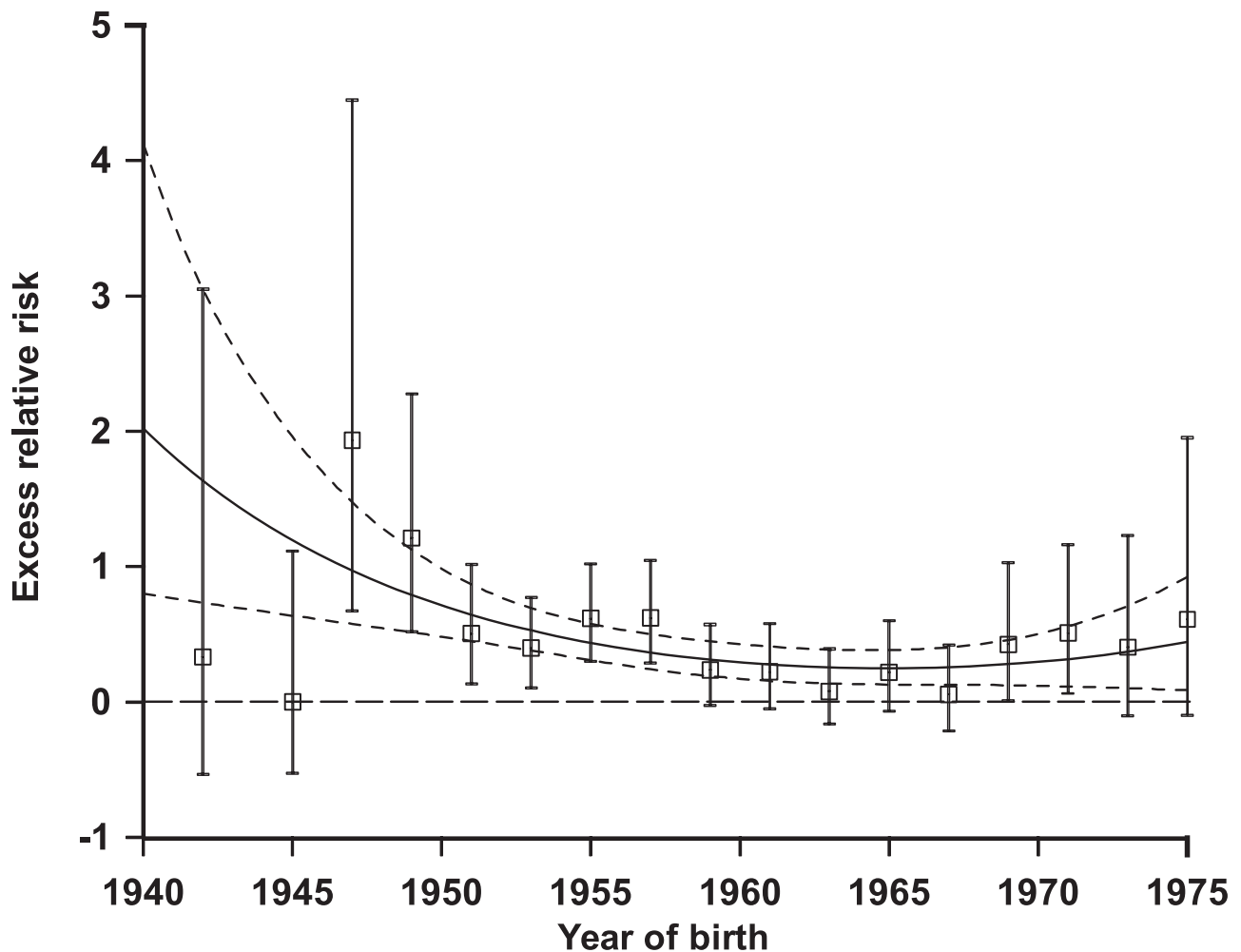
Carried out in four successive periods (1943–49, 1950–54, 1955–59, 1960–65), by Ardran ([Stewart & Kneale, 1970](#)) and UNSCEAR (1972); also shown is the estimate for 1958 (4.47 mGy) by [Mole \(1990\)](#) from the Adrian Committee data. The curve represents the fit of a log-linear model to the UNSCEAR (1972) dose estimates (see [Bithell & Stiller, 1988](#)) (reproduced from [Wakeford & Little, 2003](#)).

same magnitude as that for childhood leukaemia (see Table 2.9 available at <http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-02-Table2.9.pdf>), implying a possible bias. However, eight cancers among those exposed in childhood and *in utero* in the Japanese A-bomb survivors developed in adolescence (ages 14–19 years), and were of various types ([Preston et al., 2008](#)). The seven of this group that developed after childhood exposure included tumours of the stomach, bone, soft tissue, skin, thyroid and two tumours of the central nervous system. The single tumour in this age group that developed after in-utero

exposure was a Wilms tumour diagnosed at the age of 14 years ([Preston et al., 2008](#)). This spectrum of tumours after early childhood exposure suggests that the lack of specificity in the spectrum of tumours in the in-utero medical exposure cohorts is not necessarily remarkable.

It has been suggested that the general elevation in risk of most cancer types in the in-utero medically exposed groups is related to recall bias or confounding, possibly by some factors operating in pregnancy that had given rise to the need for radiographic examination. Recall bias has been more or less excluded by cohort studies

**Fig. 2.3** The variation of the excess relative risk of childhood cancer associated with an obstetric X-ray examination by year of birth (1940–76) within the Oxford Survey of Childhood Cancers



Data are taken from [Mole \(1990\)](#), with 95% CIs; the curve (solid line) represents the fit of a log-linear-quadratic model to the data, with 95% CI (short dashed lines) similar to that fitted by [Bithell \(1993\)](#). The long dashed horizontal line indicates zero excess relative risk (reproduced from [Wakeford & Little, 2003](#)).

in which similar risks are observed ([MacMahon, 1962](#); [Monson & MacMahon, 1984](#)), also by the high degree of confirmation of mothers' recalled exposures by medical records ([Knox \*et al.\*, 1987](#)). Moreover, the idea that the association might be due to confounding became less plausible after the Oxford Survey of Childhood Cancers ([Mole, 1990](#)), which showed quantitatively similar relationships (risks per film) in singletons and twins, despite the fact that 55% of twins had received diagnostic exposures compared with 10% of singletons. The lack of indication of excess risk

in earlier studies among the in-utero exposed Japanese A-bomb survivors has also been cited as a difficulty in interpreting the indications of excess in the medically exposed groups to be causal ([Boice & Miller, 1999](#)). However, there is a statistically significant excess risk of solid cancers after in-utero and early childhood radiation exposure (age < 6 years at exposure) in the children and adults (at ages 12–55 years) in the Japanese A-bomb survivors ([Preston \*et al.\*, 2008](#)) with a strong decline in ERR with attained age, which is consistent with results of the Oxford

Survey of Childhood Cancers. Although there are no leukaemia cases in the Japanese in-utero cohort in childhood (there were two cases at a later age, [Yoshimoto \*et al.\*, 1994](#)), the lack of excess is nevertheless consistent with the excess risk observed in the Oxford Survey of Childhood Cancers, and in other in-utero medically irradiated groups ([Wakeford & Little, 2003](#)). The lack of cases among the Japanese and possible inconsistency with some of other groups may also be plausibly accounted for by cell-sterilization effect ([Little, 2008](#)). The fact that risk reduces with calendar time, almost exactly paralleling the reduction in in-utero dose (see Fig. 2.2 and 2.3) substantially increases the plausibility of the observed association in the medical groups ([Doll & Wakeford, 1997](#); [Wakeford & Little, 2003](#)), as does the dose–response relationship observed in the Oxford Survey of Childhood Cancers ([Bithell, 1993](#)). A meta-analysis, which covered only studies published after 1990, did not find any association between in-utero medical radiation and risk of childhood cancer ([Schulze-Rath \*et al.\*, 2008](#)). [The Working Group noted that because in-utero diagnostic doses are substantially lower than those in the 1950s discussed above, the findings of this meta-analysis may not be comparable with those of the earlier medical in-utero studies.]

In summary, there is substantial evidence that suggests a causal association between exposure to diagnostic radiation *in utero* and childhood cancers. This association is supported by the fact that the Japanese A-bomb survivors exposed *in utero* and in early childhood are at higher risk for a wide range of solid cancers in adulthood, and that risks among the in-utero and childhood-exposed groups are very similar. This indicates that the increased risk of cancer following in-utero exposure to radiation starts in childhood, and persists long into adulthood.

### 3. Cancer in Experimental Animals

#### 3.1 Previous evaluation

Both X-rays and  $\gamma$ -rays have been shown to increase the risk for the development of a variety of cancers in experimental animals. This work was extensively reviewed in the previous *IARC Monograph*, which covered work up to the year 2000 ([IARC, 2000](#)).

X-rays and  $\gamma$ -rays have been tested for carcinogenicity at various doses and under various conditions in mice, rats, rabbits, dogs, and rhesus monkeys. They have also been tested by exposure of mice and dogs *in utero*, and by parental exposure of mice ([IARC, 2000](#)).

In adult animals, the incidences of leukaemia and of a variety of neoplasms including mammary, lung and thyroid tumours were increased in a dose-dependent manner with both types of radiation. In mice, X-rays and  $\gamma$ -rays clearly increased the incidence of myeloid leukaemia, malignant lymphoma (including thymic lymphoma), malignant tumours of the ovary, and lung and mammary adenocarcinomas ([Upton \*et al.\*, 1970](#); [Ullrich & Storer, 1979a, b, c](#); [Ullrich, 1983](#); [Ullrich & Preston, 1987](#); [Grahn \*et al.\*, 1992](#); [IARC, 2000](#)). Benign and malignant tumours of the liver, Harderian gland, pituitary gland, and adrenal gland were also induced ([Ullrich & Storer, 1979b, c](#); [Grahn \*et al.\*, 1992](#); [IARC, 2000](#)). In rats, X-rays and  $\gamma$ -rays clearly increased the incidence of malignant mammary tumours ([Shellabarger \*et al.\*, 1966, 1980](#); [Broerse \*et al.\*, 1986, 1987](#); [IARC, 2000](#)) and of follicular carcinomas of the thyroid ([Lee \*et al.\*, 1982](#); [IARC, 2000](#)). In rhesus monkeys, X-rays clearly increased the incidence of kidney adenocarcinomas ([Broerse \*et al.\*, 1981](#)). When enough data were available over a range of doses and dose rates, the dose–response relationship was generally consistent with a linear–quadratic model, while lowering the dose rate resulted in a diminution of the quadratic portion of the curve. The effects of

fractionation of the dose were highly dependent on fractionation size. Most importantly, low-dose fractions were equivalent to low-dose rates with respect to carcinogenic effectiveness ([IARC, 2000](#)).

Prenatal exposure of mice to X-rays in two studies and to  $\gamma$ -rays in one study and of dogs to  $\gamma$ -rays at late fetal stages resulted in significant increases in the incidences of malignant lymphoma ([Lumniczky et al., 1998](#)), malignant lung and liver tumours in mice ([Sasaki et al., 1978a, b](#); [IARC, 2000](#)), and malignant lymphoma, haemangiosarcoma and mammary carcinoma in dogs ([Benjamin et al., 1991](#); [IARC, 2000](#)). Exposure at early fetal stages, however, did not increase the incidence of tumours in the offspring of either species ([IARC, 2000](#)).

Parental effects in mice appear to depend on the strain tested. Parental exposure of mice of two strains to X-rays resulted in increased incidences of lung adenomas and lymphocytic leukaemias in the offspring; however, studies with other strains of mice showed no increase in the incidence of neoplasms ([IARC, 2000](#)).

## 3.2 Studies published since the previous *IARC Monograph*

The following text (see also [Table 3.1](#)) provides an update of studies published since that time. Most studies published over the period 2001 to 2009 have examined effects of X-rays and  $\gamma$ -rays in adult rodents (mice and rats). In particular, the majority of mouse studies have focused on the use of genetically engineered mouse model systems.

## 3.3 Studies in adult animals

### 3.3.1 Mouse

Studies in adult mice have focused on the effects of low doses and dose rates in an attempt to provide more information that could provide

insight into risks at doses for which data for humans is not sufficient to establish the shape of the dose–response relationship.

[Di Majo et al. \(2003\)](#) published a summary of several series of studies conducted over several years examining the carcinogenic effects of ionizing radiation. This summary was meant to examine the dose response at low doses using a synthesis of data from previously conducted studies. This paper did not present new data but rather presented a different analysis. Only a small portion of this paper described data for X-radiation, with most examining effects of neutrons. For X-radiation, cancer development was analysed in female B6C3F1 mice irradiated at 1 month of age with doses of 40, 80, 160 and 320 mGy of 250 kVp X-rays. The sample sizes ( $n = 52\text{--}97$ ) were quite small but the data provided limited evidence for an increase in cancer risks. No increase in the incidence of lymphomas or myeloid leukemias was observed at any dose used. For solid tumours, an apparent decrease in frequency was observed at the 40 mGy dose, and at higher doses there was a slight but not significant increase at 80 and 160 mGy with little evidence of a dose response. For ovarian tumours, significant increases were found at doses of 80, 160, and 320 mGy.

A large study of effects of very low dose rates of  $\gamma$ -rays was conducted by Tanaka and co-workers ([Tanaka et al., 2007](#)) using 4000 B6C3F1 mice (8 weeks of age). These mice were irradiated with  $\gamma$ -rays at dose rates of 0.05, 1.1, and 21 mGy per day over a 400-day time period, which resulted in total doses of 20, 400, and 8000 mGy. A previous report on life-shortening ([Tanaka et al., 2003](#)) had found an increase in life-shortening at the 21 mGy per day dose rate (8000 mGy total dose) in males, but no effect at lower doses or dose rates and an increase in females exposed at 1.1 and 21 mGy per day dose rates (400 and 8000 mGy) but not following 0.05 mGy per day (20 mGy total dose) in females. The 2007 study on neoplasia found significant increases in

**Table 3.1 Studies in experimental animals exposed to X- and γ-rays identified since the previous IARC Monograph (IARC, 2000)**

| Species, strain (sex)<br>Duration<br>Reference                                 | Number/group at start<br>Dosing regimen                                                                                                                                                                                | Incidence of tumours                                                                                                                                                                                                                                                                                                                                                                                                                                     | Significance                                                                                    |
|--------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Mouse, B6C3F1, (F)<br>Lifespan<br><a href="#">Di Majo et al. (2003)</a>        | Acute exposure<br>0, 40, 80, 160, 320 mGy (250 kVp X-rays)<br>52–97; 335 controls                                                                                                                                      | Solid tumours (%):<br>38.2, 34.0, 45.6, 46.2, 39.3<br>Ovarian tumours (%):<br>9.9, 9.3, 20.3 <sup>a</sup> , 59.6 <sup>b</sup> , 80.4 <sup>b</sup>                                                                                                                                                                                                                                                                                                        | <sup>a</sup> $P \leq 0.01$ (Fisher test)<br><br><sup>b</sup> $P \leq 0.001$ (Peto's trend test) |
| Mouse, B6C3F1, (M, F)<br>Lifespan<br><a href="#">Tanaka et al. (2007)</a>      | 0, 20, 400, 8000 mGy <sup>137</sup> Cs (total dose)<br>0.05, 1.1, 21 mGy/d<br>495–500; 498 controls                                                                                                                    | <i>Males:</i><br>Myeloid leukaemia–<br>7/498 (1%); 10/495 (2%); 10/500<br>(2%); 24/499 (5%) <sup>a,b</sup><br>Hemangiosarcomas–<br>5/498 (1%); 51/495 (10%); 62/500<br>(12%); 84/499 (17%) <sup>b</sup><br><i>Females:</i><br>Hemangiosarcomas–<br>21/500 (4%); 21/495 (4%); 32/497<br>(6%); 47/500 (9%) <sup>a,b</sup><br>Ovarian tumours (malignant<br>granulosa cell)–<br>1/500 (0.2%); 2/495 (0.4%); 0; <sup>a</sup> ,<br>13/500 (2.6%) <sup>b</sup> | <sup>a</sup> $P \leq 0.01$ (Fisher test)<br><sup>b</sup> $P \leq 0.001$ (Peto's trend test)     |
| Mouse, Car-R and Car-S, (M)<br><a href="#">Pazzaglia et al. (2002a)</a>        | Car-S: 4 weekly doses of 0, 1500, 2000, 2500 mGy<br>plus TPA<br>Car-R: 4 weekly doses of 2000, 5000 mGy<br>TPA 1 µg was given 7 d after the last irradiation<br>biweekly for 200 d to all groups<br>26–35; 94 controls | Skin tumours (%):<br>Car-S–25.5, 54.5, 28.6, 58.3<br>Car-R–0,0                                                                                                                                                                                                                                                                                                                                                                                           | $P < 0.001$ (in all groups)                                                                     |
| Mouse, Min (M, F)<br>Lifespan<br><a href="#">Okamoto &amp; Yonekawa (2005)</a> | 0, 250, 500, 1000, 2000 mGy X-rays<br>1000, 2000 mGy at 2-, 10-, 24-, 42-, 48-d-old<br>Number/group at start (NR)                                                                                                      | Small intestine (~multiplicity):<br>77.6, 120, 125, 150, 207<br>Colon (~multiplicity):<br>3.5, 2.5, 2.8, 6.3, 16.8<br><i>Age (days)</i><br>Small intestine (~multiplicity):<br>2 d–125, 160<br>10 d–148, 210<br>24 d–140, 160<br>42 d–77, 125<br>48 d–NR, 80                                                                                                                                                                                             |                                                                                                 |

Table 3.1 (continued)

| Species, strain (sex)<br>Duration<br>Reference                                                                                        | Number/group at start<br>Dosing regimen                                                                                                                                                                              | Incidence of tumours                                                                                                                                                                        | Significance                                                                                                                                                                                                          |
|---------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mouse, C57BL/6, C57BL/6-Min (F)<br>18 wk<br><a href="#">Imaoka et al. (2006)</a>                                                      | 0, 2000 mGy X-rays at 2-, 5-, 7-, 10-wk-old<br>Number/group at start (NR)                                                                                                                                            | Mammary tumours<br>(adenocarcinomas):<br>C57BL/6 0 at all doses<br>Controls-2/10 (20%)<br>2 wk-2/7 (29%)<br>5 wk-2/13 (15%)<br>7 wk-7/11 (64%) <sup>c</sup><br>10 wk-6/9 (67%) <sup>c</sup> | <sup>c</sup> <i>P</i> < 0.002 compared to wild<br>type; <i>P</i> < 0.05 compared to 0<br>mGy                                                                                                                          |
| Mouse, Min <i>Prkdc</i> <sup>BALB/BALB</sup> ,<br>Min <i>Prkdc</i> <sup>BALB/C57BL</sup> (M, F)<br><a href="#">Degg et al. (2003)</a> | 0, 2000 mGy X-rays<br>84 M, 58 F; controls 60 M, 51 F                                                                                                                                                                | Small intestine (multiplicity):<br>Min <i>Prkdc</i> <sup>BALB/BALB</sup> -20.9, 51.7<br>Min <i>Prkdc</i> <sup>BALB/C57BL</sup> -29.4, 37.1                                                  |                                                                                                                                                                                                                       |
| Mouse, <i>Apc</i> <sup>Min/+</sup> (F, F)<br>CBA/F (F)<br><a href="#">Ellender et al. (2006)</a>                                      | 0 or 2000 mGy X-rays at 2-, 10-, 35-d-old<br>0, 500, 1000, 2000 mGy at 7 days post conception<br>(PC) (pregnant CBA/H mice)<br>50/group                                                                              | Intestinal tumours: incidence<br>Controls-27.8<br>2 d-85.2 <sup>d,e</sup><br>10 d-125.5 <sup>d,f</sup><br>35 d-71.3 <sup>d</sup><br>7 d PC-29.9, 35.6, 34.3, 37.0                           | <sup>d</sup> <i>P</i> < 0.001 compared to<br>controls; <sup>e</sup> <i>P</i> = 0.02 compared<br>to 35 days<br><sup>f</sup> <i>P</i> < 0.001 compared to 35 days                                                       |
| Mouse, C57BL, C57BL <i>Apc</i> <sup>mini/+</sup><br><a href="#">Nakayama et al. (2007)</a>                                            | 0, 5000 mGy X-rays<br>Controls; wild type 13 M, 18 F; <i>Apc</i> <sup>mini/+</sup> 32 M, 32 F,<br>killed after 28 wk<br>X-rays: wild type 13 M, 16 F; <i>Apc</i> <sup>mini/+</sup> 44 M, 33 F,<br>killed after 20 wk | Intestinal tumours (multiplicity):<br>M-9/32 (28%); 24/44 (55%) <sup>g</sup><br>F-4/32 (13%); 16/33 (49%) <sup>h</sup><br>Mammary tumours (%):<br>1/32 (3%); 10/33 (30%) <sup>i</sup>       | <sup>g</sup> <i>P</i> < 0.05 vs control <i>Apc</i> <sup>mini/+</sup><br><sup>h</sup> <i>P</i> < 0.005 vs control <i>Apc</i> <sup>mini/+</sup><br><sup>i</sup> <i>P</i> < 0.01 vs control <i>Apc</i> <sup>mini/+</sup> |
| Mouse, C57BL wild type and <i>Apc</i> <sup>1638N</sup> ,<br>(M, F)<br><a href="#">van der Houven van Oordt et al. (1997)</a>          | 0, 5000 mGy X-rays<br>Controls: <i>Apc</i> <sup>1638N</sup> 19 M, 8 F, killed at 6-16 mo<br>X-rays: wild type 15 M, 24 F; <i>Apc</i> <sup>1638N</sup> 15 M, 16 F<br>killed after 250 d                               | Intestinal tumours (multiplicity):<br>Wild type-0, 0<br><i>Apc</i> <sup>1638N</sup> -2.7, 21.0<br>Mammary tumours (%):<br>Wild type-0, 0<br><i>Apc</i> <sup>1638N</sup> -0, 63              |                                                                                                                                                                                                                       |

Species, strain (sex)

[illegible]

Table 3.1 (continued)

[illegible]

**Table 3.1 (continued)**

| Species, strain (sex)<br>Duration<br>Reference                                                                                                         | Number/group at start<br>Dosing regimen                                                                                                                                                                                                                                             | Incidence of tumours                                                                                                                                                                                                                                                                                                        | Significance                                                    |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| Mouse, BALB/C <i>p53</i> -/-, +/-, +/- (M, F)<br>Lifespan<br><a href="#">Mori et al. (2003)</a>                                                        | 0 or 4000 mGy X-rays<br><i>p53</i> +/-: 44 F, 19 M<br><i>p53</i> +/-: 31 F, 18 M<br>0 or 4 x 700 mGy<br><i>p53</i> +/-: 23<br><i>p53</i> +/-: 26                                                                                                                                    | Thymic lymphomas:<br>4000 mGy; 4 x 700 mGy<br><i>p53</i> +/- M-13/19 (68%); NR<br><i>p53</i> +/- M-3/18 (17%); NR<br><i>p53</i> +/- F-26/44 (59%); 15/23 (65%)<br><i>p53</i> +/- F-4/31 (13%); 0<br>Mammary tumours:<br>4000 mGy; 4x700 mGy<br><i>p53</i> +/- F- 15/44 (34%); 7/23 (30%)<br><i>p53</i> +/- F-0; 15/23 (65%) | NR                                                              |
| Mouse, BALB/CxMSMF1 <i>p53</i> +/+, +/- and <i>Atm</i> +/- and +/- (M, F)<br>Lifespan<br><a href="#">Umesako et al. (2005)</a>                         | 0, 5000 mGy X-rays at 5 wk<br>Number/group at start (NR)                                                                                                                                                                                                                            | Mammary tumours:<br><i>p53</i> +/- <i>Atm</i> +/- 0, 1/53 (2%)<br><i>p53</i> +/- <i>Atm</i> +/- 0, 0<br><i>p53</i> +/- <i>Atm</i> +/- 7/22 (32%); 19/61 (31%)<br><i>p53</i> +/- <i>Atm</i> +/-14/28 (50%); 32/55 (58%) <sup>a</sup>                                                                                         | <sup>a</sup> <i>P</i> = 0.0034 vs <i>p53</i> +/- <i>Atm</i> +/- |
| Mouse, C57BL/6 <i>Eu-pim-1</i> and wild type C57BL/6 (M, F)<br>250 d after the last exposure<br><a href="#">van der Houven van Oordt et al. (1998)</a> | Controls:<br>13 F, 12 M <i>Eu-pim-1</i><br>13 F, 11 M wild type<br>4 x 1500 mGy:<br>12 F, 14 M <i>Eu-pim-1</i><br>15 F, 18 M wild type<br>4 x 1000 mGy:<br>15 F, 11 M <i>Eu-pim-1</i><br>15 F, 16 M wild type<br>4 x 500 mGy:<br>32 F, 31 M <i>Eu-pim-1</i><br>25 F, 38 M wild type | (10%)<br>0<br><br>26/26 (100%)<br>19/31 (61%)<br><br>20/22 (90%)<br>6/31 (19%)<br><br>17/61 (28%)<br>0/62 (0%)                                                                                                                                                                                                              |                                                                 |
| Rat, Sprague-Dawley (F)<br>Lifespan<br><a href="#">Dicello et al. (2004)</a>                                                                           | 0, 500, 1600, 5000 mGy <sup>137</sup> Cs and <sup>60</sup> Co at ~60-d-old<br>18–36/group                                                                                                                                                                                           | Mammary tumours excess incidence (%):<br><sup>137</sup> Cs and <sup>60</sup> Co<br>12, 20                                                                                                                                                                                                                                   |                                                                 |

Table 3.1 (continued)

| Species, strain (sex)<br>Duration<br>Reference                                                                         | Number/group at start<br>Dosing regimen                                                                               | Incidence of tumours                                                                                                                                                                                                                                                                                                                                  | Significance                                         |
|------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|
| Rat, Sprague-Dawley (F)<br>1 yr<br><a href="#">Imaoka et al. (2007)</a>                                                | 0, 500, 1000, 2000 mGy <sup>137</sup> Cs whole body at 8-wk-old                                                       | Mammary tumours:<br>3/45 (7%); 4/20 (20%); 6/20 (30%);<br>11/20 (55%) <sup>s</sup>                                                                                                                                                                                                                                                                    | <sup>r</sup> $P < 0.05$<br><sup>s</sup> $P < 0.0001$ |
| Rat<br>Otsuka Long-Evans Tokushima Fatty (M)<br>564 d<br><a href="#">Watanabe &amp; Kamiya (2008)</a>                  | X-rays—two doses of 10000 mGy with a 3-d interval<br>(total dose 20000 mGy) at 5-wk-old<br>Number/group at start (NR) | Insulinoma [pancreatic adenomas]:<br>0–6/19 (32%)<br>2x10000–19/30 (63%)                                                                                                                                                                                                                                                                              | $P < 0.01$                                           |
| Rhesus Monkeys (M, F)<br>Lifespan<br><a href="#">Broerse et al. (2000)</a> and <a href="#">Hollander et al. (2003)</a> | X-rays—2800–8600 mGy, average dose 7100 mGy<br>20, 21 controls                                                        | Malignant tumours<br>Controls—7/21 (30%)<br>X-rays—10/20 (50%)<br>Mean age:<br>Controls—28.4 yr<br>X-rays—15.0 yr                                                                                                                                                                                                                                     | NR                                                   |
| Mouse, C57BL/6 (F) and B6C3F1<br>offspring (M, F)<br>120 wk<br><a href="#">Dasenbrock et al. (2005)</a>                | 0; 2x2000 mGy X-rays<br>F0: 216 M; 450 F<br>F1: 1690 animals (M, F)                                                   | Hepatocellular carcinomas:<br>Mothers—<br>Controls 1/219 (0.4%)<br>X-rays 9/230 (4%)<br>Male offspring—<br>Maternal 0 (16%) historical controls<br>Maternal X-rays 53/210 (25%)<br>Lung tumours:<br>Mothers—<br>Controls 7/219 (3%)<br>X-rays 25/230 (11%)<br>Male Offspring—<br>Maternal 0 (27%) historical controls<br>Maternal X-rays 82/210 (39%) | $P < 0.05$<br>$P < 0.01$<br>$P < 0.05$               |

| Table 3.1 (continued)                                                    |                                                                                                                        |                                                                                                                                                                                                                            |              |  |
|--------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|--|
| Species, strain (sex)<br>Duration<br>Reference                           | Number/group at start<br>Dosing regimen                                                                                | Incidence of tumours                                                                                                                                                                                                       | Significance |  |
| Mouse, B6C3F1 (F)<br>550 d<br><a href="#">Sasaki &amp; Fukuda (2008)</a> | <sup>137</sup> Cs γ-rays doses from 100 to 5700 mGy at 17 day<br>prenatal and Days 0, 7, 35, 105, 240, 365, 550 of age | ERR at 1000 mGy<br>Ovarian tumours:<br>17 day prenatal 1.43 ± 0.21<br>Day 0–15.8 ± 1.5<br>Day 7–29.2 ± 5.0<br>Day 35–21.7 ± 6.0<br>Day 105–10.9 ± 1.1<br>Day 240–1.54 ± 0.04<br>Day 365–1.23 ± 0.20<br>Day 550–1.26 ± 0.06 |              |  |

d, day or days; ERR, excess relative risk; F, female; M, male; mo, month or months; NR, not reported; NS, not significant; PC, post conception; TPA, 12-*O*-tetradecanoylphorbol-13 acetate; vs, versus; wk, week or weeks; yr, year or years

<sup>1</sup> A1; Anagen 1, mouse dorsal skin at postnatal day 3 (P3)  
<sup>2</sup> A2; Anagen 2, mouse dorsal skin at postnatal day 35 (P35)  
<sup>3</sup> T2; Telogen 2, mouse dorsal skin at postnatal day 60 (P60)

soft-tissue sarcomas and haemangiosarcomas in both sexes, and an increase in myeloid leukaemia in males and malignant granulosa cell tumours in females. An increase in multiple primary tumours was seen in both male and female mice at the dose of 21 mGy per day (8000 mGy total dose) but not at the lower doses and dose rates.

[Pazzaglia et al. \(2002a\)](#) used the CAR-S and CAR-R mice (10–12 weeks of age) that had been selected based on genetic susceptibility to skin-tumour induction by chemical carcinogens to examine the genetic control of skin tumorigenesis following X-ray initiation and TPA (12-*O*-tetradecanoylphorbol-13-acetate). These studies used four weekly fractions of 1500, 2000 and 2500 mGy followed by TPA. An increase in frequency of tumours and shortening of latency was observed in all groups in CAR-S (carcinogenesis sensitive) mice, while no effect was seen in CAR-R (carcinogenesis resistant) mice, which were selectively bred based on sensitivity to chemical carcinogens.

### 3.3.2 Transgenic mice

Several recent studies have used genetically engineered mice to examine effects of X-rays and  $\gamma$ -rays on tumorigenesis. Most studies focused on effects in either *Apc*<sup>Min+</sup> mice (Min mice) that contain a nonsense mutation in the *Apc* gene at codon 850 resulting in a truncated protein, as well as *Apc*1638N mice or *Ptch*1<sup>±</sup> mice containing only one allele of the *Patched1* gene. The *Apc*<sup>Min</sup> mutation is the mouse homologue of human familial adenomatous polyposis. This heterozygous mutation predisposes mice to the spontaneous development of small intestine tumours and to radiation-induced tumorigenesis in both the small intestine and mammary gland. *Apc*1638N mice display a relatively more mild phenotype with respect to multiplicity in non-treated controls. In all instances, the tumours that arise involve the loss of the wild-type allele. *Ptch*1 mice are analogous to individuals with

Gorlin Syndrome who inherit a germ-cell mutation in *Ptch*. These individuals and their murine counterparts have an increased incidence of basal cell carcinoma and medulloblastoma. These mice and humans are also hypersensitive to radiation-induced tumours in terms of both basal cell carcinoma and medulloblastoma. As in the case of *Apc*, loss of the wild-type *Ptch* allele has been shown to be involved in radiation-induced tumorigenesis.

[Okamoto & Yonekawa \(2005\)](#) reported on the induction of intestinal tumours as a function of X-ray dose and age at exposure in *Apc*<sup>Min+</sup> mice. Doses used were 250, 500, 1000 and 2000 mGy at ages of 2, 10, 24, 42, and 48 days of age. Doses of 1000 and 2000 mGy resulted in a significant increase in the multiplicity of tumours of the small intestine in all age groups with a peak at 10 days of age. Using 10-day-old mice, these investigators reported a proportional increase in multiplicity at all doses used. For colon tumours, no increase was seen at doses of 250 and 500 mGy while significant increases were observed at 1000 and 2000 mGy. The peak in sensitivity as a function of age shifted slightly with peak sensitivity at 2 days of age. Irradiation at 24 days or later resulted in no significant increase in colon tumours.

[Imaoka et al. \(2006\)](#) examined the age dependency of mammary tumours in Min mice following a dose of 2000 mGy at 2, 5, 7, and 10 weeks of age. While the number of animals in each group was small, mice irradiated at 7 and 10 weeks of age were found to have a significant increase in the frequency of adenoacanthomas, while mice irradiated at 2 and 5 weeks of age did not. Rather, these mice developed cystic nodules with metaplasia.

[Degg et al. \(2003\)](#) examined adenoma multiplicity in the small intestine of Min mice on the BALB/c background after a dose of 2000 mGy, and linked sensitivity to a segment of chromosome 16 containing a variant form of *Prkdc*, the gene encoding DNA-dependent protein kinase.

A later study from the same laboratory ([Ellender et al., 2005](#)) found that direct single gene mutational events in the *Apc* gene could account for increased frequencies of intestinal tumours after doses of 2000 and 5000 mGy. Further, this laboratory ([Ellender et al., 2006](#)) reported on *in utero* and neonatal sensitivity to increased frequency of intestinal tumours. The data for 2-, 10- and 35-day-old animals were similar to that of [Okamoto & Yonekawa \(2005\)](#), with peak sensitivity at 10 days of age. No increase in the frequency of tumours was observed in mice irradiated *in utero* at 7 or 14 days post conception ([Okamoto & Yonekawa, 2005](#)).

The studies above focused on all intestinal tumours but mainly adenoma, [Nakayama et al. \(2007\)](#) reported a significant increase in the frequency and multiplicity of invasive carcinoma in the small intestine in the *Apc<sup>Min+</sup>* mice following a single dose of X-rays of 5000 mGy. An increased frequency of mammary tumours was also seen but no increase in colon tumours was observed.

Using the *Apc1638N* mouse model, [van der Houven van Oordt et al. \(1997\)](#) first demonstrated their sensitivity to intestinal and mammary tumorigenesis. Sensitivity to the induction of both intestinal tumours and mammary tumours was later shown to be dependent on the genetic background of the mice after a 5000 mGy dose of X-rays. In one study, background sensitivity to the induction of ovarian tumours was also observed ([van der Houven van Oordt et al., 1999](#)).

[Pazzaglia et al. \(2002b\)](#) first reported a significantly increased frequency of medulloblastoma following 3000 mGy of X-radiation in *Ptch1* heterozygous mice irradiated at 4 days of age. Subsequently, significantly increased frequencies of basal cell carcinoma were reported following doses of 3 and 4 Gy in *Ptch1*-deficient mice by the same investigators ([Mancuso et al., 2004](#)). It was also demonstrated that susceptibility to basal cell carcinoma could be modified by genetic background ([Pazzaglia et al., 2004](#)). Hair

cycle phase was also shown to be important in the carcinogenic effect of radiation ([Mancuso et al., 2006](#)). During growth phases in the hair cycle, both a quantitative increase in frequency of tumours and a qualitative effect on tumour type were observed. The stage of development was also shown to be an important factor that linked sensitivity to DNA damage and apoptosis ([Pazzaglia et al., 2006](#)).

A following study examined the dose response for the induction of medulloblastoma in the *Ptch1*-knockout mice after X-ray doses of 100, 250, and 500 mGy ([Pazzaglia et al., 2009](#)). A significantly increased frequency of these tumours and concomitant decrease in survival time was observed in mice irradiated at doses of 250 and 500 mGy, with a linear dose–response relationship adequately describing the entire data set. Sensitivity to induction was age-dependent with a decrease in sensitivity with increasing age over the 1–10-day age time period following a 3000 mGy dose of X-rays.. This sensitivity was correlated to a resistance to apoptosis in cells from younger mice ([Pazzaglia et al., 2006, 2009](#)). These investigators also published evidence for the participation of bystander effects in the induction of medulloblastoma following 3000 mGy of X-radiation ([Mancuso et al., 2008](#)).

Mammary tumorigenesis has been studied in BALB/c *p53<sup>+/-</sup>* mice. [Mori et al. \(2003\)](#) compared effects following a 4000 mGy dose delivered as a single dose versus weekly fractions. With both single dose and fractionated doses, *p53<sup>+/-</sup>* mice were significantly more sensitive to tumour induction following irradiation. After a single dose, lymphomas were the primary cause of death although an increase in mammary tumours and sarcomas were observed. Following fractionation, mammary carcinomas were dominant with these tumours showing a frequent loss of the *p53* wild-type allele ([Mori et al., 2003](#)). [Umesako et al. \(2005\)](#) subsequently demonstrated that ataxia-telangiectasia mutated (*Atm*) heterozygosity enhanced the development of mammary

tumours in BALB/c *p53*<sup>+/-</sup> mice after 5000 mGy of X-rays. Loss of the wild-type *p53* allele but not *Atm* was found in these tumours.

Studies of E $\mu$ -*pim*-1 transgenic mice following four weekly fractions of 500, 1000, or 1500 mGy were reported by [van der Houven van Oordt et al. \(1998\)](#). An increased frequency of lymphomas was observed at all total doses with the highest effect observed in the 4  $\times$  1000 mGy group, with 91% of the mice developing lymphomas. In this model, molecular events appear to involve alterations in *myc* expression.

### 3.3.3 Rat

Two studies in rats focused on the induction of mammary carcinoma in adult rats. In the first study, [Dicello et al. \(2004\)](#) examined the effect of <sup>137</sup>Cs and <sup>60</sup>Co  $\gamma$ -rays in Sprague-Dawley rats as part of a study that focused on comparing effects of  $\gamma$ -rays with 250 MeV protons and 1 GeV/nucleon <sup>56</sup>Fe ions. Dose of  $\gamma$ -rays used were 500, 1600, and 5000 mGy. A significant increase in frequency of mammary tumours was observed at doses of 1600 and 5000 mGy, and a slight but not statistically significant decrease was found at a dose of 500 mGy. In spite of the slight decrease at 500 mGy, a linear dose–response relationship was the best fit for the data.

In the second study, [Imaoka et al. \(2007\)](#) examined rat mammary induction following <sup>137</sup>Cs irradiation as part of a study comparing 290 MeV/nucleon carbon ions in Sprague-Dawley rats at doses of 500, 1000 and 2000 mGy. A significant increased frequency and multiplicity of carcinomas was observed at all three doses with an apparent linear dose–response relationship.

[Bartel-Friedrich et al. \(1999\)](#) reported a significant increase in malignant tumours of the head and neck (squamous cell carcinoma and adenoid cystic carcinoma in the irradiated field) in the Wistar strain of rats following partial body irradiation at 2000 mGy per day fractionated

exposures of X-radiation to a total dose of 60000 mGy.

[Watanabe & Kamiya \(2008\)](#) reported a significant increase in insulinomas [islet cell adenomas] in Otsuka Long-Evans Tokushima Fatty rats following two doses of 10000 mGy separated by 3 days (20000 mGy total dose) of X-rays to the gastric region. No tumours were seen in controls, but 19/30 rats (63.3%) developed insulinomas following irradiation.

### 3.3.4 Rhesus monkey

Two reports of studies on tumorigenesis in monkeys following exposure to radiation have been published on the same cohort ([Broerse et al., 2000](#); [Hollander et al., 2003](#)). Both publications reported the tumour frequencies of X-irradiated monkey that were approximately 3 years of age at the time of irradiation. The 20 animals received doses ranging from 2800–8600 mGy with an average dose of 7100 mGy. An increased frequency (50%) and decreased latent period (12 years) of malignant tumours were observed when compared to 21 controls (30% and 28.4 years respectively). The tumours seen were very diverse. A specific increase in kidney cortical carcinoma (with none being found in controls) was observed (38%; 8/21). An increase in benign tumours was also found.

## 3.4 Prenatal exposure

After prenatal exposure of mice to <sup>137</sup>Cs  $\gamma$ -rays, Sasaki & Fukuda (2008) compared ovarian tumorigenesis as a function of age from 17 days post conception through 550 days of age. This study suggests that sensitivity to prenatal radiation exposure is determined by the developmental stage of the organ system, which impacts the number and proliferative activity of target cells.

### 3.5 Neonatal exposure

The characteristics of life-shortening and carcinogenesis were investigated in neonatal B6WF<sub>1</sub> mice irradiated with X-rays. Animals were irradiated within 24 hours after birth with 0 (control), 200, 400, or 600 R [an exposure to 1R is approximately equivalent to 10 mGy] of X-rays, and allowed to complete their normal lifespan ( $n = 532$ ) or observed until 500 days old ( $n = 35$  males). Mean lifespan was shortened linearly with dose at a rate of 9.1% per 100 R for females and 9.8% for males. The spectrum of neoplastic diseases was apparently modulated by irradiation with X-rays, showing neonatal B6WF<sub>1</sub> mice to be highly susceptible to the induction of thymic lymphoma (tumour incidence: 1%, 2%, 14% ( $P < 0.05$ ), and 48% ( $P < 0.05$ ), in females; 0%, 5%, 13% ( $P < 0.05$ ), and 43% ( $P < 0.05$ ), in males; respectively, for increasing doses), liver carcinoma (tumour incidence: 0%, 6% ( $P < 0.05$ ), 16% ( $P < 0.05$ ), and 12% ( $P < 0.05$ ), in females; 0%, 12% ( $P < 0.05$ ), 36% ( $P < 0.05$ ), and 14% ( $P < 0.05$ ), in males; respectively, for increasing doses), and pituitary tumour [tumour type not specified] (tumour incidence: 5%, 14% ( $P < 0.05$ ), 24% ( $P < 0.05$ ), and 12% ( $P < 0.05$ ), in females; respectively, for increasing doses). The dose–response relationship for thymic lymphoma could be described by a linear–quadratic model, and linearity could be rejected. Thymic lymphoma developed after a short latent period, resulting in death between 100 and 450 days of age. Liver and pituitary tumours increased with increasing dose up to 400 R and decreased thereafter. The latent period for liver tumour development was apparently shortened with increasing doses. Pituitary tumours developed in excess only in females after a long latent period. An increase in the incidence of ovarian tumours [tumour severity not specified] (1%, 10% ( $P < 0.05$ ), 12% ( $P < 0.05$ ), and 4%; respectively, for increasing doses), of Harderian gland tumours [tumour severity not specified] (1%, 6%, 8% ( $P < 0.05$ ),

and 3%; respectively, for increasing doses), and of vascular tumours (haemangioma and haemangiosarcoma combined; 9%, 16%, 24% ( $P < 0.05$ ), 1%; respectively, for increasing doses) was also observed in female mice ([Sasaki & Kasuga, 1981](#)).

### 3.6 Parental exposure

Only one report of parental exposure has been published ([Dasenbrock \*et al.\*, 2005](#)). In this study, female C57BL6/6N mice received two 2000 mGy doses separated by 2 weeks (4000 mGy total dose) before mating with non-irradiated C3H/HeN males. After weaning, half the offspring were exposed to ciclosporin, with the other half remaining untreated and maintained for their lifespan. Significant increases in lung adenoma and hepatocellular carcinoma were observed in the irradiated females. A significantly increased incidence of benign and malignant lung tumours combined and hepatocellular carcinoma was found in the non-irradiated male progeny of irradiated mothers ([Table 3.1](#)).

### 3.7 Synthesis

Studies conducted since the year 2000 have provided new information on radiation-induced cancer that includes dose–response relationships for tumour induction. Significantly increased frequency of tumours and/or tumour multiplicity were observed in mice, rats, and monkeys. Often, the use of X- or  $\gamma$ -rays was mainly for the purpose of comparing other types of radiations to measure differences in effectiveness. The studies focusing directly on the effects of X- and  $\gamma$ -rays were designed either to address effects at low doses or to use transgenic or genetically sensitive or resistant mice mainly to address potential mechanisms of action or genetic control of sensitivity. In the case of *Ptch1* mice, this very sensitive model was also exploited to examine cancer risk as a function of dose. All of the data

in all species examined confirmed that exposure to X- and  $\gamma$ -rays can increase the risk for tumour induction. It is important to emphasize that risks can be modified substantially by dose and dose rate, age at exposure, and genetic background. Studies in *Apc<sup>min+</sup>* and *Ptch1* mice also provided information suggesting that stem cells or early progenitor cells are a likely target for these carcinogenic effects, and/or variance in sensitivity as a function of age.

X-rays and  $\gamma$ -rays cause malignant lymphoma (including thymic lymphoma), myeloid leukaemia, malignant mammary tumours, ovary cancer, liver cancer, intestine (small) and colon tumours, haemangiosarcoma and skin basal cell carcinoma in mice; malignant mammary tumours and thyroid cancer in rats. X-rays cause a variety of malignant tumours including kidney cortical carcinomas in monkeys.

## 4. Other Relevant Data

### 4.1 Radionuclides: determining the distribution of dose

Most radionuclides are in themselves not toxic—uranium is a notable exception. This is because during their period of existence within the body, they are rarely present in sufficient mass to exhibit any chemical toxicity. It is only when they cease to exist and their decay is accompanied by the release of radiation that toxic effects may be produced. With respect to toxicity, the most important of the radiations produced by radionuclide decay are  $\alpha$ -particles and  $\beta$ -particles (positrons and negatrons), but other emissions such as fission fragments may also be important (e.g. for  $^{252}\text{Cf}$ ). It follows that the characteristics of the radionuclides in the cytotoxic and carcinogenic processes determine the eventual distribution of the emitted radiations within the cells and tissues of the body.

Occupational and environmental intakes of radionuclides result from exposures to either radionuclides within aerosols by inhalation ([Khokhryakov \*et al.\*, 2000](#); [Gilbert \*et al.\*, 2004](#)), radionuclides present in food and water by ingestion ([Ham \*et al.\*, 1994](#); [Hunt, 1998](#)), radionuclides deposited on the skin by skin absorption or by puncture wounds that result in the transfer of radionuclides from contaminated surfaces. These processes are often independent of the physicochemical form of the radionuclide, but do depend upon factors such as the age of the subject and the size of the radionuclide uptake. For example, radionuclide uptake from the gut is higher in infants than in adults ([Bomford & Harrison, 1986](#)), the mass of radionuclide in the gut can influence uptake, and the deposition and retention of radionuclides in the lung depends upon both the mass inhaled and the size of the lungs and their airways ([ICRP, 1995](#)). All subsequent behaviour of radionuclides in the body is a function of their ability to dissolve/disperse within tissue fluids, and a function of their chemical affinity to body components ([Priest, 1990](#)). Unabsorbed radionuclides present either on the skin or in the lungs and gastrointestinal tract irradiate local cells and tissues, and tumours may result. For example, there is a wide body of evidence demonstrating the carcinogenicity of inhaled radionuclides in man (e.g. [Gilbert \*et al.\*, 2004](#)).

Following transfer from their site of initial deposition, most radionuclides enter the bloodstream where they remain until they either deposit in organs and tissues or are excreted in urine, faeces and, less commonly, in sweat, hair, skin, and nails. Most elements are polyvalent metals and these tend to interact with the metabolic pathways that exist in the body for essential metals—most importantly calcium and iron. The radionuclides of these elements, therefore, tend to deposit at sites of calcium and iron deposition and storage within the body – including, but not exclusively, within the skeleton – and are

commonly referred to as bone-seeking radionuclides. Other monovalent metals and non-metals do not interact with the metabolic pathways for calcium and iron and are either deposited specifically at other sites (e.g. iodine in the thyroid gland) or become widely distributed throughout (e.g. potassium and caesium) and/or incorporated in all body tissues (e.g. hydrogen, carbon, sulfur, and phosphorus). It follows that for ease of description, radionuclides can be categorized as either bone-seeking or as non-bone-seeking.

#### 4.1.1 Internal dose assessment

As mentioned in Section 1.2, radionuclides can enter the body by inhalation, ingestion, absorption or injection/wound, this is known as an internal exposure. The threshold of detection for direct measurement ('Whole Body Monitoring') of some internal  $\alpha$ - or  $\beta$ -particles emitters *in vivo* can be many times greater than the recommended annual dose limits, and others are essentially undetectable *in vivo*. Hence, individuals' doses from internal exposures are commonly "assessed" indirectly using mathematical models that describe radionuclide absorption, distribution, metabolism and excretion (ADME). The ICRP are the principal source of information on this topic, and their current recommended models of radionuclide ADME and dosimetry can be found in their recent publications.

It should be noted that internal dose assessment is still an incomplete science, and there are several issues that should be considered when evaluating the results of epidemiological studies involving internally deposited radionuclides. The methodology employed to calculate internal doses has continued to improve, over time, as knowledge of radionuclide ADME has improved (much of the evolution of models of radionuclide ADME can be seen by reviewing the previous publications of the ICRP). A primary route of absorption of many internally deposited

radionuclides is through inhalation. Modelling the transport of radionuclides from the lung to the blood with true fidelity remains a key issue as this can have a substantial impact on assessed doses ([Riddell, 2002](#)). Internal dose assessments often also rely on radionuclide measurements either in the environment (e.g. air concentration) or bioassay samples (e.g. urinalysis). The resolution and reliability of radionuclide measurement techniques have also shown significant improvements over time. To a certain extent, the internal dose assessment process still requires some measure of expert judgement. Consequently, the dose estimates produced for one epidemiological study may not be comparable, in terms of both accuracy and precision, with those from another. Furthermore, the uncertainties associated with internal dose estimates, particularly for the lung following the inhalation of radionuclides, are generally significantly greater than those associated with external radiation exposures. Finally, the assessment of doses from radionuclides released into the environment may also be based on mathematical models of environmental transport of these radionuclides. Because different environmental transport models may be used for studies and because of the complexity of the processes being modelled, these models may not give consistent and/or unbiased estimates of individual exposures. These considerations are important because, all other things being equal, the accuracy and reliability of the risk estimates produced by epidemiological research is directly correlated to that of the dosimetry data.

Internal exposures can be to naturally occurring or man-made radionuclides made available through natural, industrial, medical, accidental or military, processes. Information on ADME, relevant routes of internal exposure, and monitoring techniques for the radionuclides under review are considered below (this information was compiled using the sources used for Section 1.2.6, above, with the further additions of ICRP publications 54 and 78; [ICRP, 1988](#),

1997). The information is provided to give some understanding of the key processes involved, the organs/tissues exposed, and the potential difficulties in providing unbiased estimates of exposure. For the purposes of brevity and clarity some simplifications have been made, and this should not be taken as a definitive statement on the extent of current knowledge.

#### (a) Tritium

The ADME of  $^3\text{H}$  is fundamentally linked to that of natural body water. The majority of  $^3\text{H}$  enters the body as tritiated water and in this form, whether ingested or inhaled, is totally absorbed. Significant amounts can also be absorbed through the skin. Upon entering the body, tritiated water rapidly becomes homogeneously distributed in the whole-body water content (including urine), and is cleared with the same biological half-life, 10 days, as other body water.  $^3\text{H}$  can also become attached to organic compounds that are retained in the body with a longer biological half-life, ICRP suggest 40 days (ICRP, 1997), although the extent, biological half-life and significance of this organically bound fraction presently remains the subject of some debate (HPA, 2007). As  $^3\text{H}$  only emits low energy  $\beta$ -particles, in-vivo monitoring is not feasible; individual dose assessments are normally based on urine monitoring or environmental transport models.

#### (b) Phosphorus-32

Knowledge of  $^{32}\text{P}$  ADME is limited but as it is mostly used for medical purposes, initial dosages (in terms of uptake of activity) are usually quite well defined. Following injection,  $^{32}\text{P}$  mainly accumulates in bone (~30%), where it is eliminated by radioactive decay, and is cleared from the body, primarily by urinary excretion, with a biological half-life of ~39 days (Spiers *et al.*, 1976).

#### (c) Strontium-90

$^{90}\text{Sr}$  behaves similarly to natural calcium when taken into the body, although it is not retained for as long, and tends to deposit on the bone surfaces. The majority of  $^{90}\text{Sr}$  (> 50%) is rapidly cleared from the body within a week following exposure, only a small amount remains after a year, largely in the skeleton. Approximately 30% of ingested  $^{90}\text{Sr}$  will be absorbed into blood from the gut in adults, but this percentage can be even higher for infants; this makes ingestion an important exposure route, particularly when  $^{90}\text{Sr}$  is released into the environment (ICRP, 1993). As  $^{90}\text{Sr}$  is a pure  $\beta$ -particle emitter, urine monitoring is the preferred method of assessing individual exposures (ICRP, 1997). However, when exposure is to a known mixture of fission products, in-vivo monitoring of other fission products, such as  $^{137}\text{Cs}$ , may be used to estimate  $^{90}\text{Sr}$  exposure.

#### (d) Iodine

As with stable iodine,  $^{131}\text{I}$  tends to accumulate in the thyroid gland. Approximately 30% of  $^{131}\text{I}$  entering the blood will go to the thyroid, the remainder being quickly excreted from the body in urine. Retention of  $^{131}\text{I}$  in the thyroid is age-dependent with a biological half-life in the range of approximately 11 days for infants to 80 days for adults (ICRP, 1979, 1989). Exposure to  $^{131}\text{I}$  can effectively be blocked by loading the thyroid with stable iodine, usually through the use of iodine tablets. All ingested iodine-131 will pass from the gut into the blood. The threshold for measuring  $^{131}\text{I}$  directly *in vivo* is three to four orders of magnitude below current recommended limits on intake, and this is the preferred method of monitoring exposure. The main consideration when calibrating is the absorption in the tissues overlaying the thyroid in the neck. If stable iodine has been used as a blocking agent, urine monitoring will be required to assess individual exposure (ICRP, 1997).

*(e) Caesium-137*

After being taken into the body  $^{137}\text{Cs}$  behaves in a similar manner to naturally occurring potassium, and is fairly uniformly distributed throughout the body, with the largest deposition being in muscle, reflecting the muscle's percentage of overall body mass. Like potassium,  $^{137}\text{Cs}$  is quickly cleared from the body; 10% with a biological half-life of 2 days, the remainder with a biological half-life of 110 days. Following ingestion,  $^{137}\text{Cs}$  exhibits almost complete uptake to blood from the gut, therefore, this is an important exposure route particularly for  $^{137}\text{Cs}$  in the environment. Because its radioactive daughter, metastable barium-137m, is a gamma emitter with a short radioactive half-life, 2.5 minutes,  $^{137}\text{Cs}$  dose can easily be assessed from in-vivo measurements, although urine monitoring may also be used for this purpose ([ICRP, 1997](#)).

*(f) Radon*

Because  $^{222}\text{Rn}$  is a gas and its most radiologically significant radioactive daughters have short half-lives, most of the dose from  $^{222}\text{Rn}$  is to the lung. Air monitoring is the preferred method of assessing  $^{222}\text{Rn}$  exposures. It is relatively easy to measure the time integrated  $^{222}\text{Rn}$  concentration at a specific location, using for example air samplers or CR-39 plastic-based measurement devices. However, it is often difficult to accurately relate measured  $^{222}\text{Rn}$  concentrations to individual exposures due to issues such as variability of occupancy, airflow, attached fraction, breathing rate and so forth ([BEIR IV, 1988](#)).

*(g) Radium*

Radium exhibits similar metabolic behaviour to calcium, and consequently a large proportion of radium that enters the blood is deposited in the skeleton and teeth. The amount in bone decreases following cessation of exposure, typically by more than 90% over a few months and 99% over a few years. Most of the radium taken into the body by

ingestion (about 80%) will rapidly be excreted in faeces with only ~20% passing from the gut into blood, but historically this has been an important mode of exposure ([ICRP, 1993](#)). Direct measurement of pure  $^{226}\text{Ra}$  and  $^{228}\text{Ra}$  *in vivo* would not be feasible due to their low penetration primary emissions; however, daughter nuclides in both of their decay chains (e.g. lead-214 and bismuth-214 for  $^{226}\text{Ra}$ , and actinium-228 for  $^{228}\text{Ra}$ ) are detectable *in vivo*. The presence of these decay chains, which can be in different states of equilibrium following the chemical processing of radium, can also make dosimetry complex. Urine monitoring can also be used for assessing radium doses ([ICRP, 1997](#)).

*(h) Thorium-232*

When  $^{232}\text{Th}$  enters the blood, ~70% deposits in bone, primarily on the endosteal surfaces, then it is slowly redistributed throughout the bone volume, where it is retained with a biological half-life of about 22 years. Of the remaining ~30% of  $^{232}\text{Th}$  entering blood, ~10% is rapidly excreted and ~20% deposits in the liver (~4%) and other organs/tissues (~16%), where it is retained with a biological half-life of 700 days ([ICRP, 1995](#)). The majority of  $^{232}\text{Th}$  that is ingested is rapidly excreted, and only about 0.02 to 0.05% is absorbed into the blood from the gut, but this is still the primary route of exposure in the general population from  $^{232}\text{Th}$  in the environment. Inhalation is an important exposure pathway for occupational exposures (e.g. miners). Direct measurement of pure  $^{232}\text{Th}$  *in vivo* would not be feasible due to the low penetration of its primary emission, however, a daughter nuclide,  $^{228}\text{Ac}$ , in its decay chain is detectable *in vivo*. The presence of this decay chain, which can be in different states of equilibrium following the chemical processing of  $^{232}\text{Th}$ , can also make dosimetry complex. Faecal and urine measurements can also be used for  $^{232}\text{Th}$  monitoring ([ICRP, 1997](#)).

*(i) Uranium*

Uranium entering the blood is mainly (~22%) deposited in the bone volume, where it is retained long-term, and kidneys (~12%), with the remainder either being distributed throughout the body (~12%) or rapidly excreted. Only a small fraction (~0.2% to ~2%) of ingested uranium is absorbed from the gut into the blood, but this is still the main source of exposure for uranium in the environment ([ICRP, 1995, 1997](#)). Inhalation is an important pathway for occupational exposures but there is considerable debate and uncertainty in relation to the rate at which uranium compounds pass from the lung to the blood, and this can make substantial (up to orders of magnitude) differences in the calculated lung doses ([Riddell, 2002](#)). Air sampling, urine and in-vivo measurements are all used for the individual monitoring of uranium depending on the exposure scenario. In-vivo monitoring is reliant on the detection of gamma emissions from  $^{235}\text{U}$ , obviously this is easier with highly enriched uranium but it is possible, with poorer sensitivity, with lower levels of  $^{235}\text{U}$  within the isotopic mix. It should be noted that the limit on occupational exposure for uranium, for common forms that are fairly readily absorbed into blood from the lung (default types 'F' (fast absorption) and 'M' (moderate absorption)) ([ICRP, 1994](#)), is commonly based on chemical toxicity in the kidney and not on the radiation dose ([ICRP, 1997](#)). It should also be noted that in certain locations, individuals could have significant levels of uranium in their urine as a result of their dietary intake of naturally occurring uranium. Conversely, in other locations, excretion due to dietary intake may be significantly lower than reference levels ([Riddell, 1995](#)).

*(j) Plutonium*

Plutonium is retained long-term by the body once it enters the blood mainly in the liver and skeleton, where it is deposited on the cortical

and trabecular surfaces of bones, and is slowly redistributed throughout the bone volume over time, with a biological half-life of the order of decades. Most exposure to plutonium has been in the occupational setting, i.e. those involved in nuclear weapons or nuclear power production, and the primary exposure pathways are inhalation and, to a much lesser extent, wounds. Considering that inhalation is the most important exposure pathway, there is still considerable debate and uncertainty in relation to the behaviour of plutonium in the lung, and this can make a substantial difference to the calculated lung doses ([Harrison, 2009](#)). Only a small percentage (~0.001% to ~0.05%) of plutonium that enters the gut is absorbed into blood, and consequently ingestion is not usually a major exposure pathway. Urine and faecal sampling, in-vivo measurements and air sampling have all been used for plutonium monitoring. Because urine is relatively easy to collect, urinalysis results are the basis of most of the assessed internal plutonium doses. The quality, in terms of resolution and freedom from adventitious contamination, and quantity of urine sample data has a fundamental impact on the accuracy and reliability of dose assessments. Urine samples collected from workers historically are known to suffer from adventitious contamination, and the analysis techniques used had poor resolution ([Riddell et al., 2000](#)). In-vivo measurements suffer from poor sensitivity, the threshold of detection often equates to a dose that is several times greater than recommended annual dose limits but may be the only option for very insoluble compounds in the lung ([ICRP, 1997](#)). As reprocessing has increasingly turned towards spent nuclear fuel from civil power reactors,  $^{241}\text{Pu}$  and its radiologically significant daughter  $^{241}\text{Am}$  have been seen in greater quantities. In such cases, measurements of  $^{241}\text{Am}$  ingrown from  $^{241}\text{Pu}$  can be used for assessing exposures from known plutonium isotope mixtures ([ICRP, 1997](#)).

### 4.1.2 Bone-seeking radionuclides

Bone-seeking radionuclides are so-called because of their tendency to be deposited in, and be retained by, bones and teeth. This group of radionuclides includes most of those that are either commercially important and/or are widely recognized to be important potential human carcinogens, including alkaline earth radionuclides (e.g.  $^{45}\text{Ca}$ ,  $^{90}\text{Sr}$ , and  $^{226}\text{Ra}$ ), transition element radionuclides (e.g.  $^{90}\text{Y}$ ,  $^{55}\text{Fe}$ , and  $^{65}\text{Zn}$ ) and the lanthanon (lanthanide) and actinon (actinide) radionuclides ( $^{147}\text{Pm}$ ,  $^{234}\text{U}$ ,  $^{239}\text{Pu}$ ,  $^{241}\text{Am}$ , and  $^{244}\text{Cm}$ ). Many reviews of the deposition, retention and toxicity of plutonium and other bone-seeking radionuclides have been published ([AEC, 1971](#); [Durbin, 1973](#); [Vaughan et al., 1973](#); [AEC, 1974](#); [ICRP, 1986](#); [BEIR IV, 1988](#); [Priest, 1990](#)).

There are of two main types of bone seeker:

1) those that are chemically related to normal bone components—examples that are known to produce cancer in either man or animals include  $^{32}\text{P}$ ,  $^{90}\text{Sr}$ ,  $^{133}\text{Ba}$ ,  $^{65}\text{Zn}$ ,  $^{226}\text{Ra}$ , and  $^{235}\text{U}$ ;

2) those that are chemically unrelated to normal bone components but bind to the mineral and matrix components of bone—examples include  $^{90}\text{Y}$ ,  $^{55}\text{Fe}$  and radionuclides of most transition metals, lanthanons (lanthanides), and actinons (actinides).

When present in the skeleton, all have the potential to irradiate radiation-sensitive cells – mostly within the bone-marrow cavity – to produce a variety of skeletal tumours including fibrosarcoma, chondrosarcoma, osteosarcoma, multiple myeloma, and leukaemias ([Durbin, 1973](#); [Koshurnikova et al., 2000](#); [Shilnikova et al., 2003](#)). In addition, many of the bone-seeking radionuclides are present in a wide variety of other tissues resulting in extra-skeletal tumours, such as hepatic carcinoma ([Gilbert et al., 2000](#)). In general, radionuclides that become extensively deposited within the volume of the bone matrix (bone-volume seekers) are less toxic than those

that mostly remain close to bone surfaces (bone-surface seekers) ([Taylor et al., 1983](#)). However, this distinction is not clear, and in practice many radionuclides are present in both bone volume and surface components. For example, all bone-volume seekers transit through bone surfaces before deposition, and the apposition of new bone onto contaminated surfaces buries bone-surface seekers. The lower toxicity of buried radionuclides results from the high fraction of the  $\alpha$ - and  $\beta$ -particles released by these that are harmlessly attenuated by the bone mineral. In contrast, bone-surface seekers are deposited and commonly retained adjacent to the radiation-sensitive cancer precursor cells found within the marrow space close to bone surfaces, and deeper within the bone marrow ([Priest, 1990](#)).

In addition to the above, radioactive colloids have sometimes been used either for radiotherapy or as a radiographic contrast agent, and these are carcinogenic. Of these, the most important is Thorotrast, a colloidal suspension of thorium ( $^{232}\text{Th}$ ) dioxide, which was used from the 1930s through to the 1950s. This was mostly injected into patients as a radiographic contrast agent, but following its injection and clearance from the blood, it became deposited within the reticulo-endothelial system – mostly in the liver, spleen, and red bone marrow. Subsequently, up to 40% of the patients injected with Thorotrast, who had survived the trauma that indicated the use of the agent, developed either malignancies or liver cirrhosis, and died as a result of irradiation by  $^{232}\text{Th}$  and its progeny ([Becker et al., 2008](#)). Most of the tumours produced were hepatic carcinomas, but myeloid leukaemia was also common. While not a bone-seeking radionuclide, the sites of Thorotrast deposition in the body are sufficiently close to those of many bone-seeking radionuclides to inform on the toxicity of the latter.

(a) *Radionuclides chemically related to normal bone components*

Classically, the most important of the radionuclides that are chemically related to normal bone components are the alkaline earth elements (beryllium, calcium, strontium, barium, and radium), the uranyl ion ( $\text{UO}_2^{2+}$ ), and those that may form anions similar to phosphate ( $\text{PO}_4^{2-}$ ). This includes several important radionuclides including  $^{32}\text{P}$ ,  $^{90}\text{Sr}$ ,  $^{133}\text{Ba}$ ,  $^{224}\text{Ra}$ ,  $^{226}\text{Ra}$ ,  $^{233}\text{U}$ , and  $^{234}\text{U}$  for which extensive animal and human toxicity data exists. All of these are deposited within bone mineral (calcium hydroxyapatite), but several mechanisms for their incorporation are possible (Priest, 1990). Following their introduction into the body, all tend to be present in blood and tissue as freely exchangeable divalent ions associated with low-molecular weight plasma components such as bicarbonate. Their uptake and retention by tissues other than the skeleton is low, consequently most of those that are not deposited within the skeleton are rapidly excreted in either the urine or faeces—where due to short-term retention they may cause kidney damage, e.g. kidney damage by uranium. [The Working Group noted that this recent evidence suggests significant uptake of radium isotopes by the thyroid gland at levels of concentration similar to those in bone, and these may contribute to the induction of thyroid cancer. Also, if such deposits are confirmed for other alkaline earth radionuclides, such as  $^{90}\text{Sr}$ , they also may, in part, explain the excess thyroid cancer seen in irradiated populations following the Chernobyl nuclear accident.]

Uranium is a special case and is worthy of further consideration (The Royal Society, 2001, 2002). Six isotopes are important:  $^{232}\text{U}$  and  $^{233}\text{U}$  are anthropogenic and produced in thorium-fuelled reactors;  $^{236}\text{U}$  is produced in reactors by neutron capture; and  $^{234}\text{U}$ ,  $^{235}\text{U}$  and  $^{238}\text{U}$  are naturally occurring isotopes. The half-life of these varies greatly and that of  $^{238}\text{U}$  is so long

( $4.47 \times 10^9$  yr) that it is minimally radioactive. It is therefore not axiomatic that any mutagenic effects of  $^{238}\text{U}$  (including both natural uranium and depleted uranium) will have been produced by tissue irradiation. Indeed, there is evidence that low specific activity forms of uranium may exert their effects as a manifestation of its chemical toxicity. In contrast, high specific activity isotopes –  $^{232}\text{U}$  and  $^{233}\text{U}$  – are most unlikely to be present in the body in sufficient quantities to produce significant chemical toxicity, and radiation effects will dominate. In addition, uranium exists in two almost similarly stable valence states:  $\text{U}^{4+}$  and  $\text{U}^{6+}$ . There is some evidence the tetravalent form behaves like other actinons; however, in biological systems hexavalent uranium (as  $\text{UO}_2^{2+}$ ) is most important. Due to the bivalency of this complex ion, it shares many characteristics in common with the alkaline earth elements that also exist in the form  $\text{M}^{2+}$ . These are all bone-seeking radionuclides that deposit in the skeleton with a pattern similar to that of calcium.

In the adult skeleton, most bone surfaces are inactive at any one time and in adult man only about 22% of trabecular bone and 3% of cortical bone surfaces are remodelled (removed and re-deposited) in any year—in children, the fraction is much higher and age-dependent. It follows that in adults, the bulk of alkaline earth radionuclides and the uranyl ion radionuclides initially transfer from tissue fluids to quiescent bone surfaces where they deposit as a close-to-infinitely thin layer (Priest, 1990). The most likely explanation for this is their uptake by ion-exchange processes either into existing bone mineral crystals or within the hydration shell that surrounds each bone crystal. On growing bone surfaces, the density of uptake is higher and the radionuclides become deposited at the bone-mineral face below the layer of un-mineralized bone matrix referred to as osteoid. At these sites, it is postulated that the radionuclide is incorporated into the forming bone crystals. Subsequently, autoradiographic studies have shown that most of the

radionuclide on the quiescent bone surfaces is lost to back-exchange, leaving radionuclide hotspots at sites of bone deposition. These then become buried as new bone is deposited, and over time successive bone turnover cycles result in a more uniform deposition of radionuclide throughout the bone volume—hence the term bone-volume seeker. It follows that the fraction of radionuclide that decays close to bone surfaces will be a function of the half-life of the radionuclide. Short-lived radionuclides such as  $^{224}\text{Ra}$  (half-life, 3.6 days) will decay close to bone surfaces and be more toxic per unit of average skeletal dose than long-lived radionuclides emitting the same radiation type such as  $^{226}\text{Ra}$  and  $^{234}\text{U}$ . This is both because of the higher fraction of radionuclide that decays near bone surfaces in general, and because more radionuclide decays near growing bone surfaces—these seem to be most sensitive with respect to the production of osteosarcoma (Taylor *et al.*, 1983; Priest, 1987). Evidence of the latter is provided by the frequency of radiation-induced osteosarcomas at sites of high bone turnover (for example at the end of long bones).

Also, the distribution of the daughters of the parent radionuclides will influence the toxicity of the radionuclides. For example  $^{90}\text{Y}$  produces a high-energy  $\beta$ -particle that can irradiate tissues much deeper into the bone marrow than the  $\beta$ -particle produced by the  $^{90}\text{Sr}$  parent. Also, radium isotopes decay into a series of progeny all of which can potentially irradiate deep into the bone marrow due to the diffusion of radon gas away from the parent radionuclide. Finally, the incidence of bone sarcomas will be influenced by the deposition of layers of fibrous material on bone surfaces (Priest, 1990; Priest *et al.*, 1995). In theory, they should be protective because these layers contain no radiation-sensitive cells, but in practice the experience with the radium-dial painter populations suggests that the threshold dose for the production of these layers is similar to the lowest skeletal doses where osteosarcoma is seen (~10 Gy average skeletal dose). The lack of

osteosarcoma at doses below this has given rise to the suggestion that there may be a threshold dose, below which osteosarcoma is unlikely (Lloyd *et al.*, 2000). The production of osteosarcoma may therefore be a result of misrepair to bone damaged by  $\alpha$ -particles and not due to a lack of sensitivity to tumour induction of the target cells.

While classical radiodosimetry suggests that  $^{226}\text{Ra}$  and other  $\alpha$ -particle-emitting radionuclides on bone surfaces will result in the induction of leukaemia, there is little evidence for this in man. Evidence provided by studies of radium-dial painters that were exposed to  $^{226}\text{Ra}$  and  $^{228}\text{Ra}$  and large animal studies with radium suggest that leukaemia is a very unlikely consequence of the deposition of  $\alpha$ -particle-emitting radionuclides on bone surfaces. The exception to this is the atypical aleukaemic leukaemia found in some radium chemists. This type of leukaemia is restricted to the bone marrow and may be associated with bone marrow stem cell failure at very high radiation doses. Together, the normal lack of leukaemia and the presence of leukaemia in patients that received Thorotrast (Becker *et al.*, 2008), which deposits throughout the bone marrow, suggests that the radiosensitive cells that give rise to leukaemia are not found close to bone surfaces. Clearly, radionuclides with high-energy  $\beta$ -particles and those that have decayed away from bone surfaces due to the diffusion of daughters do show leukaemia in human populations. In this way, both higher and lower doses of  $^{224}\text{Ra}$  (daughter  $^{220}\text{Rn}$ ) injected into patients for the treatment of ankylosing spondylitis and tuberculosis do result in a small number of leukaemias (Wick *et al.*, 2008, 2009). The diffusion of radon ( $^{222}\text{Rn}$ ) away from bone surfaces into the sinuses of the head is also considered to be the cause of head carcinomas seen in the radium-dial painters (Rowland *et al.*, 1978).

(b) *Radionuclides that are chemically unrelated to normal bone components but bind to the matrix and/or mineral components of bone*

This group of radionuclides includes many that are present in nuclear fuels and are potentially toxic to man. These include fuel components and activation products such as  $^{239}\text{Pu}$ ,  $^{241}\text{Am}$  and  $^{242}\text{Cm}$  (all actinons), and heavy-fraction fission products such as  $^{144}\text{Ce}$ ,  $^{147}\text{Pm}$  and  $^{152}\text{Eu}$  (all lanthanons). Human exposures are rare, and most of the toxicity data for these materials has been produced using laboratory animals. These show that these bone-surface-seeking radionuclides when present in the body produce a variety of tumour types—mostly skeletal tumours, leukaemia, and liver tumours ([Humphreys et al., 1985](#); [Gillett et al., 1987](#); [Miller et al., 2003](#)). Human toxicological data exist only for plutonium within the population of former nuclear workers at Mayak within the former Soviet Union ([Gilbert et al., 2000](#); [Koshurnikova et al., 2000](#); [Sokolnikov et al., 2008](#)). Experience with these suggests that exposures to plutonium isotopes (with  $^{241}\text{Am}$ ) result in a variety of tumour types, reflecting the distribution of these radionuclides in the liver and the skeleton. The ERR per unit dose of hepatic carcinoma and osteosarcoma in these workers is similar. Given the animal experimental data with a wide range of radionuclides and the human data with plutonium, any consideration of the toxicity of this group of bone seekers needs to consider both skeletal and extra-skeletal deposits.

Lanthanons and actinons, like many other metal bone-seeking elements are multivalent and easily form complexes with organic molecules. It follows that radionuclides such as  $^{144}\text{Ce}$ , a lanthanon,  $^{239}\text{Pu}$  and  $^{241}\text{Am}$ , both actinons, are present in the blood complexed to both large (transferrin and albumin) and small (citrate) molecules ([Taylor et al., 1987](#)). These radionuclides are much less likely to be filtered by the kidney and excreted than those present as loosely

bound ionic species in the blood ([Talbot et al., 1993](#)). Plutonium in particular binds strongly to the iron-transport protein transferrin. In rats, 60% of uranium and 47% of radium are excreted in the first 24 hours after intake, but only 9% of americium and 6% of plutonium ([Priest, 1990](#)). Similar excretion patterns are seen in man. Because proteins tend to be retained within blood vessels, those radionuclides such as plutonium that are strongly bound to proteins tend to deposit most readily in those organs and tissues that have a sinusoidal blood supply. Sinusoids have a discontinuous endothelial lining, are irregular tubular spaces for the passage of blood, taking the place of capillaries and venules in the liver, spleen, and red bone marrow. The sinusoids form from branches of the portal vein in the liver and from arterioles in other organs including glands such as the adrenal glands and sex glands. The walls of the sinusoids are lined with phagocytic cells—macrophages that digest old erythrocytes and clear the bloodstream of toxins. Within the liver, both these cells and hepatocytes remove plutonium and other similar elements from the bloodstream ([Priest, 1990](#)).

In general, lanthanons and actinons deposit in either the liver or the skeleton on bone surfaces. No complete data set is available for man, but experiments with rodents suggest that bivalent metals (including the uranyl ion) do not deposit in the liver to any appreciable extent, that the trivalent metal ions (including the lanthanons, americium and curium) have a high fractional deposition in the liver, that the pentavalent ions, such as those of neptunium and protactinium, deposit to a higher extent in the skeleton than in the liver, but that tetravalent plutonium has a distribution that is intermediate between these extremes ([Durbin, 1972](#)). To a large extent, this deposition pattern is likely to result from differences in the charge density of the ion since research has shown that trivalent radionuclides deposit in rodents with a predictable pattern ([Durbin, 1973](#)). The research showed that there is a progressive shift towards

deposition in the skeleton with decreasing ionic size with large ions such as those of lanthanum and cerium depositing mostly in the liver, and small ions such as those of holmium and lutetium depositing mostly in the skeleton. In another experiment, [Priest \(2007\)](#) showed that the lanthanon  $^{147}\text{Pm}$  and the actinon  $^{242}\text{Cm}$ , which have the same valency ( $3^+$ ) and the same ionic radius, behave identically in the body. Why this should be so is not clear. However, as binding to plasma proteins has been shown to be dependent on ion size and as the uptake of non-colloidal cations by the liver involves the active transport of metal ions across cell membranes, which is also likely to be an ion-size-dependent process, it has been speculated that these represent the distribution-determining processes ([Durbin, 1973](#)). In contrast, the uptake of metal ions by bone surfaces has been regarded as a less specific, passive process, independent of ionic size ([Taylor et al., 1971](#)). Consequently, it is less likely to be important in determining the final distribution of the radionuclide ([Priest, 1990](#)). Another factor affecting the early distribution of bone-seeking radionuclides may be their rate of loss from the liver, as has been demonstrated in human volunteer studies using  $^{237}\text{Pu}$  and  $^{244}\text{Pu}$  ([Etherington et al., 2003](#)). These indicate a high early uptake of plutonium by the liver (~90%) but a gradual loss thereafter to the skeleton. It would seem that plutonium cycles fast through the human liver, being alternatively released then recaptured, but that during each cycle a small amount of the radionuclide is captured by the skeleton producing the observed gradual transfer of radionuclide from liver to bone surfaces. A similar transfer is seen in animals ([Priest, 1990](#)).

The binding of radionuclides to plasma proteins also seems to affect the deposition pattern of these within the bone, at least in rodents.  $^{239}\text{Pu}$ , which binds strongly to plasma proteins, seems unable to easily pass through the walls of blood vessels, and is preferentially deposited on internal endosteal bone surfaces adjacent to the

blood sinusoids within the red bone marrow. In contrast,  $^{241}\text{Am}$  (and other trivalent metal ions) – presumably because of the higher fraction bound to small plasma molecules such as citrate – diffuses more easily through the walls of blood vessels, and deposits more evenly on all types of bone surface ([Priest, 1990](#)). The radionuclides also bind to surfaces at other sites of calcification including on dentinal surfaces adjacent to the pulp cavity in teeth and on mineralized cartilage surfaces. The mechanism of metal deposition on the bone surfaces is unclear but it is likely that a substantial fraction bind to phosphoproteins and other acidic proteins that are concentrated at the mineralized bone matrix front ([Priest, 1990](#)).

Subsequent to their deposition on bone surfaces, all long-lived lanthanons and actinons, as well as some other metals including iron and aluminium, will tend to remain on these surfaces unless removed by bone growth and remodelling processes. At lower levels of radionuclide accumulation, two outcomes are possible:

- 1) the contaminated bone surface can become buried by the apposition of new bone onto a growing bone surface;
- 2) bone surface deposits can be removed by osteoclasts during bone surface removal by these cells at sites of bone resorption.

Studies have shown that osteoclasts retain radionuclides such as  $^{26}\text{Al}$ ,  $^{55}\text{Fe}$ ,  $^{239}\text{Pu}$  and  $^{241}\text{Am}$  for a short time before they are passed to adjacent macrophages lying deeper within the bone marrow. The presence of macrophages containing  $^{239}\text{Pu}$  and other similar radionuclides led to the speculation that the irradiation of surrounding bone-marrow cells could lead to the induction of leukaemia ([Vaughan et al., 1973](#)), and myeloid leukaemia is seen in rodents treated with  $^{239}\text{Pu}$  and  $^{241}\text{Am}$  ([Oghiso et al., 1994](#); [Ellender et al., 2001](#)). In contrast, it was not identified in the Mayak worker population exposed to plutonium ([Sokolnikov et al., 2008](#)). Given that similar, albeit somewhat deeper buried, Thorotrast deposits in the red bone marrow do produce leukaemia, it is

not clear as to why this has not been observed for plutonium in humans.

Biokinetic studies suggest that plutonium remains in the bone marrow, associated with iron stores in ferritin, for approximately 80–100 days, and is then released in a soluble form into the surrounding tissue fluids. Much of this re-deposits on local bone surfaces maintaining the surface deposition pattern, but some returns to the bloodstream and most is either re-deposited in the liver, other organs, or is excreted. This small loss to excretion results in a slow loss of plutonium and similar metals from the skeleton giving half-times of retention that may exceed 50 years ([ICRP, 1986](#)).

Alternatively, if the radiation doses to bone surfaces are high following significant radionuclide intakes, such as seen in the radium-dial painters, the surfaces may become covered either with a layer of abnormal bone or by a layer of fibrous ‘scar’ tissue. Such pathologies have been seen in dogs following high actinon intakes, in baboons following intakes of plutonium, in humans following an accidental intake of  $^{241}\text{Am}$ , and in the skeleton of a Mayak worker that had large occupational exposures to plutonium ([Priest et al., 1987, 1995](#); [Suslova et al., 2002](#)).

While most  $^{239}\text{Pu}$  and other bone-surface seekers are deposited in the liver and spleen, smaller amounts are deposited in a wide variety of tissues and these could potentially give rise to other tumour types. For example, a mice study using injected  $^{242}\text{Cm}$   $\alpha$ -particles as a source of tissue irradiation produced a wide range of tumours that were in excess of those found in control animals—namely, mammary carcinoma, liver carcinoma, lung adenocarcinoma, uterine carcinoma, malignant lymphoma, liver histiocytic sarcoma, and lymph node histiocytic carcinoma ([Priest et al., 2010](#)). All of these could be potentially caused by plutonium in humans but to date insufficient numbers of contaminated subjects are available to either confirm or reject this suggestion.

### 4.1.3 Non-bone-seeking radionuclides

This group includes important radiopharmaceutical/medical diagnostic agents (e.g.  $^{11}\text{C}$ ,  $^{131}\text{I}$ ,  $^{18}\text{F}$ ,  $^{99\text{m}}\text{Tc}$ ), other common commercially important radionuclides used by industry and for research (e.g.  $^3\text{H}$ ,  $^{14}\text{C}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^{210}\text{Po}$ ), and radionuclides of inert gases that may become dissolved in tissue fluids (e.g.  $^{85}\text{Kr}$  and  $^{222}\text{Rn}$ ). These are considered separately below.

### 4.1.4 Radiopharmaceutical/medical diagnostic agents

A wide range of radionuclides are used for either radiotherapy or for medical imaging (including for positron emission tomography (PET) and single photon emission computed tomography (SPECT)):  $^{47}\text{Ca}$ ;  $^{11}\text{C}$ ;  $^{14}\text{C}$ ;  $^{51}\text{Cr}$ ;  $^{57}\text{Co}$ ;  $^{58}\text{Co}$ ;  $^{169}\text{Er}$ ;  $^{18}\text{F}$ ;  $^{67}\text{Ga}$ ;  $^{68}\text{Ga}$ ;  $^3\text{H}$ ;  $^{111}\text{In}$ ;  $^{123}\text{I}$ ;  $^{131}\text{I}$ ;  $^{59}\text{Fe}$ ;  $^{81\text{m}}\text{Kr}$ ;  $^{13}\text{N}$ ;  $^{15}\text{O}$ ;  $^{32}\text{P}$ ;  $^{153}\text{Sm}$ ;  $^{71}\text{Se}$ ;  $^{22}\text{Na}$ ;  $^{24}\text{Na}$ ;  $^{186}\text{Re}$ ;  $^{89}\text{Sr}$ ;  $^{99\text{m}}\text{Tc}$ ;  $^{201}\text{Tl}$ ;  $^{133}\text{Xe}$ ; and  $^{90}\text{Y}$  ([NRPB, 1998](#)). Some of these may be administered to patients as free ionic species:  $^{18}\text{F}$ ;  $^{67}\text{Ga}$ ;  $^{123}\text{I}$ ;  $^{131}\text{I}$ ;  $^{59}\text{Fe}$ ;  $^{32}\text{P}$ ;  $^{22}\text{Na}$ ;  $^{89}\text{Sr}$ ;  $^{99\text{m}}\text{Tc}$ ;  $^{201}\text{Tl}$ ; and  $^{90}\text{Y}$ . The distribution of these within the body is a function of their affinity for different organs and tissues within the body, and many are bone-seekers ( $^{18}\text{F}$ ,  $^{67}\text{Ga}$ ,  $^{59}\text{Fe}$ ,  $^{32}\text{P}$  (as phosphate),  $^{89}\text{Sr}$ ,  $^{99\text{m}}\text{Tc}$  (as pertechnetate)) with variable levels of uptake in other body tissues including the liver, spleen, and red bone marrow. Other radionuclides administered as ionic species either become more uniformly distributed among body tissues (e.g.  $^{22}\text{Na}$  and  $^{99\text{m}}\text{Tc}$ ) or like  $^{123}\text{I}$  deposit mostly within a single organ—in this case the thyroid gland. In addition,  $^3\text{H}$  and  $^{15}\text{O}$  may be administered in molecular form as water, and become uniformly distributed and irradiate all body tissues. Noble gas radionuclides  $^{81\text{m}}\text{Kr}$  and  $^{133}\text{Xe}$  are also administered as molecular species. These can be used either for lung perfusion studies following inhalation of the gases or following administration of the gases dissolved in water. Finally,  $^{169}\text{Er}$  is administered

as a colloid and becomes distributed in the body with the same pattern as Thorotrast, with a high uptake by macrophages in the spleen, liver, lymph nodes, and red bone marrow.  $^{99m}\text{Tc}$  can also be administered as a colloid and is deposited similarly. In contrast,  $^{99m}\text{Tc}$  and  $^{99}\text{Tc}$  as pertechnetate become more evenly distributed throughout the body with a higher uptake in the thyroid, salivary glands, stomach wall, colon wall, and liver (Beasley *et al.*, 1966).

In addition to the above, many radionuclides are used to tag (radiolabel) compounds that target specific cells, organs, and tissues within the body. In such cases, the distribution of the radionuclide within the body is not a function of the label employed, but of the moiety to which it is attached. Examples are many but some radiolabelled pharmaceuticals are currently used more than others – most today employ  $^{99m}\text{Tc}$  as the radiolabel, because relative to other possible isotopes the radiation dose per investigation is lower.  $^{99m}\text{Tc}$ -labelled exametazime crosses the blood/brain barrier,  $^{99m}\text{Tc}$ -labelled sestamibi is used to study myocardial infarctions,  $^{99m}\text{Tc}$ -labelled mercapto-acetyl-triglycine (MAG3) is retained within the bloodstream, and is used to assay renal function (Taylor *et al.*, 1988; Slosman *et al.*, 2001; Tanaka *et al.*, 2006).  $^{99m}\text{Tc}$ -labelled bisphosphonates (methylene diphosphonate and dicarboxypropane diphosphonate) are deposited preferentially in the skeleton (Murphy *et al.*, 1997).

The recent explosion in the use of PET for diagnostic nuclear medicine has resulted in a range of new short-lived, cyclotron-produced, positron-emitting radionuclides being administered to patients at levels of administration of up to 400 MBq per investigation. These radionuclides include  $^{11}\text{C}$  (half-life, 20 min),  $^{13}\text{N}$  (half-life, 10 min) and  $^{15}\text{O}$  (half-life, 2 min), but the most commonly used is  $^{18}\text{F}$  (half-life, 110 min) (Shinotoh *et al.*, 1997; Young *et al.*, 1999). These radionuclides are sometimes used as labels for simple substances such as water, ammonia, and

glucose.  $^{18}\text{F}$ -labelled glucose and glucose derivatives (e.g.  $^{18}\text{F}$ -fluorodeoxyglucose) are taken up, and in the case of  $^{18}\text{F}$ -fluorodeoxyglucose retained, preferentially by metabolically active cells with a high requirement for glucose—including in the brain, liver, and most tumours (Young *et al.*, 1999). Other  $^{18}\text{F}$ - (and  $^{11}\text{C}$ -) labelled compounds, e.g. raclopride and 6-fluoro-L-dopa, concentrate preferentially at dopamine receptors in the brain, and are used for PET brain scans (Shinotoh *et al.*, 1997).

Finally, some radionuclides have been used for radiotherapy (UNSCEAR, 2000). The efficient targeting of some tumour types with monoclonal antibodies labelled with radionuclides such as  $^{211}\text{At}$ , which delivers a high  $\alpha$ -particle dose to targeted cells, is sometimes possible (McDevitt *et al.*, 1998), but most radionuclides administered for radiotherapy use the ability of radionuclides to target cells by following metabolic pathways that exist for the transport of stable isotopes. In this way,  $^{131}\text{I}$  is used to ablate the thyroid and treat thyroid cancer,  $^{89}\text{Sr}$  and  $^{186}\text{Re}$ -HEDP ( $\alpha$ -hydroxyethylidene diphosphonate) are used for the palliative treatment of skeletal metastases, and  $^{32}\text{P}$ -orthophosphate to bind to bone surfaces and treat *polycythaemia vera*—a benign bone marrow disease (Harman & Ledlie, 1967; Spiers *et al.*, 1976; Tennvall *et al.*, 2000; Giammarile *et al.*, 2001; Orlandi *et al.*, 2001).

#### 4.1.5 Commercially important radionuclides used by industry and for research, and non-bone seeking fission products

This group of radionuclides includes  $^3\text{H}$ ,  $^{14}\text{C}$ ,  $^{32}\text{P}$  and  $^{35}\text{S}$ , which are normal components of either all or a wide range of biomolecules.  $^3\text{H}$  administered as the gas results in inconsequential doses to organs and tissues, and for this reason is widely used in industry to power emergency light sources. If it is administered as radiolabelled water, it mixes with cell and tissue fluids and delivers a much higher relatively uniform dose

to all body tissues until it is lost to excretion. In contrast, if  $^3\text{H}$ -labelled compounds (including drugs administered to human subjects as part of the drug approval process) are administered then the distribution of dose within the body may well be highly heterogeneous with some target organs and tissues absorbing 90% or more of the total energy deposited in the body. Given the infinitely wide range of possible labelled biomolecules, it is not possible to specify any characteristic deposition pattern for  $^3\text{H}$ -labelled compounds (reviewed by [Hill & Johnson, 1993](#)).

Similar considerations can be made for  $^{14}\text{C}$ -labelled compounds that are also widely administered to human subjects within constraints recommended by the WHO for Category 1 human volunteer projects (maximum committed dose of  $500\ \mu\text{Sv}$  per administration)—again it is not possible to specify any characteristic deposition pattern. Of more concern are intakes of  $^3\text{H}$  and  $^{14}\text{C}$  that are incorporated into food products following their release to the environment by nuclear industries and/or following the testing of thermonuclear devices. These will be digested in the gut, absorbed as labelled amino acids, fatty acids and carbohydrates, then metabolized within cells, and then either retained within the body as structural proteins, carbohydrates, etc. or excreted as carbon dioxide or water. [Richardson \(2009a\)](#) has developed a biokinetic model, the hydrogen, carbon, nitrogen and oxygen (HCNO) model that describes the distribution, retention and dosimetry of  $^3\text{H}$  and  $^{14}\text{C}$  intakes by the body. (NB: this model has been incorporated into the GenmodPC radionuclide dosimetry programme that is available from Atomic Energy of Canada Limited (AECL) for infants and children ([Richardson & Dunford, 2001, 2003](#); [Richardson, 2009b](#)).

$^{35}\text{S}$ ,  $^{32}\text{P}$  and  $\text{P}^{33}$  are used for research in laboratory studies to label specific biomolecules, but these are not normally administered to man. Again, it is not possible to specify any characteristic distribution pattern for these in the body.

However,  $^{32}\text{P}$  and  $^{33}\text{P}$  administered as phosphate ions will be incorporated in hydroxyapatite (bone mineral) and other phosphated molecules including DNA, and  $^{35}\text{S}$  administered as the sulfate ion will be incorporated widely into sulfated proteoglycans and glycoproteins that are present in bone, in cartilage, other connective tissues, and in mast cells ([ICRP, 1979, 1993](#)).

Other commercially important non-bone seeking radionuclides include  $^{24}\text{Na}$ ,  $^{40}\text{K}$ ,  $^{137}\text{Cs}$  and  $^{210}\text{Po}$ .  $^{24}\text{Na}$ ,  $^{40}\text{K}$  and  $^{137}\text{Cs}$  are all isotopes of alkali metals in Group 1 of the periodic table.  $^{24}\text{Na}$  is produced from stable  $^{23}\text{Na}$  by neutron capture,  $^{40}\text{K}$  is a natural isotope and  $^{137}\text{Cs}$  is mostly a long-lived decay product of the fission product  $^{137}\text{Xe}$ . All of these isotopes have soluble ions that are, therefore, widely distributed within the body. In general,  $^{24}\text{Na}$  will mix with stable sodium in the body and  $^{137}\text{Cs}$  follows many of the metabolic pathways of potassium – including its natural radioactive isotope  $^{40}\text{K}$  – and becomes relatively uniformly distributed until lost to excretion at a rate that is faster in women than in men ([Melo et al., 1997](#)).

Finally, this group includes miscellaneous radionuclides:  $^{60}\text{Co}$ ,  $^{106}\text{Ru}$ ,  $^{207}\text{Bi}$ , and  $^{210}\text{Po}$  that are either used commercially or are important fission products.  $^{60}\text{Co}$  is an important industrial radionuclide used in the manufacture of  $\gamma$ -beam sources for radiotherapy. The biokinetic properties of this essential element have been reviewed by [Kim \(2006\)](#) for the IPCS ([WHO, 2006](#)). Cobalt distribution and retention in man have been studied using  $^{55}\text{Co}$  and  $^{56}\text{Co}$ , and in rats using  $^{57}\text{Co}$  and  $^{60}\text{Co}$ . Following intravenous injection, the highest cobalt concentrations are found in the liver and kidney—with lower concentrations in other tissues including muscle, the brain, and testes. While much cobalt is rapidly cleared from the body some is retained, and is presumably incorporated within vitamin B12 (cobalamin), which is stored in the liver. In an interspecies comparison study using mice, rats, guinea-pigs, rabbits, dogs and baboons, large interspecies

differences in the lung clearance and retention of inhaled ionic cobalt were found ([Patrick \*et al.\*, 1994](#)). This study also identified the uptake of cobalt by cartilage structures. Relatively little is known about the biokinetics of ruthenium even though  $^{106}\text{Ru}$  is an important, longer-lived fission product. The limited data available for rats ([Dziura \*et al.\*, 1998](#)) suggest that it is poorly absorbed from the gut, and is rapidly eliminated from the body. It has no specific affinity for any organ or tissue other than the kidney in which it accumulates to some extent.  $^{106}\text{Ru}$  has a high-energy,  $\beta$ -emitting daughter  $^{106}\text{Rh}$ , and has been used for the treatment of some eye conditions ([Schueler \*et al.\*, 2006](#)). The metabolism and retention of bismuth as  $^{207}\text{Bi}$  in man has been studied ([Newton \*et al.\*, 2001](#)). A healthy male volunteer received an intravenous injection of  $^{207}\text{Bi}$  as the citrate. After a rapid initial excretion, with 55% lost during the first 47 hours, principally in urine, longer-term losses were much slower, and 0.6% remained in the body at 924 days, when the contemporary rate of loss implied a half-life of 1.9 years. Integration of the retention pattern suggested that steady exposure to bismuth compounds could lead ultimately to a body content of 24 times the daily systemic uptake. The largest organ deposit was in the liver, which after 3 days contained approximately 60% of the contemporary whole-body content. This distribution is contrary to that previously described by the [ICRP \(1980\)](#), which envisages a terminal half-life in the body of only 5 days, and kidney as the site of the highest deposition.  $^{210}\text{Po}$  is used in the manufacture of antistatic brushes as a relatively non-toxic  $\alpha$ -particle source. However, when present in the body in  $\sim\text{GBq}$  quantities, it has been shown to be toxic. The distribution and dosimetry of this isotope has been described by [Harrison \*et al.\* \(2007\)](#), and  $^{210}\text{Po}$  is reported to be generally distributed throughout soft tissues in the body including in the liver, muscles and bone marrow, and is generally retained. No affinity of  $^{210}\text{Po}$  for bone was identified.

#### 4.1.6 Inert gases

Humans are potentially irradiated by both natural and anthropogenic radioisotopes of the noble gases. The most important are  $^{85}\text{Kr}$  and  $^{133}\text{Xe}$  released from nuclear reactors, and  $^{220}\text{Rn}$  and  $^{222}\text{Rn}$ , which are natural daughter products derived from uranium- and thorium-containing minerals. The latter are important because the inhalation of radon isotopes always contribute significantly to, and may dominate, the natural background dose to members of the public. Noble gases in Group 18 of the Periodic Table exist as diatomic molecules that are completely unreactive. It follows that the principle organ irradiated by exposure to noble gas radionuclides is to the lungs. However, krypton and radon are soluble in water so they will be absorbed by blood within the lungs, and circulated around the body where they may irradiate all tissues. Moreover, these gases are reported to be 16 times more soluble in lipids, and it is likely that adipose tissue and the bone marrow may be irradiated, particularly by  $^{222}\text{Rn}$ , to a much greater extent than to other body tissues ([Richardson & Henshaw, 1992](#)). A similar distribution of dose may be expected following lung perfusion studies using other noble gas isotopes  $^{81\text{m}}\text{Kr}$  and  $^{133}\text{Xe}$  ([Loken & Westgate, 1968](#); [Yano \*et al.\*, 1970](#)).

### 4.2 Mechanisms of carcinogenesis induced by all ionizing radiation

#### 4.2.1 Introduction

The traditional approach to the mechanism of radiation-induced carcinogenesis is quite well explained in a recent review ([Mullenders \*et al.\*, 2009](#)), albeit in the context of low-dose radiation. Essentially, the radiation-induced damage to the genomic DNA, more or less regardless of the dose, stimulates a DNA-damage response, which attempts to affect repair of the damage before the cell goes into mitosis, whereupon residual damage

would be “fixed” and, if consistent with further cell division, replicated in all future generation of that cell. Cells with unrepaired or misrepaired damage are assumed to follow pathways through which they acquire the so-called “hallmarks of cancer” ([Hanahan & Weinberg, 2000](#)) or phenotypic features of malignancy, for example, loss of senescence and anchorage-free growth. In this approach, this process is assumed to be purely genetic, that is, these acquired features are attributable to mutations of a few specific genes, for example oncogenes or tumour-suppressor genes. This is the basis for the so-called “mutational theory of cancer” ([Weinberg, 1998](#)), and ionizing radiation, being a mutagenic agent, is considered a prime candidate for initiating such a process.

However, the mutational theory has been challenged (see for example, [Soto & Sonnenschein, 2004](#); [Bizzarri et al., 2008](#)). In addition, several recent developments in biology have placed a question mark over the validity and general applicability of the mutational theory.

First, genome-wide sequencing of several cancers of the same type have indicated that the carcinogenic process is not driven by a few mutated genes along a single pathway but by many genes along several pathways ([Greenman et al., 2007](#); [Jones et al., 2008](#); [NCI, 2008](#)). For example, in 24 pancreatic cancers, a total of 12 genetic pathways were identified ([Jones et al., 2008](#)). The application of the newly developed high-throughput short-hairpin RNA (shRNA) screening is another powerful instrument that can reveal such multiple genetic changes and pathways in carcinogenesis ([Bernards et al., 2006](#)).

Second, there is an emerging view that any cellular phenotype is more complex than assumed in the mutational theory, and is best represented by a pattern of active gene products (mainly proteins but also RNAs; [Baverstock & Rönkkö, 2008](#); [Huang, 2009](#)). An essential prerequisite of this approach is to view the cell as a dynamic entity rather than as traditionally, a mechanistic

entity. In the emerging view, phenotype is seen as an emergent property derived from the dynamic interaction of several (typically in the human cell, thousands) gene products, the profile of which can conveniently be described as a high dimensional dynamic attractor that endows phenotypic stability (attractors are a stable or stationary states of dynamical systems in which there is no continuum of stability, thus transitions between attractors are jumps). Two important features of this model are that transitions between phenotypes (attractor transitions) can take place without changes in gene sequence, i.e. can be purely epigenetic, and by several “pathways” as would be consistent with the evidence from genome-wide sequencing referenced above. The term “epigenetic,” as used here, does not imply any specific mechanism such as chromatin marking but rather that the process is not related to specific changes to the DNA sequence.

On the basis of this concept of phenotype, both the initiation ([Baverstock, 2000](#)) and the progression ([Brock et al., 2009](#)) of cancer can be seen as epigenetic and, in principle, reversible processes with the characteristic mutations accumulated as a consequence of the mutator phenotype typical for carcinogenesis ([Bielas et al., 2006](#)). However, consequential mutations to specific genes could and most probably would serve to block the reversal of the carcinogenic process.

An important feature of this model, where initiation of cancer is concerned, is that it is not confined to radiation because the attractor transition is deemed to be a response to stress on the routine cellular processes, such as DNA-damage detection and repair ([Baverstock & Rönkkö, 2008](#)), and any agent capable of causing stress would be, in principle, able to cause cancer.

Third, the phenotypes of eukaryotes (including human cells) are mediated by the active protein products of the gene-coding sequences, and not the genes themselves. In most cases, the transcription of such a sequence produces an inactive

product that needs to be translated to a peptide, folded into a protein, which then often undergoes posttranslational modification and/or activation through, for example, phosphorylation (phosphoregulation). Thus, between the transcription of sequences and the presence in the cell of active proteins, there are many processes the control of which is far from clear. However, [Beltrao \*et al.\* \(2009\)](#) have shown in three strains of yeast that phosphoregulation provides a significant source of variation. Phosphoregulation derives from the binding of kinases at specific peptide sequences but there has to be present at least one other contributing controlling factor because cells exposed to ionizing radiation very rapidly (within a few minutes) show the presence of phosphorylated histone  $\gamma$ -H2AX sites (formed by such kinase activity) at strand breaks ([Rogakou \*et al.\*, 1999](#)). This is a clear example where purely epigenetic factors can intervene in influencing phenotype.

At the present state of knowledge, the carcinogenic process cannot be confidently attributed to either a purely genetic or purely epigenetic process and in all probability is a mixture of the two, the proportions differing from between cancer types and even case to case. This makes its perception as a mechanism, with the implication of determinism, problematic. However, the process is generally assumed to be a multistep process resulting from damage to a single cell with a normal phenotype, leading to an abnormal phenotype in which growth is not under normal control, and functionality is altered. Typically, tumour cells at the time of diagnosis carry large numbers of mutations but also may be heterogeneous in their gene-product profiles ([Brock \*et al.\*, 2009](#)). However, they have undergone many cell divisions and consequent processing of the molecular damage since their induction to the tumorigenic state, so the initial damage is likely to be obscured. Thus, the distinction between causal and consequential events in

carcinogenesis can be difficult, if not impossible, to make.

Ionizing radiation, in addition to being capable of producing mutations—mainly by large-scale gene deletion – and gross chromosomal damage, can also induce epigenetic changes. For example, genomic instability as a late-occurring event appears several cell generations after irradiation, and results in a reduced ability to replicate the genotype faithfully ([Kadhim \*et al.\*, 1992, 1994](#); [Lorimore & Wright, 2003](#); [Morgan, 2003a, b](#); [Barcellos-Hoff, 2005](#)). The events indicating instability include chromosomal aberrations, gene-sequence and mini-satellite mutations, and apoptosis. While many of these events can be seen as advancing cell transformation, an increase in apoptosis has been shown to have a protective effect against transformed cells *in vitro* ([Portess \*et al.\*, 2007](#)); these mechanisms could inhibit the neoplastic process. Molecular and cellular data indicate that the frequency of occurrence of genomic instability in relation to dose is such that it will not be due to specific genes affected by the initial ionizing event ([Baverstock, 2000](#)). It has also been proposed, given the similarity of processes leading to tumour formation and that of genomic instability, that genomic instability may be a potential candidate for the initial event of tumourigenesis ([Baverstock, 2000](#); [Little, 2000](#)).

The bystander effect ([Nagasawa & Little, 1992](#)) is another feature of the influence of ionizing radiation on cells that might influence tumour formation through epigenetic processes. Cells that have not been subject to direct irradiation can exhibit the phenotypic features of genomic instability if they are in the neighbourhood of cells that have been subject to ionizing events ([Lorimore \*et al.\*, 1998](#)). This effect can be mediated through various mechanisms including cell-to-cell communication or signalling by way of gap junctions ([Azzam \*et al.\*, 1998, 2001](#); [Bishayee \*et al.\*, 2001](#)), and secretion of chemicals into the intracellular matrix ([Mothersill & Seymour, 1997a, b](#); [Barcellos-Hoff \*et al.\*, 2005](#);

see Section 4.2.6). Bystander effects and genetic instability have also been observed after exposure to other carcinogenic agents, e.g. UV ([Dahle & Kvam, 2003](#)) and some chemicals ([Asur \*et al.\*, 2009](#)). In addition, there may be abscopal effects, where irradiation of an organism at a specific site remotely mediates cellular or phenotypic responses ([Mancuso \*et al.\*, 2008](#)). Some of these abscopal effects may be due to clastogenic factors generated by radiation in blood plasma ([Emerit, 1990](#)), and result in damage that is similar to that caused directly by radiation in tissues through which the plasma passes.

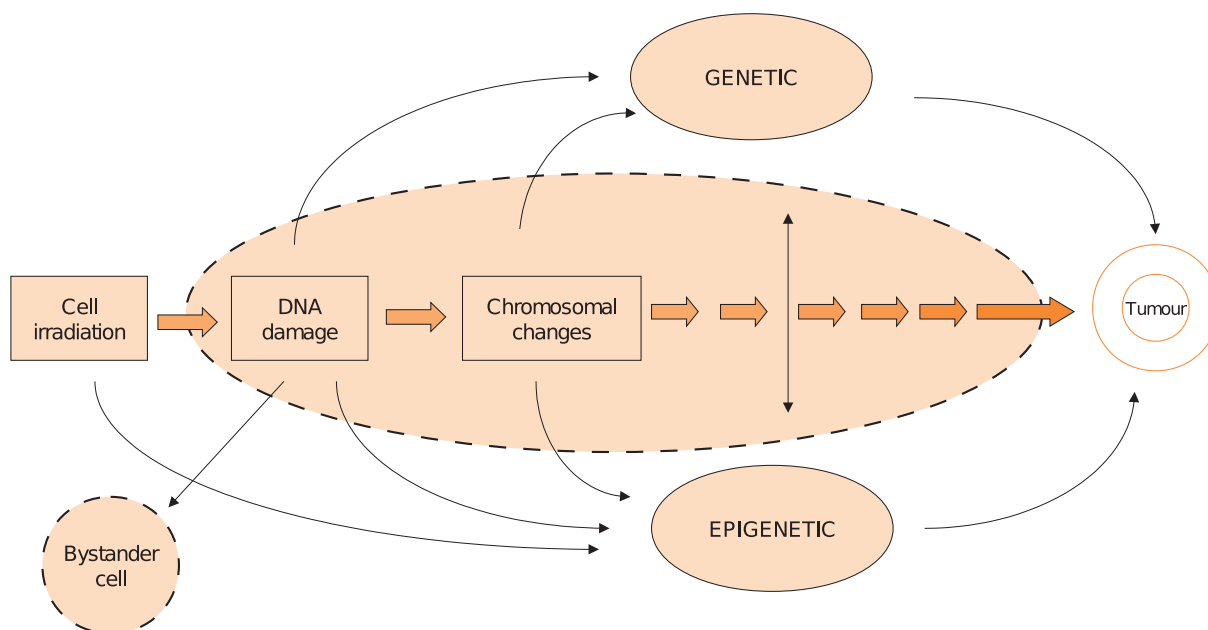
The bystander effect implies that the specific environment, e.g. the niche, in which a stem cell grows, has an important influence on its regulation ([Scadden, 2006](#)). This implies also the opposite process when a phenotypically abnormal cell may disrupt cells in its environment. In addition, other host factors – some of which are influenced by aging – will have an impact on the phenotypic state of an irradiated cell, usually to facilitate the return to the initial phenotypic state. Thus, there is a dynamic interplay between individual cells and their tissue and host environments, which is necessary for sustaining tissue integrity, but which – if disrupted – can lead to disease, including tumour formation ([Li & Neaves, 2006](#)).

Therefore, it would appear that there are several mechanisms for cancer development, and that radiation effects may play a role in many aspects of carcinogenesis, that is in the acquisition of genetic mutations and epigenetic changes, and in the interactions between nearby and distant cells in an organism. This is likely to proscribe a detailed description at the molecular level of the events that intervene between the normal and malignant phenotype. Fig. 4.1 gives a schematic representation of this emerging concept for carcinogenesis.

#### 4.2.2 The deposition of ionizing energy

Interactions of ionizing radiations with molecular structures in mammalian cells induce many different types of molecular damage, which subsequently lead to a diversity of cellular responses, including cell killing, chromosomal aberrations, mutations, and cell transformation ([BEIR VI, 1999](#); [UNSCEAR, 2000](#); [ICRP, 2002, 2005, 2007](#); [BEIR VII, 2006](#)). Their efficiency in causing damage and subsequent biological effects is related not only to the amount of energy transferred per unit mass and rate of transfer, i.e. the absorbed dose and dose rate, but also to the micro-distribution of energy, which is determined by the type of radiation. Typically, the effectiveness per unit of absorbed dose for different biological end-points increases with the linear energy transfer (LET) up to a maximum at approximately 100 keV/ $\mu\text{m}$ . For different types of ionizing radiation, the numbers of charged particles per unit dose and the structures of their radiation tracks are different at the tissue, cellular, and subcellular levels. Ionizing radiation deposits energy in the form of atomic and molecular ionizations and excitations from the interaction of the individual moving particles with the medium. The highly structured spatial pattern of interactions from a particle and its secondary particles is termed the *radiation track* of the particle.

Generally speaking, most of the energy deposition is produced by secondary or higher-order electrons set in motion following interactions of the primary radiation, be it a photon (X-ray or  $\gamma$ -ray), a neutron, or a charged particle. The energy depositions occur in clusters along the trajectories of electrons and charged particles, and the resulting non-homogeneity of the microdistribution can be substantial. The microscopic energy depositions and the track structure vary greatly with the stochastic nature of each atomic interaction ([ICRU, 1983](#); [Kellerer, 1985](#); [Goodhead, 1987, 1992](#)). A diagrammatic representation

**Fig. 4.1 Schematic representation of many aspects of carcinogenesis induced by ionizing radiation**

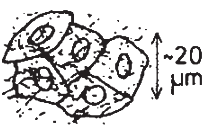
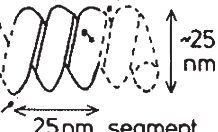
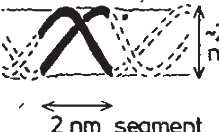
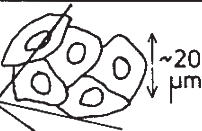
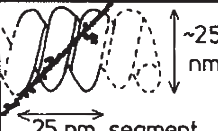
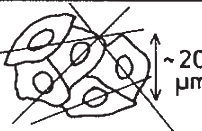
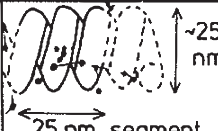
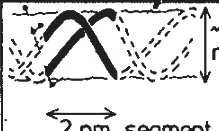
of the microscopic patterns of radiation tracks associated with external  $\gamma$ -rays,  $\alpha$ -particles from internal  $^{220}\text{Rn}$  decays, and external 10-MeV neutrons is given in Fig. 4.2.

All ionizing radiation ultimately leads to the production of electrons, through which energy will be deposited. X-rays and  $\gamma$ -rays interact within tissues producing fast electrons that interact with atoms or nuclei, producing additional electrons as they slow and deposit energy. Charged particles such as  $\alpha$ -particles and protons also interact to produce a trail of secondary electrons along the path of the primary particles. Uncharged neutrons also interact within tissue and deposit their energy via lower-energy charged particles such as protons, deuterons,  $\alpha$ -particles and heavy-ion recoils, in addition to interactions leading to the production of  $\gamma$ -rays. These charged particles ultimately lead to energy deposition via secondary electrons. Therefore, energy deposition by way of electrons is common to all ionizing radiations, including neutrons.

The effects of low-energy electrons (0.1–5 keV) can be studied using ultra-soft X-rays. Data from

several laboratories show that low-energy electrons from ultrasoft X-rays are more effective in producing a wide range of biological end-points than equal doses of conventional X-rays or  $\gamma$ -rays (reviewed by [Goodhead & Nikjoo, 1990](#); [Goodhead, 1994](#); [Hill et al., 2001](#); [Hill, 2004](#)). The end-points include DNA double-strand breaks, cellular inactivation, chromosomal aberrations, mutations, and cell transformation. This greater effectiveness is due to the increased local ionization density produced by low-energy electrons, which results in greater clustering of events on and around the DNA. Low-energy electrons are not unique to ultra-soft X-rays, but are produced by all ionizing radiations ([Goodhead, 1991](#); [Chetioui et al., 1994](#); see also Section 1). The percentage of the absorbed dose deposited by low-energy electrons (0.1–5.0 keV) increases from ~33% for  $^{60}\text{Co}$   $\gamma$ -rays to 78% for  $\beta$ -particles emitted by  $^3\text{H}$  ([Nikjoo & Goodhead, 1991](#)). Low-energy electron track-ends have been proposed as the biologically critical component of low-LET radiation rather than the isolated ionization and excitation events along the path

Fig. 4.2 Microscopic consequences of 1 cGy absorbed dose

|                                                         | Whole tissue                                                                       | Individual cells                                                                                            | Chromatin fibre<br>(total $\sim 5$ cm per cell)                                                                                                    | DNA<br>(total $\sim 2$ m per cell)                                                                                                                | Mean number<br>lethal lesions<br>per cell |
|---------------------------------------------------------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| <b>External</b><br>$\gamma$ rays                        |   | <br>$\sim 20 \mu\text{m}$  | <br>$\sim 25 \text{ nm}$<br>$\longleftrightarrow$ 25 nm segment  | <br>$\sim 2 \text{ nm}$<br>$\longleftrightarrow$ 2 nm segment  | $\sim 0.001$                              |
| Dose<br>uniformity                                      | Uniform<br>Dose = 1 cGy                                                            | $\sim$ Uniform<br>Dose $\approx$ 1 cGy                                                                      | Very large fluctuations<br>Doses = 0 to $\sim 10^3$ Gy                                                                                             | Very large fluctuations<br>Doses = 0 to $\sim 10^6$ Gy                                                                                            |                                           |
| Mean number<br>of tracks                                | $10^9 \text{ gram}^{-1}$                                                           | $\sim 50 \text{ cell}^{-1}$<br>No cells unirradiated                                                        | $\sim 10^{-6} \text{ segment}^{-1}$<br>$\sim 20$ segments hit $\text{cell}^{-1}$                                                                   | $\sim 10^{-8} \text{ segment}^{-1}$<br>$\sim 10$ segments hit $\text{cell}^{-1}$                                                                  |                                           |
| <b>Internal</b><br>$^{220}\text{Rn}$<br>(3 $\alpha$ 's) |   | <br>$\sim 20 \mu\text{m}$  | <br>$\sim 25 \text{ nm}$<br>$\longleftrightarrow$ 25 nm segment  | <br>$\sim 2 \text{ nm}$<br>$\longleftrightarrow$ 2 nm segment  | $\sim 0.01$                               |
| Dose<br>uniformity                                      | Variable<br>Doses = 0 to $\sim 2$ cGy                                              | Large fluctuations<br>Doses = 0 to $\sim 30$ cGy                                                            | Very large fluctuations<br>Doses = 0 to $\sim 10^4$ Gy                                                                                             | Very large fluctuations<br>Doses = 0 to $\sim 2 \times 10^6$ Gy                                                                                   |                                           |
| Mean number<br>of tracks                                | $\sim 10^7 \text{ gram}^{-1}$                                                      | $\sim 0.1 \text{ cell}^{-1}$<br>$\sim 90\%$ of cells unirrad.                                               | $\sim 6 \times 10^{-7} \text{ segment}^{-1}$<br>$\sim 1$ segment hit $\text{cell}^{-1}$                                                            | $\sim 10^{-8} \text{ segment}^{-1}$<br>$\sim 10$ segments hit $\text{cell}^{-1}$                                                                  |                                           |
| <b>External</b><br>10 MeV<br>neutrons                   |  | <br>$\sim 20 \mu\text{m}$ | <br>$\sim 25 \text{ nm}$<br>$\longleftrightarrow$ 25 nm segment | <br>$\sim 2 \text{ nm}$<br>$\longleftrightarrow$ 2 nm segment | $\sim 0.005$                              |
| Dose<br>uniformity                                      | Uniform<br>Dose = 1 cGy                                                            | Large fluctuations<br>Doses = 0 to $\sim 5$ cGy                                                             | Very large fluctuations<br>Doses = 0 to $\sim 5 \times 10^3$ Gy                                                                                    | Very large fluctuations<br>Doses = 0 to $\sim 10^6$ Gy                                                                                            |                                           |
| Mean number<br>of tracks                                | $\sim 10^7 \text{ gram}^{-1}$                                                      | $\sim 1 \text{ cell}^{-1}$<br>$\sim 37\%$ of cells unirrad.                                                 | $\sim 4 \times 10^{-6} \text{ segment}^{-1}$<br>$\sim 8$ segments hit $\text{cell}^{-1}$                                                           | $\sim 10^{-8} \text{ segment}^{-1}$<br>$\sim 10$ segments hit $\text{cell}^{-1}$                                                                  |                                           |

Adapted from [Goodhead \(1987\)](#). Copyright Elsevier.

of fast electrons ([Goodhead & Nikjoo, 1990](#); [Botchway et al., 1997](#)).

Recent studies have also proposed that inner-shell ionization events in DNA that lead to the production of low-energy Auger electrons may be a major factor in DNA damage and cell death. ([Fayard et al., 2002](#), [Boissière et al. 2007](#); NB: following the removal of an inner-shell electron, an electron from a higher energy level may fall into the vacancy, resulting in a release of energy. This is either released in the form of a characteristic X-ray or the energy can also be transferred to another electron, which is ejected from the atom, called an Auger electron.)

$^3\text{H}$  also leads to the production of low-energy electrons. It decays solely by  $\beta$  decay, emitting an electron with a range of energies of up to a maximum of 18.6 keV (mean energy of 5.7 keV) with an average track length of  $0.56 \mu\text{m}$  and a maximum track length of  $6 \mu\text{m}$  ([Carsten, 1979](#)). A subgroup of the Advisory Group on Ionizing Radiation has recently reviewed the risks associated with  $^3\text{H}$  ([HPA, 2007](#)); it noted that tritiated water has generally been observed to be between 1–2 times more effective than a similar dose of orthovoltage X-rays, and 2–3 times more effective than  $\gamma$ -rays, in producing a range of cellular and genetic end-points (including cellular inactivation and induction of DNA strand breaks,

chromosomal aberration formation and mutation). The potential for tritiated DNA precursors to result in substantially higher doses and effects than other forms of tritium has long been recognized, and has received considerable attention in terms of experimental studies and theoretical considerations (e.g. [ICRP, 1979](#); [NCRP, 1979](#)). Exposure to  $^3\text{H}$  has also been observed to produce chromosomal aberrations in the lymphocytes of the exposed person ([Lloyd \*et al.\*, 1986, 1998](#)).

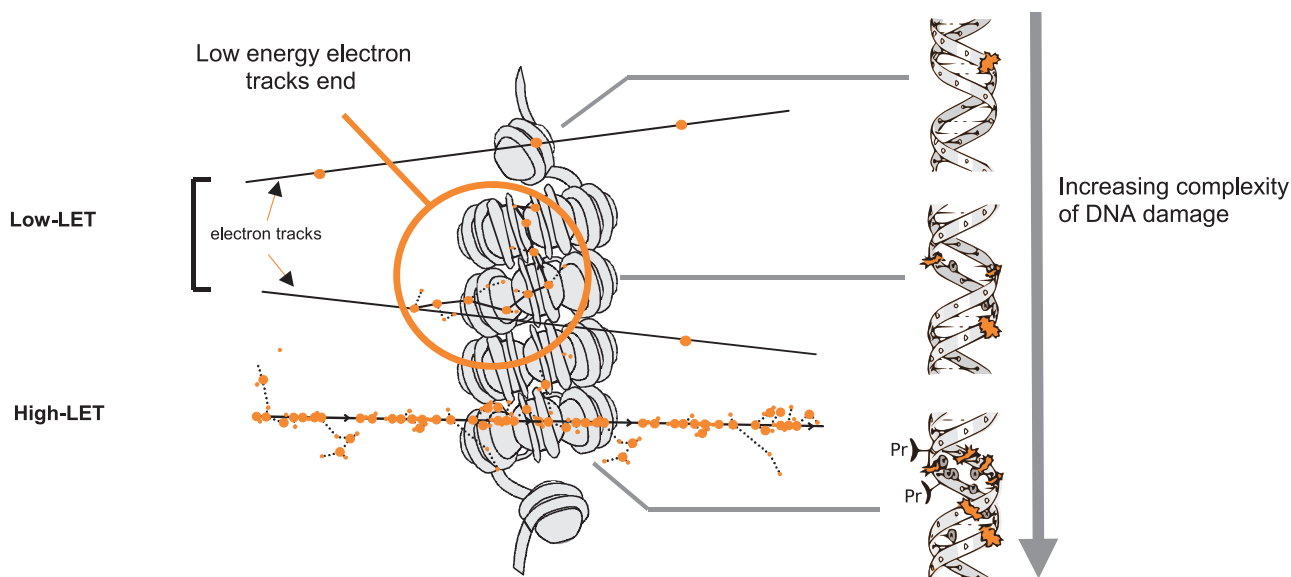
For many biological end-points, nuclear DNA is believed to be the critical target of ionizing radiation ([UNSCEAR, 1993](#)). Evidence for this comes from the greater biological effectiveness of radionuclides incorporated into nuclear DNA, rather than more generally distributed ([Hofer \*et al.\* 1975](#), [Hofer & Wartens, 1985](#)) in the cell, along with cell irradiation that included, rather than excluded, the nucleus (e.g. [Munro, 1970](#)). In addition, many studies in cells and animals deficient in DNA-damage response (processing/repair) have shown an increase in the frequency of radiobiological effects, including cancer induction ([UNSCEAR, 1993, 2000](#); [ICRP, 1998](#); [BEIR VII, 2006](#)). Ionizing radiation can result in DNA damage, either directly by ionization of its constituent atoms, indirectly by reactions with free radicals produced by interactions with water molecules – most notably the hydroxyl radical, which can result in a DNA strand break – or combinations of these two. Hydroxyl radicals will typically only diffuse a few nanometres, thus preserving the spatial structure of the radiation tracks. Subsequent reactions may lead to the production of longer-lived radicals, which may diffuse over longer distances, and are unlikely to contribute to the production of clustered DNA damage. Ionizing radiation can induce a range of different types of molecular damage in DNA, such as base damage, single-strand breaks, double-strand breaks, DNA–protein cross-links, and combinations of these. The pattern and frequency of these lesions is determined by the clustering of ionization events, which ultimately

produces clustering of damage over the dimensions of the DNA helix and larger. The more complex forms of damage are unique to ionizing radiation, and are not seen spontaneously or with other DNA-damaging agents. Analyses of track structures caused by different types of radiation show that clustered DNA damage more complex than a simple double-strand break can occur at biologically relevant frequencies with all types of ionizing radiation ([Goodhead, 1987](#); [Brenner & Ward, 1992](#); [Goodhead, 1994](#)). Such clustered damage in DNA is produced mainly within a single track, with a probability that increases with increasing ionization density (see Fig. 4.3).

The correlation of damage with a single track can also occur over larger dimensions in a cell, including within the chromatin structure, among chromosomes and among adjacent cells, if the particle range is sufficient.

At the level of the DNA and its structure, most of the information comes from theoretical simulations ([Pomplun \*et al.\*, 1996](#); [Nikjoo \*et al.\*, 1997](#)). These led to quantitative estimates of the DNA-damage spectrum, which includes base damage, single-strand breaks, simple double-strand breaks, and complex double-strand breaks (double-strand breaks with additional damage within a few base pairs). Calculations and experimental measurements showed that the total yield of double-strand breaks per unit of absorbed dose is fairly independent of LET for a variety of common radiations. However, theoretical simulations have predicted that the percentage of complex double-strand breaks (defined as having additional strand breaks within 10 base pairs), which is 20–30% from low- to medium-energy electrons (similar to those produced by X-rays and  $\gamma$ -rays), will increase with increasing ionization density (LET) of the radiation to approximately 50% for 0.3-MeV protons, and to more than 70% for high-LET 2-MeV  $\alpha$ -particles ([Nikjoo \*et al.\* 2001, 2002](#)). The number of double-strand breaks classified as complex increases to approximately 96% for 2-MeV  $\alpha$ -particles if double-strand

**Fig. 4.3 Schematic illustration of the clustering of ionization events and the ensuing DNA damage by high-LET and low-LET radiation tracks**



Adapted from [Goodhead \(1988, 1994\)](#). Reproduced by kind permission of Mark Hill, University of Oxford, United Kingdom

breaks with additional base damage are also classified as complex. Not only is there an increase in the frequency of complex double-strand breaks with increasing LET, but also an increase in the overall complexity of the spectrum of damage produced. The ultimate biological consequence is dependent on how this damage is processed by the cell, whether it is repaired and with what fidelity. It has been plausibly hypothesized that the more complex components of the damage spectrum are less repairable, and therefore dominate the biological response ([Goodhead, 1994](#)). Under this hypothesis, the differences in biological effectiveness between radiations of different quality, such as  $\alpha$ -particles, protons and X-rays, for a given absorbed dose and a range of biological end-points (including cell survival, gene mutation, chromosomal aberration induction and transformation) are due predominantly to the greater yield of complex damage, and its greater degree of complexity from high-LET radiations ([Goodhead, 1994](#); [Ward, 1994](#)). Model systems have shown that clustered DNA damage also compromises the effectiveness of DNA

repair and can lead to an increase in mutation frequency ([Gulston et al., 2004](#); [Pearson et al., 2004](#)). Clustering of damage is not just confined to DNA but can occur in all biomolecules within the cell.

There are also significant differences in track structure on the cellular/nuclear scale. When a cell is traversed by an  $\alpha$ -particle, the energy deposition is highly heterogeneous across the cell with a greater probability of correlated damage and double-strand breaks within a single chromosome or adjacent chromosomes along the path of the particle. By use of R-banding and fluorescence in-situ hybridization (FISH) it was demonstrated that the traversal of the cell nucleus by a single particle with LET above 50 keV/ $\mu$ m efficiently induced complex chromosomal rearrangements ([Sabatier et al., 1987](#); [Testard et al., 1997](#); [Cornforth, 2006](#); see Fig. 4.4 and 4.5). Studies with Multiplex fluorescence in-situ hybridization (mFISH) show that commonly four and up to a maximum of eight different chromosomes were observed to be involved in rearrangements following a nuclear traversal

**Fig. 4.4 mFISH “painted” human metaphase (A) and karyotype (B) chromosomes showing the characteristic and extensive chromosomal damage induced after  $\alpha$ -particle irradiation. The chromosome exchange is very complex, involving six chromosomes (4, 8, 13, 18, 18, and 21) with a minimum of seven breaks (white arrows). Lymphocytes in  $G_0$  of the cell cycle were exposed to 0.5 Gy of  $\alpha$ -particles from  $\alpha$   $^{238}\text{Pu}$  plutonium source (mean tracks per cell = 1).**

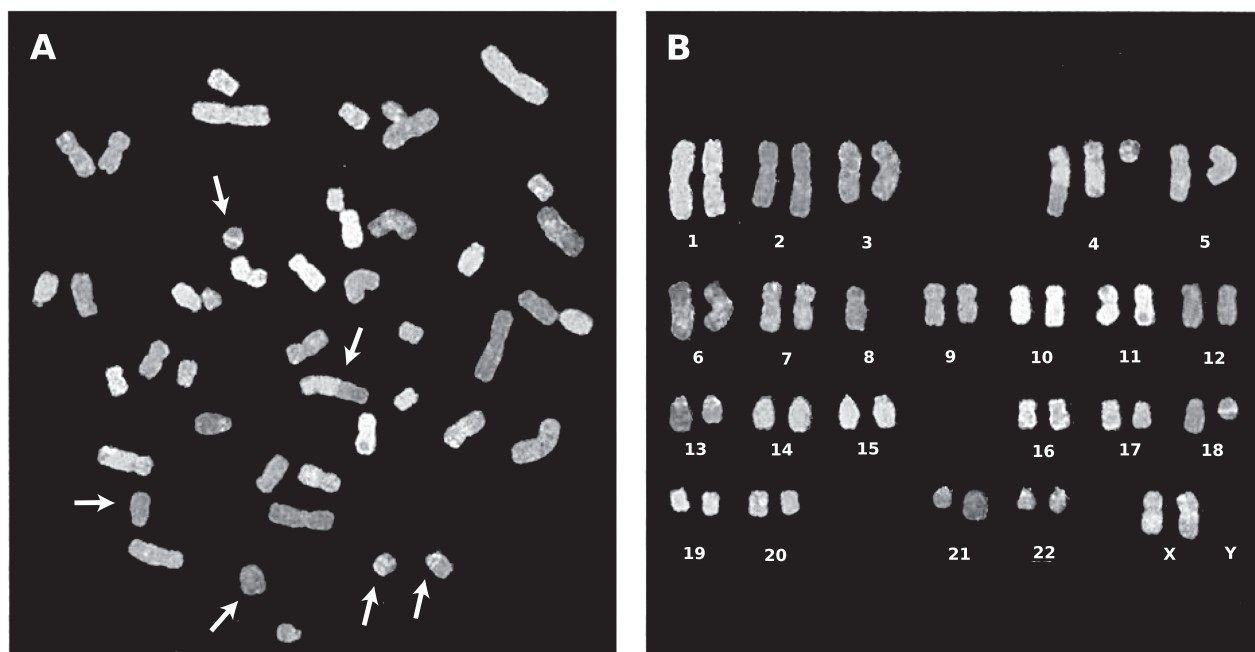


Image courtesy of Rhone Anderson, Brunel University, West London, UK  
Image adapted from [Savage \(2000\)](#). Cancer: Proximity matters. *Science*, 290:62–63

of a human peripheral blood lymphocyte by an  $\alpha$ -particle ([Anderson et al., 2002, 2006](#)), with a similar response seen in human  $\text{CD34}^+$  haematopoietic stem cells ([Anderson et al., 2007](#)). This is in contrast to the production of mainly simple rearrangements between two chromosomes observed for low doses of low-LET X-rays.

In a study of a small group of workers with a large body burden of  $\alpha$ -particle-emitting plutonium, unstable cells containing non-transmissible complex aberrations (exchanges involving three or more breaks in two or more chromosomes) were found in all the plutonium-exposed subjects when their lymphocytes were analysed by use of mFISH ([Anderson et al. 2005](#)). In a separate study, stable intrachromosomal rearrangements in lymphocytes of former nuclear-weapon workers exposed to plutonium were

seen. Many years after exposure, more than half of the blood cells of healthy plutonium workers contained large ( $> 6$  Mb (mega base pairs)) intrachromosomal rearrangements in amounts that correlated with the plutonium dose to the bone marrow, while very few intrachromosomal aberrations were observed in control groups ([Hande et al., 2003](#)).

The consequence for background radiation is that individual cells may receive no track at all or only single tracks, well isolated in time (approximately 1 mGy/year for low-LET radiation). Each cell nucleus in a tissue will experience on average approximately one electron track per year (assuming a spherical nucleus of 8  $\mu\text{m}$  diameter). Increasing the tissue dose above 1 mGy will essentially increase the nuclear dose to all cells. In comparison, with 1 mGy of  $\alpha$  radiation (such as

**Fig. 4.5 mFISH karyotype showing an  $\alpha$ -particle-induced complex involving chromosomes 3, 7, 8, 11, 12, and 18 (arrows).**

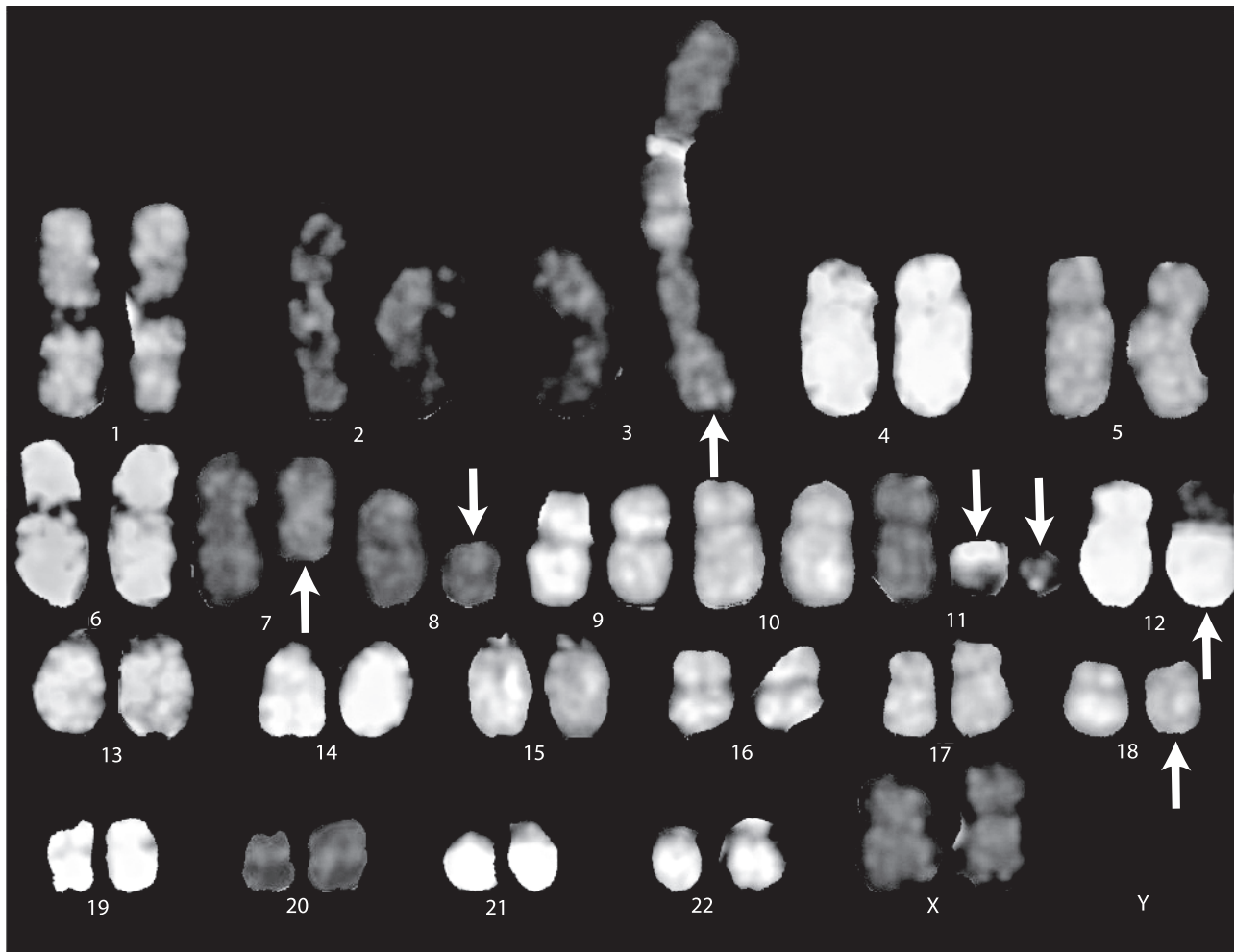


Image adapted from [Anderson et al. \(2002\)](#). Copyright 2002 National Academy of Sciences, USA

from radon) only about 0.3% of the nuclei in the irradiated tissue is hit by a track, the remaining 99.7% are totally un-irradiated. However, the cells that are traversed will receive a substantial amount of energy deposition, with an average nuclear dose of approximately 370 mGy for the traversed cell, with individual nuclei potentially receiving up to 1 Gy. Therefore, for high LET tracks, it is the fraction of cells traversed that varies with tissue dose, rather than the energy deposited in the nucleus from single-track events ([Goodhead, 1992](#)).

While external irradiation with photons is highly penetrating and will often result in a relatively uniform dose-distribution across the absorbing tissue, emission from internal radio-isotopes typically occurs from specific locations occupied by the emitting nuclide. This will often lead to a non-uniform dose to the body, especially if the emitted radiation has only a short range (for  $\beta$ -particles, from centimetres down to microns; for  $\alpha$ -particles, typically less than 80  $\mu$ m). The overall exposure is dependent on several factors. Biokinetic models ([ICRP, 1989, 1993, 1994, 1995, 1996, 2001](#)) are used to model

the spatial and temporal uptake of radionuclides, their subsequent distribution, and their ultimate excretion, to calculate the total number of radioactive decays within specified tissues. Dosimetry models ([Eckerman, 1994](#)) are subsequently used to calculate the deposition of energy in organ or tissue, taking account of the physical characteristics of the isotope (type and emission energy, and any radioactive progeny).

In the case of Auger decay, most Auger electrons are confined to single cells or subcellular compartments. The biological effects vary greatly depending on whether the Auger emitter is attached to DNA, free in the nucleus or in the cytoplasm. Large differences in energy deposition, even at the organ and tissue levels, can occur with different radionuclides or radiolabelled compounds, because of the heterogeneous distribution of radionuclides, the stochastic nature of the radionuclide-decay processes, and the emission of short-range radiation (i.e.  $\alpha$ -particles, low-energy  $\beta$ -particles, Auger electrons, and low-energy X-rays). Detailed knowledge of the cellular and subcellular localization in the relevant tissue of the particular radionuclide and any associated molecule may be relevant before a full assessment can be made of the implications of the internal emitter. Additional mechanisms of DNA-damage induction may result from the presence of the nuclide within the cell. These include molecular effects after transmutation of a radionuclide to a different progeny, recoil of the progeny nucleus, and charge accumulation on the progeny atom after an Auger cascade. If the decaying atom is appropriately positioned, the recoil nucleus may have considerable energy and can cause substantial cellular damage. The effects of the recoil nucleus are not considered in this *Monograph*. The induced damage can be misrepaired and have cellular consequences ([IARC, 2001](#)).

#### 4.2.3 Processing of radiation-induced genetic damage at the cellular level

As discussed above, ionizing radiation is able to produce DNA double-strand breaks, DNA single-strand breaks, and a variety of base damages, and combinations of these to form a unique type of damage in which multiple lesions are encountered within close spatial proximity. Even a single track of ionizing radiation through a cell is likely to induce these unique, clustered damages. This type of damage is unlikely to be frequently generated endogenously or by other exogenous agents ([ICRP, 2006](#)).

Cells have a vast array of damage-response mechanisms, including pathways of DNA repair, the operation of cell-cycle checkpoints, and the onset of apoptosis. These processes facilitate the repair of DNA damage and the removal of damaged cells; however, these mechanisms are not error-free. It is generally accepted that unrepaired or misrepaired double-strand breaks are the principal lesions of importance in the induction of chromosomal abnormalities and gene mutations ([Goodhead, 1994](#); [Ward, 1994](#)). Two mechanistically distinct pathways for double-strand-break repair have been described: non-homologous end-joining, which requires little or no homology at the junctions and is generally considered to be error-prone, and homologous repair that uses extensive homology and is considered error-free. A third process is single-strand annealing, which uses short direct-repeat sequences (see [ICRP, 2006](#)). Base damage is repaired via the base-excision-repair pathway, the latter stages of which repair single-strand breaks. Clustered radiation-induced lesions pose a particular problem; and currently, emerging evidence suggests that closely spaced lesions can compromise the repair machinery. For instance, the ability of glycosylase to recognize and remove a damaged base is impeded by the presence of a nearby single-strand break in the opposite strand ([David-Cordonnier et al., 2000, 2001](#)). On this

basis, there is no strong evidence for a radiation dose below which all radiation-induced damage can be repaired with fidelity. While many of the cells containing such radiation-induced damage may be eliminated by damage-response processes, it is clear from the analysis of cytogenetics and mutagenesis that damaged or altered cells are capable of escaping these pathways and propagating (ICRP, 2006).

The idea that molecular damage directly caused by ionizing radiation might be a detectable marker of radiation exposure in tumour cells at diagnosis has been extensively investigated, particularly in relation to the radiation-induced childhood thyroid cancers following the Chernobyl accident. However, such a marker has not been conclusively observed. Likewise, in a recent study looking at the expression of cell cycle regulatory proteins, no such biomarkers were found to differentiate between radiation-induced and sporadic papillary thyroid carcinoma (Achille *et al.*, 2009).

However, specific mutations of the *TP53* gene in human radiation-induced sarcomas have been found. About half of the radiation-induced sarcomas contained a somatic inactivating mutation for one allele of *TP53*, systematically associated with a loss of the other allele, and some other features may be related to exposure to ionizing radiation. (Gonin-Laurent *et al.*, 2006).

A study of eight radiation-induced solid tumours has described a common cytogenetic profile after irradiation: the occurrence of chromosome imbalances, creating large loss of heterozygosity. Such a profile is also observed in radiation-induced tumours whereas spontaneous cases of the same tumour type are characterized by a specific balanced translocation. These results support a proposed mechanism for cancer induction where accumulated recessive damage in the genome is unmasked (for example after telomere loss), allowing transcription of the mutated allele, which could provide a cellular

proliferation advantage (Chauveinc *et al.*, 1999; Ayouaz *et al.*, 2008).

In a mouse model for radiation-induced acute myeloid leukaemia, the loss of specific genetic material (*Sfp11*/PU.1) on chromosome 2 was observed to be correlated with strong growth advantage (Bouffler *et al.*, 1997; Peng *et al.*, 2009). This is however a feature of the model, missense mutation at codon 235 in the DNA-binding transcription factors Ets domain of the PU.1, which was not observed in human therapy-related acute myeloid leukaemia (Suraweera *et al.*, 2005).

#### 4.2.4 Genomic instability

Situations in which the cellular capacity to repair damage caused by irradiation is saturated have the potential of stressing the cell, which leads to the modification of the genome-wide gene-product profile, thus precipitating a phenotypic transition without specific, or indeed any, genotypic damage. This is postulated to be a possible origin of genomic instability (Baverstock & Rönkkö, 2008).

Genomic instability has also been attributed to an anti-inflammatory-type response that is both persistent and causes a predisposition towards malignancy (Lorimore *et al.*, 2003; Barcellos-Hoff *et al.*, 2005).

Genomic instability could be linked to the loss of telomere maintenance. Many studies have described the presence of dysfunctional (too short) telomeres as a universal mechanism in the early phase of cancer development (Rudolph *et al.*, 1999; Meeker *et al.*, 2004; Raynaud *et al.*, 2008; Batista & Artandi, 2009). It has been proposed that short telomeres will contribute to genomic instability in the aged progeny of irradiated cells (Sabatier *et al.*, 1992, 1995; Martins *et al.*, 1993; Ayouaz *et al.*, 2008). Moreover, dysfunctional telomeres are associated with radiation-induced genomic instability and radiosensitivity (Goytisolo *et al.*, 2000; McIlrath *et al.*, 2001; Williams *et al.*, 2009). Even

after telomerase activation, the loss of telomeres can generate most of the types of chromosomal rearrangements detected in cancer cells such as gene amplification and chromosome imbalances ([Murnane & Sabatier, 2004](#); [Sabatier et al., 2005](#)).

#### 4.2.5 Adaptive response

Low-LET radiation has been shown to modulate gene expression in a dose-dependent manner (reviewed by [Brooks, 2005](#)), and to induce an adaptive response to a test dose given after an adaptive dose in the mGy range ([Coleman et al., 2005](#)). An adaptive response has also been seen in a pKZ1 mouse-prostate model when the test dose of 1 Gy was given before the adaptive dose of 0.01–1 mGy ([Day et al., 2007](#)). An adaptive response had been shown in certain model systems *in vitro* to increase the repair of chromosomal breaks ([Broome et al., 1999](#)), and to modulate the cellular level of certain redox pathways ([Spitz et al., 2004](#)). The adaptive response after an adaptive dose given alone (i.e. in the absence of a challenge dose) reduces the frequency of radiation-induced neoplastic transformation in human and rodent cells *in vitro* ([Azzam et al., 1996](#); [Redpath & Antoniono, 1998](#); [Mitchel, 2006](#)). In C57BL6 and CBA mice, such an adaptive response results in an increased latency of spontaneous and radiation-induced tumours ([Mitchel et al., 1999, 2003, 2004](#)). This is proposed to be part of a general cellular stress response, such as that against heat stress, that appeared very early in evolution ([Mitchel, 2006](#)). In mammalian cells, including human cells *in vitro*, and in mice *in vivo*, the adaptive response is induced within a dose range from about 1–100 mGy, although this can vary with tissue type ([Azzam et al., 1996](#); [Redpath & Antoniono, 1998](#); [Mitchel et al., 2003, 2004](#)). Above or below these doses, increased cancer rates have been seen in C57BL6 mice *in vivo* ([Mitchel et al., 2004, 2008](#)). Protective adaptive responses to radiation in mammals are dependent on a fully or partially

functional *Tp53* gene, and do not occur in *Tp53*-null cells ([Sasaki et al., 2002](#)) or animals ([Mitchel, 2005](#)). [The Working Group noted that protective effects as described here were discussed but not endorsed by [BEIR VII \(2006\)](#) and [ICRP \(2007\)](#), but supported by the French [Academy of Sciences \(2005\)](#). The Working Group concluded also that although an adaptive response has been shown, the final impact on cancer risk cannot be clearly determined because it depends on many factors including dose, time and the genetic make-up of the irradiated organism.]

#### 4.2.6 Intercellular communication and the bystander effect

Tissues in multicellular organisms are self-organized “colonies” of communicating cells that mutually reinforce each other’s phenotypic state ([Park et al., 2003](#)). Radiation-induced transitions of individual cells to abnormal phenotypic states has been shown to disrupt these essential communications through the bystander effect, which may lead to loss or gain of function, and thus modify behaviour at the tissue level ([Barcellos-Hoff, 2001](#)). Thus, although tumour formation is recognized to have been initiated in a single cell, it is influenced by neighbouring cells for its full development. One consequence of this inter-cellular communication is the bystander effect in cells subject to ionizing radiation ([Nagasawa & Little, 1992](#)) where chemical signalling from an irradiated cell influences the phenotype of un-irradiated neighbouring cells, presumably through modification of the genome-wide protein profile or through modification of the genotype by some indirect means. Bystander cells thus exhibit many of the properties observed in cells rendered genomically unstable by radiation ([Morgan, 2003a, b](#); see also Section 4.2.1). Genomic instability may be of particular significance in carcinogenesis, because it is a mutator phenotype, as seen in tumours ([Bielas et al., 2006](#)). Such perturbation of communication can

lead to the presence in tissue of cells that have lost important functions or gained new functions that are inappropriate to their location. One such function would be a selective advantage in growth that may be endowed by the acquisition of mutations to, for example, genes that control the cell cycle, called “gatekeepers”, and genes that are thought to stabilize the genome, called “caretakers” ([Kinzler & Vogelstein, 1997](#)).

#### (a) *The cancer stem cell concept*

More recently, accumulating evidence described a hierarchical organization of tumours by introducing the concept of cancer stem-cells (NB: Cancer stem cells are not to be confused with normal stem cells. They are cancer cells that are able to divide but whose growth is restricted by the surrounding differentiated cells within the tissue.)

Cancer stem cells differ in that they have lost control over their own population size (for a review, see [Visvader & Lindeman, 2008](#)). Data to support a cancer stem cell concept for solid tumours have been reported ([Al-Hajj et al., 2003](#); [Hemmati et al., 2003](#); [Passequé et al., 2003](#); [Singh et al., 2003](#); [Serakinci et al., 2004](#)).

In the context of the “cancer stem cell” model, normal tissue may contain quiescent foci of cancer stem cells surrounded by non-dividing differentiated cancer cells that limit the further growth of the tumour ([Enderling et al., 2009](#)). It has been postulated that removal through a cell-death process such as apoptosis of the differentiated peripheral cells can release the stem-cell population, and lead to further growth of the tumour.

The radiosensitivity of cancer stem cells differs from that of other cell types, and several studies have shown that they are usually more radioresistant ([Rachidi et al., 2007](#); [Altaner, 2008](#); [Lomonaco et al., 2009](#); [Woodward & Bristow, 2009](#)).

The overall effect of this complexity is that ionizing radiation, in the context of

carcinogenesis, may serve to both initiate new tumours and promote, as well as in some circumstances inhibit, existing subclinical tumours ([Woodward & Bristow, 2009](#)). Thus, the tumourigenic effects of radiation are dependent not only on the nature of the energy-deposition process, but also on the properties of the host tissue/organism.

Indeed, some models ([Heidenreich et al., 2007](#); [Heidenreich & Paretzke, 2008](#)) propose that radiation can also promote very efficiently tumour progression in particular for organisms such as humans for which senescence is an efficient barrier, and in which “dormant” cells at different stages of tumour progression have been found in an increased number of organs ([Corvi et al., 2001](#)).

#### 4.2.7 *Host factors*

Genetic variation in specific genes including those involved in human radiation-sensitive cancer syndromes such as ataxia-telangiectasia mutated (ATM), and tumour-suppressor genes such as *TP53*; familial inheritance of mutated genes such as breast cancer *BRCA1* and *BRCA2* – involved in the repair of DNA double-strand breaks, and abnormal reactive oxygen species levels due to, e.g. inflammation, might increase the host susceptibility to radiation-induced cancers. In addition, age, the acquisition of sequence mutations, chromosomal damage, modifications of allelic imprinting and telomere dysfunction may modulate the processing efficiency of abnormal phenotypes in the irradiated tissue ([IARC, 2000](#); [ICRP, 2005](#); [BEIR VII, 2006](#); [Allan, 2008](#)).

### 4.3 Mechanism of carcinogenesis of neutrons: an example of ionizing radiation

Because studies of human exposures to neutrons are extremely limited, mechanistic data for this ionizing radiation were given a special emphasis in this chapter.

#### 4.3.1 Specificity of the exposure to neutrons

Neutrons are uniquely a particle radiation with no charge; however they produce charged particles (e.g. protons) through their interactions with atomic nuclei, and are therefore an ionizing radiation.

The densely ionizing particles formed upon interaction of neutrons with atomic nuclei produce a spectrum of molecular damage that overlaps with that induced by sparsely ionizing radiation. However, neutrons are more effective in causing biological damage because they release more of their energy in clusters of ionizing events, giving rise to more severe local damage, including clustered and complex DNA lesions that are not readily repaired. Although neutrons, like X- and  $\gamma$ -rays, produce double-strand breaks, the neutron-induced DNA breaks are repaired much more slowly than those produced by the sparsely ionizing radiation types ([Sakai et al., 1987](#); [Peak et al., 1989](#); [Kysela et al., 1993](#)); this is also the case for other high-LET radiation such as  $\alpha$ -particles ([Goodhead, 1994](#); [Ward, 1995](#); [Gulston et al., 2004](#); [Pearson et al., 2004](#)).

#### 4.3.2 Induction of chromosomal aberrations following exposure to neutrons

##### (a) Studies in humans

Chromosomal aberrations including rings, dicentric and acentric fragments were induced in the circulating lymphocytes of eight men exposed during an accident involving the release of  $\gamma$ -radiation and fission neutrons in a nuclear

plant. The neutrons contributed about 26% of the total dose. About 16–17 years after the accident, six of the men still had residual chromosomal aberrations ([Bender & Gooch, 1963](#); [Goh, 1975](#); [Littlefield & Joiner, 1978](#)). Similar results were reported after critical accidents also involving mixed exposures in Belgium ([Jammet et al., 1980](#)), and Serbia and Montenegro, formerly Yugoslavia ([Pendic & Djordjevic, 1968](#); 19-yr follow-up, [Pendić et al., 1980](#)).

The same types of chromosomal aberration were found in the lymphocytes of patients exposed during neutron therapy, with 5–15% of contaminating  $\gamma$ -rays ([Schmid et al., 1980](#)). Within the limits of the studies mentioned above, the effects were found to be dose-dependent.

An evaluation of the persistence of chromosomal aberrations in patients receiving fractionated neutron therapy to tumours located at various sites showed that neutron-induced dicentric and rings disappeared from the peripheral circulation within the first 3 years after exposure, while translocations persisted for more than 17 years ([Littlefield et al., 2000](#)).

Chromosomal aberrations, micronuclei, and sister chromatid exchange were analysed in the peripheral lymphocytes of 18 British pilots of the supersonic airplane Concorde and ten [non-British] controls ([Heimers, 2000](#)). Based on in-flight radiation monitoring, the average total annual dose to aircrew members was estimated to be about 3 mSv. The frequency of dicentric chromosomes was increased 8-fold ( $P < 0.05$ ) in the group of pilots. The frequency of micronuclei was significantly elevated, but that of sister chromatid exchange did not differ from that in the control group. The yield of dicentric was higher in flight crews on supersonic flights than on subsonic routes, but the difference was not significant. The overdispersion of dicentric chromosomes showed the influence of high-LET cosmic radiation.

*(b) Studies in exposed animals*

Fission neutrons were reported to induce germ-line mutations in mice, including visible dominant mutations ([Batchelor et al., 1966](#)), dominant lethal mutations ([Grahn et al., 1979, 1984, 1986](#)), visible recessive mutations ([Russell, 1965, 1972](#)), and specific locus mutations ([Russell, 1967](#); [Cattanach, 1971](#)). Neutrons have also been shown to induce *Hprt* mutations in splenic lymphocytes of mice ([Kataoka et al., 1993](#)). Point mutations in *K-Ras* and *N-Ras* oncogenes were found in malignant tissue from mice exposed to neutrons, but the mutations could not be directly ascribed to the exposure ([Zhang & Woloschak, 1998](#)). Sister chromatid exchange was induced in bone-marrow cells of young rats exposed to fission neutrons ([Poncy et al., 1988](#)), while micronuclei and chromosomal aberrations were observed in splenocytes of mice exposed to neutrons *in vivo* ([Darroudi et al., 1992](#)). Reciprocal translocations were induced in stem-cell spermatogonia of rhesus monkeys exposed to neutrons ([van Buul, 1989](#)). In all these experiments, the fission neutrons were many-fold more effective, on the basis of absorbed dose, than sparsely ionizing radiation.

*(c) Studies in cultured cells*

DNA breaks induced by fast neutrons in L5178Y mouse lymphoma cells were classified into three types on the basis of their repair profiles: rapidly repaired breaks (half-time, 3–5 minutes), slowly repaired breaks (half-time, 70 minutes), and non-repaired breaks. Neutrons induced less of the rapidly repaired damage, a nearly equal amount of slowly repaired damage, and more non-repaired damage when compared with equal doses of X- or  $\gamma$ -radiation ([Sakai et al., 1987](#)).

In mammalian cells, neutrons were more efficient than the same absorbed dose of X-rays or  $\gamma$ -rays at inducing gene mutation and chromosomal aberrations ([Fabry et al., 1985](#); [Roberts &](#)

[Holt, 1985](#); [Hei et al., 1988](#); [Nakamura & Sawada, 1988](#); [Kronenberg & Little, 1989](#); [Kronenberg, 1991](#)), and transformation ([Balcer-Kubiczek et al., 1988](#); [Miller et al., 1989](#); [Komatsu et al., 1993](#)). In addition, extensive measurements of the induction of chromosomal aberrations (dicentric or dicentric plus centric rings) in human lymphocytes as a function of the neutron energy have been performed ([Lloyd et al., 1976](#); [Sevan'kaev et al., 1979](#); [Edwards, 1999](#); [Schmid et al., 2003](#)).

## 4.4 Synthesis

- The energy-deposition characteristics of all sources of ionizing radiation are relatively well understood.
- All types of ionizing radiation, including neutron radiation, transfer their energy to biological material in clusters of ionization and excitation events, primarily through a free-electron-mediated mechanism.
- In cells, energy deposition from all types of ionizing radiation results in a wide variety of molecular damage; in DNA, this includes base damage and single- and double-strand breaks, some of which may be clustered and form complex lesions. Subsequent processing of these lesions may lead to chromosomal aberrations and mutations.
- Much evidence points to damage to DNA being of primary importance in the biological outcome of exposure to ionizing radiation, particularly the loss of cellular ability to form clones. It is generally assumed that the same DNA damage leads to tumorigenesis, and there is some evidence to support this.
- How the cell processes the initially produced damage to DNA to yield tumours is unknown; although many hypotheses have been the subject of research, few have gained wide consensus.

- Genome-wide sequencing of tumours has shown wide heterogeneity in constituent mutations, indicating there may be multiple pathways to tumour formation.
- Tumours produced after exposure to ionizing radiation have not been shown to carry any characteristic molecular markers.
- There is emerging consensus that epigenetic factors are important in tumorigenic processes. Notably, radiation induces effects such as genomic instability and bystander effects, which are epigenetic in origin.
- Also important are the interactions at the tissue level between radiation-damaged cells and normal cells, which may serve to modulate the effects of radiation. In addition, host factors such as age, gender, changes in immune status, telomere dysfunction, and genetic variations in specific genes may play a role, as well as modulation of gene expression.

## 5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of X-radiation and of  $\gamma$ -radiation. X-radiation and  $\gamma$ -radiation cause cancer of the salivary gland, oesophagus, stomach, colon, lung, bone, basal cell of the skin, female breast, kidney, urinary bladder, brain and CNS, thyroid, and leukaemia (excluding chronic lymphocytic leukaemia). Also, positive associations have been observed between X-radiation and  $\gamma$ -radiation and cancer of the rectum, liver, pancreas, ovary, and prostate, and non-Hodgkin lymphoma and multiple myeloma.

In-utero exposure to X-radiation and  $\gamma$ -radiation causes cancer.

There is *sufficient evidence* in experimental animals for the carcinogenicity of X-radiation and of  $\gamma$ -radiation.

X-radiation and  $\gamma$ -radiation are *carcinogenic to humans (Group 1)*.

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