2 Biological effects of ionising radiation

This Chapter describes the effects of ionising radiation on the body. It covers both effects at the subcellular and cellular level as well as on the whole body. Acute effects can result from high radiation doses and in extreme cases can cause severe tissue damage and even death. For most exposures of people to radiation it is low doses that are of most concern. These can give rise to radiation-induced cancer in those exposed and hereditary disease in future generations. The chapter discusses the sources of information on radiation damage and includes estimates of risk for these different effects.

2.1 Introduction

Within a few weeks of Wilhelm Conrad Roentgen's discovery of X-rays on 8 November 1895, for which he received the Nobel Prize for physics in 1901, the potential of the technique for diagnosing fractures and other medical problems had become apparent, but acute adverse effects (such as hair loss, erythema and dermatitis) were also found. Similar undesirable effects were reported shortly after the discovery of radium (by Henri Becquerel in 1896) and its subsequent medical applications. In 1904, the first death of a person exposed to X-rays was reported; X-ray burns had developed into cancer. This death was soon followed by a steady stream of 'martyrs to science through roentgen rays' to use the title of a book by a radiologist who subsequently died of cancer. The widespread use of X-rays and radium in treating disease in the early 1900s led to the recognition of a cancer risk in many organs and tissues following high radiation doses which caused gross tissue damage. There was, however, a delay of about 40 years before it became clear that there was a risk of radiation-induced cancer from irradiation at lower doses and that there is no apparent threshold dose below which exposure to radiation can be considered safe. This delay can be attributed to the fact that radiation-induced cancers do not differ in any known way from those occurring naturally or caused by other agents. For many cancers there is also a long interval between exposure and the appearance of the tumour. It is now believed that any radiation dose, whether from external radiation or from incorporated radionuclides, is capable of inducing cancer and that the probability of its occurrence, but not its severity, depends on the radiation dose. Animal studies have shown that an increased incidence of certain types of inherited disorders can also occur in the descendants of irradiated parents. For both cancer and inherited disorders the probability of their occurrence, but not their severity, depends on the radiation dose. In radiological protection terminology they are termed *stochastic effects*.

A second type of damage is seen after exposure of the whole or parts of the body to high doses of radiation between a few gray and a few tens of gray. It is a reflection of impairment of the functional capacity of tissues and is referred to as a *deterministic effect*. Severity of the damage is related to the extent of radiation exposure and it is assumed that there is a threshold below which the clinically detectable damage does not occur. If damage is extensive death may result. Following radiation exposure *in utero* serious mental retardation has been observed in the children of the atomic bomb survivors in Japan. Current evidence suggests this phenomenon is deterministic with a threshold related to the minimum shift in intelligence quotient (IQ) that can be measured.

This Chapter reviews the sources of information available on the response of the body to radiation damage, and considers the extent to which dose-response relationships can be determined and quantified.

2.2 Cellular effects

2.2.1 Primary events following exposure to ionising radiation

Ionising radiations, hereafter abbreviated to radiation(s), can be classified into directly or indirectly ionising. Charged particles such as alpha particles and beta particles emitted from radionuclides are directly ionising if they have sufficient kinetic energy to disrupt atomic structure. Other types of radiation such as X-rays (generated artificially) or gamma rays (from nuclear transitions) are indirectly ionising. When passing through matter, they give up their energy to the atoms with which they collide and high velocity charged electrons are ejected from these atoms leaving behind positive ions. These electrons move randomly along a trajectory and may ionise other atoms in their path. If this occurs, more electrons are ejected, while the incident electrons continue on their trajectory with decreased energy and velocity, having transferred some of their energy to the newly formed electrons and eventually come to rest. Neutrons also lose energy in various ways, an important means being through collisions with hydrogen nuclei, which are single protons. The protons are set in motion and, being charged, they again deposit energy through electrical interactions. The unique feature of ionising radiation, then, is the localised release of energy in sufficient amounts to alter atomic and molecular structure.

The *particle track* is the ensemble of ionisations (and excitations) along the trajectory of the electron or proton. One way of expressing the amount of atomic disruption is to quote the average energy loss along the track. This is referred to as the unrestricted *linear energy transfer* (LET or *L).* LET quantities are given in terms of average energy lost per unit path length, expressed in terms of kiloelectronvolts per micron (keV μm^{-1}). This physical quantity has been used extensively in experimental radiobiology as a simplistic approach in order to relate the quality of radiation to cellular damage [91I2].

The rate of energy loss in biological material can vary greatly along the particle track depending upon kinetic energy and charge. In general terms, photons and electrons have LET values in the range of about 0.2 to 10 keV μm^{-1}; for example, 1 MeV, 100 keV, 10 keV and 1 keV electrons have LET values of 0.2, 0.5, 2, and 10 keV μm^{-1} respectively. Protons, alpha particles and neutrons have LET values between about 10 and 100 keV μm^{-1}; and heavy charged particles (e.g. nuclei of elements such as C, Ne and Si) can have still higher values to about 2000 keV μm^{-1}.

LET does not address the magnitude of the individual energy-loss events that occur along the track; nor does it address the amount of energy lost to matter in the volume of interest. This can be expressed as mean lineal energy which, in concept is more meaningful than LET [93I4].

The random nature of the particle track can be simulated by computer analysis using Monte Carlo techniques. A two-dimensional clustering of ionisations is shown in Fig. 2.1. This is only an approximation of the more complex three-dimensional events that involve random clustering of ionisations on a sub-atomic scale. Nevertheless, the figure illustrates the concept that low energy electrons are *sparsely ionising* because the ionisations are well separated spatially. Alpha particles, in contrast, are *densely ionising* because the ionisations are closely packed together along the track. It has been calculated that a single particle track of low-LET radiation (e.g. 1 MeV gamma-rays) passing through an 8 μm diameter spherical nucleus delivers an absorbed dose of about 1 mGy [94G2]. The gamma-rays are about one hundred times less damaging than high-LET radiation, for example 1 MeV neutrons which deliver an absorbed dose of a few hundred mGy in the same shape of nucleus.

Each ionisation can result in energy being deposited within the atoms of a target molecule in sufficient amounts to disrupt chemical bonds. Alternatively, it may indirectly break the chemical bonds in a nearby molecule. It is the predominant reaction in water molecules in cells after exposure to X-rays. Free hydroxyl and other related radicals are produced and during their short existence of about a microsecond, these highly reactive radicals are capable of diffusing a few micrometres to reach and damage a target molecule such as deoxyribonucleic acid (DNA).

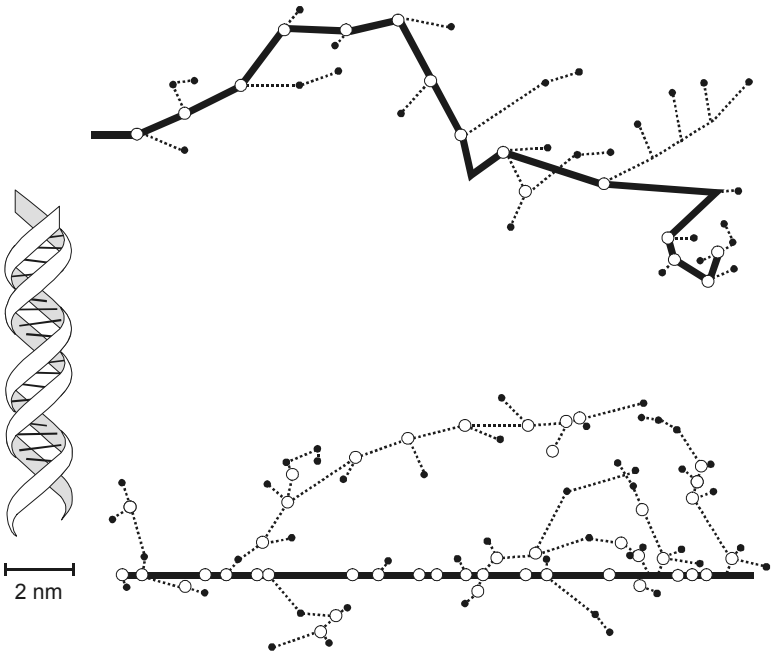

Fig. 2.1. Simulated low energy electron track (upper: initial energy 500 eV) and simulated short portion of an alpha particle track (lower: 4 MeV). Large circles are ionisations, small circles are excitations. A Section of DNA is shown to give a perspective on dimensions; [94G2].

The temporal sequence of ionisations (and excitations) leading to biological effects is illustrated in Fig. 2.2. Physico-chemical events are completed rapidly, the repair of damage may be completed within tens of minutes while effects in cells can arise within hours or days. The biological manifestations in multi-cellular organisms, including man, can be delayed for many years or, as in the case of hereditary disease, only be manifest in future generations.

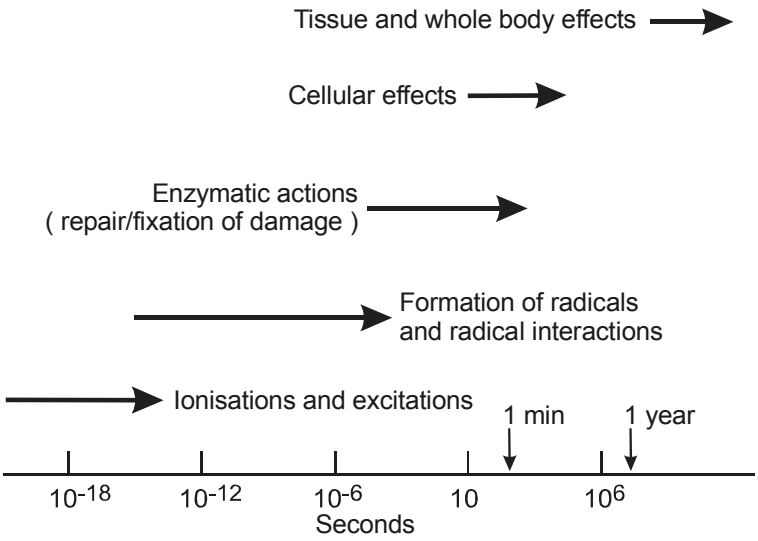

Fig. 2.2. Timescale of events leading to radiation effects following exposure to ionising radiations.

2.2.2 Cellular damage and repair following the primary radiation events

It is widely accepted that the most important cellular constituent to be damaged by radiation is nuclear DNA. The molecular structure consists of a double helix (Fig. 2.1), formed from two complementary strands of nucleotides. These are purine and pyrimidine bases linked to sugar molecules with phosphate

molecules joined by ester linkages. The two strands are held together by hydrogen bonds between guanine-cytosine and adenine-thymine base pairs. The cell's genetic information is carried in a linear sequence of nucleotides that make up the estimated 100,000 genes in the human genome. Each gene controls a discrete characteristic.

Just as cells inherit genes, they also inherit a set of instructions that tell the genes when to become active. These gene regulatory proteins recognise short stretches of nucleotide sequences on the double helix and determine which of the genes in the cell will be transcribed. About two-thirds of genes provide instructions for cell division and for the synthesis of tens of thousands of proteins that provide the structural components of cells, as well as numerous enzymes promoting and controlling cellular activity. Ribonucleic acid (RNA) is the molecule that helps to transport, translate and implement the coded instructions from the genes in the nucleus to the body of the cell. All cell types contain the same genes, but encoding sets of genes is cell-specific. This uniqueness ensures that cells in each tissue produce their own proteins.

Maintaining stability in the gene is essential for cell survival. This stability requires not only extremely accurate mechanisms for DNA synthesis and replication, but also mechanisms for repairing DNA damage before replication. Observations with proliferating cells in the laboratory indicate that DNA is subjected to only an estimated few tens of base-pair or nucleotide permanent changes per year during normal metabolism, despite the fact that metabolic processes alter thousands of bases and nucleotides every day.

DNA single strand breaks, without base involvement, are effectively ligated enzymatically. Base excision repair pathways require different groups of enzymes that identify and excise the damaged base site, make a complementary copy of the information bases on the opposite undamaged strand, and seal the correct sequence of copied bases in the gap. If nucleotide damage occurs, nucleotide excision repair pathways are able to repair the more extensive damage on one strand. Once the lesion is identified along the strand, the damaged nucleotides are removed and repair proceeds thereafter as for base damage.

DNA double strand damage with or without base damage, occurs much less frequently than damage to single strands during normal cellular activity. Recombination repair pathways are available, but they are not totally effective, since there is no undamaged strand to act as a template for base or nucleotide replacement. Damage to bases can result in their alteration or loss. When the repair processes fail, the resulting misrepair is referred to as a *mutation*.

DNA damage due to radiation causes similar lesions to those occurring after normal metabolism, but double strand breaks, multiple gene losses and the translocation of gene sequences occur more frequently as a dose-related effect. The probability of misrepair is greater under these circumstances. Estimated yields of damage caused by low-LET radiation are shown in Table 2.1 [88W1].

Table 2.1. Examples of damage in a mammalian cell nucleus from 1 Gy of low-LET radiation.

Initial physical damage	
Ionisations in cell nucleus	~ 100,000
Ionisations directly in DNA	~ 2,000
Excitations directly in DNA	~ 2,000
Selected biochemical damage	
DNA single-strand breaks	~ 1,000
Base (8-hydroxyadenine) damage	~ 700
Base (thymine) damage	~ 250
DNA double-strand breaks	~ 40
DNA-protein cross links	~ 150
Selected biochemical damage	
Lethal events	~ 0.2-0.8
Chromosome aberrations	~ 0.4
Hprt(1) gene mutations	0.6×10^{-5}
Translocation frequency (2 loci)	1.2×10^{-4}

(modified from 88W1)
(1) hypoxanthine-phosphoribosyl transferase

Recent investigations have revealed that DNA repair pathways may work in conjunction with other intracellular activities in order to minimise cell damage. These include delay in cell-cycling (as a means of maximising the chances of repair); and programmed cell death (apoptosis), whereby severely damaged cells are eliminated to stimulate cell proliferation.

2.2.3 Classification of radiation-induced damage

Laboratory techniques have been available for many years to observe radiation effects in proliferating cells. These techniques include measuring changes in cell survival, in the frequency of chromosomal aberrations (deletions and translocations), in gene structure (mutations), and in oncogenic transformation (neoplasia).

2.2.3.1 Cell survival

Cellular damage can be classified into three arbitrary categories: lethal damage which results in cell death; sublethal damage, which may be repaired; and potentially lethal damage, defined as damage that can be repaired by altering the growth conditions as for cells in culture.

Cell lines of fibroblasts from rodent and human tissues have been used extensively to establish dose-response relationships [93U6]. Expressed graphically as the logarithm of cell survival plotted against absorbed dose on a linear scale, the dose-response is linear for low-LET radiation at low doses, followed by a curvature at higher doses.

Expressed mathematically, the relationship can be represented by a linear-quadratic equation:

$$S = e^{-(\alpha D + \beta D^2)} \tag{1}$$

where S is the surviving fraction after exposure to dose D and α and β are coefficients representing the linear and quadratic components for cell killing. The initial slope of the relationship is determined by α, while the quadratic component, reflects the curvature in the dose-survival relationship (Fig. 2.3). The dose at which the linear and quadratic components are equal is the ratio of α and β. The response to high-LET radiation is also shown in Fig. 2.3 where survival is best expressed as a linear function of dose passing through the origin.

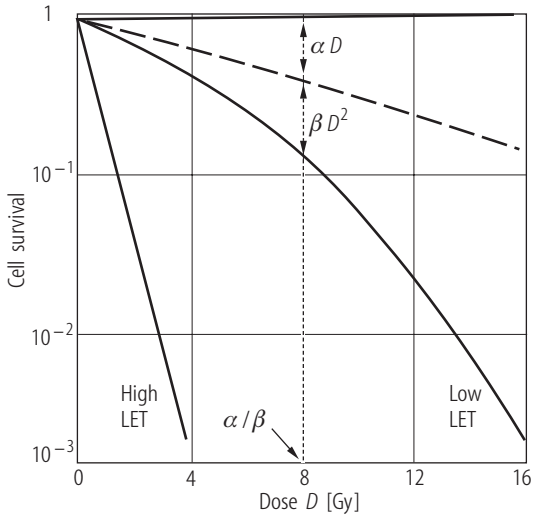

Fig. 2.3. Typical survival curves for cultured cells exposed at high dose-rate (>0.1 Gy min^{-1}). The curves illustrate the linear-quadratic relationship for low-LET radiations and linear relationship for high-LET radiations.

A plausible explanation of the linear component following exposure to low-LET radiation at low doses is that the majority of DNA interactions are single particle track events [94G2]. Under these circumstances, DNA damage can be effectively repaired. As the dose increases, multi-track events reflecting the quadratic component, and which are associated with clustered DNA damage, increasingly predominate with a consequent increase in the probability of misrepair and lethal events. At 1 Gy, for example, lethal events have a frequency of about 0.2 to 0.8 per cell (Table 2.1).

Protracted exposure to low-LET radiation results in less damage, per unit of dose, compared with acute exposure [93U6, 00U8]. This is referred to as the *dose rate effect* and is due to the ability of cells to repair more sublethal damage as the dose rate is reduced. Below about 1 Gy min^{-1}, the slope on the exponential portion of the survival curve typically becomes progressively shallower as more and more sublethal damage is repaired. Below about 0.01 Gy min^{-1}, undamaged cells are able to proliferate at a sufficient rate to offset the reduction in cell numbers while repair is progressing. This response is illustrated in Fig. 2.4. A dose rate effect is not observed after exposure to high-LET radiation, suggesting little repair of damage.

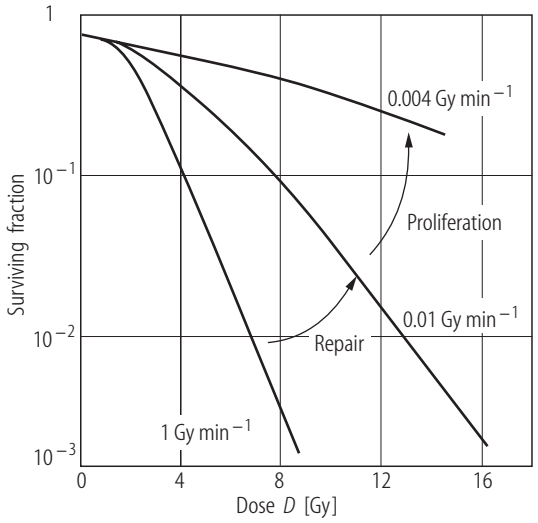

Fig. 2.4. Dose-rate effect showing the influence of repair and repopulation on the dose-survival relationship for cells.

The *relative biological effectiveness* (RBE) of different types of radiation is defined as the ratio of a dose of a reference low-LET radiation to a dose of the test radiation that gives an identical biological endpoint [90N3]. RBE values are influenced by variations in LET, dose and dose rate. RBE values increase to a maximum at about 100 keV μm^{-1}, decreasing thereafter because of an "overkill effect". The absolute value of the RBE is not unique but depends on the level of biological damage and, therefore, on the absorbed dose [86B1]. For irradiation by alpha particles, for example, the RBE is generally taken to be 20 for stochastic effects (cancer and hereditary disease) but to have a lower value of around 5 for deterministic effects.

2.2.3.2 Damage to viable cells

Chromosome aberrations and gene mutations

The technique of culturing human lymphocytes *in vitro* has been available for many years. It provides a means of measuring the frequency of unstable and stable chromosome aberrations at various stages in the cell-cycle. In terms of unstable aberrations, their frequency increases from a background level of about 10^{-3} to a rate of about 4×10^{-2} Gy^{-1} after exposure to low-LET radiations. Dose-response relationships for different types of radiation are illustrated in Fig. 2.5 [89E1]. Neutrons are more damaging than X-rays

or gamma-rays and low energy neutrons are more damaging than high energy neutrons. For low-LET radiations a linear-quadratic relationship is consistent with the data.
That is:

$$E = \alpha D + \beta D^2 \tag{2}$$

where E is the frequency of chromosome aberrations (i.e. a stochastic effect), D is the dose, and α and β are the linear and quadratic coefficients for the induction of the aberrations.

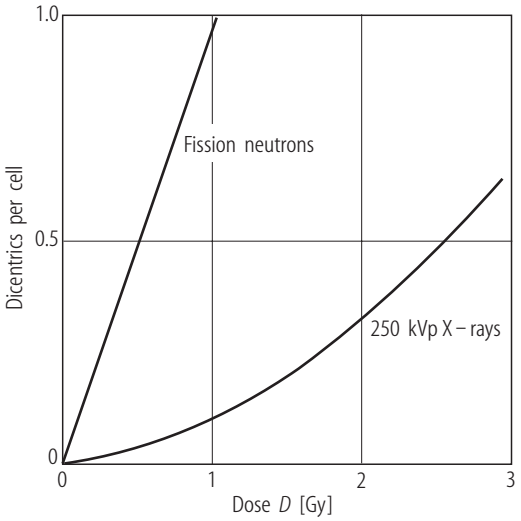

Fig. 2.5. Dicentric yield in chromosomes per cultured human lymphocyte as a function of dose for selected radiations; [89E1].

A number of specific-locus mutation test systems using mouse, hamster and human fibroblasts have been developed to measure mutagenesis. One cell line, the human B-lymphoblastoid TK6, illustrates the use of the test [89K4]. Cultured cells were exposed to radiation and the mutation frequency at two loci *(hgprt* and *tk)* was measured under different exposure conditions. For acute radiation exposure, 100 kVp X-rays (0-2 Gy) and (Pu, Be) neutrons (0-0.2 Gy) both showed a linear dose-response relationship in terms of induced mutants. The induced mutant frequency per 0.01 Gy per surviving cell was 0.55×10^{-7} (CI 0.09) and 1.92×10^{-7} (CI 0.03) respectively.

Protracted exposure to X-rays (0.01-0.1 Gy per day) for 5 to 20 days showed a slight increase in the mutation frequency (0.84×10^{-7} (CI 0.17)); while continuous exposure to neutrons (0-0.4 Gy) resulted in a substantial increase (6.00×10^{-7} (CI 0.7)). These data demonstrate an 'inverse dose-rate effect' for neutron-induced mutation in human cells. Syrian hamster embryo cells showed a similar effect, but other cell lines did not. It is concluded that there are a number of difficulties in interpreting the results of somatic cell mutations.

Estimated yields of chromosome aberrations and mutation frequency are shown in Table 2.1.

Cell transformation

An established technique for studying carcinogenic potential is that of culturing cells that can grow indefinitely, provided that they are frequently transferred to fresh media. Under specific conditions, cells that have acquired this ability are said to be immortalised. A characteristic of these immortalised cells is that they stop dividing when they come into contact with similar cells in the culture medium (contact inhibition). They are not classified as malignant cells because they do not cause tumours when injected into immunologically-suppressed animals. Occasionally, an immortalised cell undergoes a spontaneous change, whereby it loses its contact inhibition and continues to proliferate by spreading over adjacent immortalised cells to form a recognised foci of cells. Such cells are said to have undergone

transformation and when they are injected into animals, they develop into tumours. Spontaneous transformation is a rare event, occurring at a rate of about one in ten thousand to one in a hundred thousand per surviving cell. The mechanism is not fully understood, but it is thought to involve the mutation of two or more genes. Two classes of mutated genes in particular have been identified and characterised. These are 'gain-of function' mutations of proto-oncogenes, whereby the mutated genes (oncogenes) stimulate cell proliferation in an uncontrolled manner; and 'loss-of function' tumour suppressor genes, whereby cells are no longer prevented from proliferating in defiance of normal controls.

The cell types used in transformation studies are mainly derived from fibroblasts. It is generally accepted that the sensitivity of the test is low, the detection limit being about 0.25 Gy. Ideally, human epithelial cells would be a better choice to represent human cancers. Future studies are in hand which aim to use this type of cell.

To illustrate the technique, C3H/1OT½ fibroblasts derived from the prostate of the C3H mouse embryo, were irradiated with low-LET radiation [98M2]. Cell survival and transformation frequencies were simultaneously measured. The survival curve was consistent with a linear-quadratic dose-response relationship (Equation 1), while the transformation frequency per surviving cell following exposure to X-rays was consistent with a linear relationship (Fig. 2.6a). However, if the number of transformants per cell at risk was plotted, the relationship to intermediate doses was consistent with a linear-quadratic equation, the transformation frequency reaching a maximum at about 2 Gy (Fig. 2.6b). This dose-response relationship is consistent with other results reported in the literature, although the maximum transformation frequency was usually in the 3 to 4 Gy range.

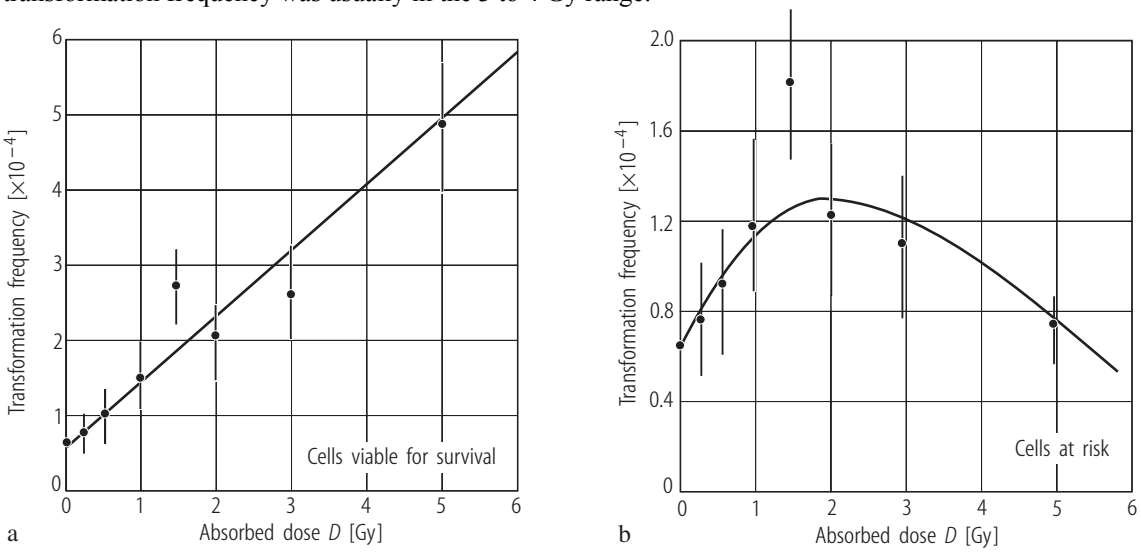

Fig. 2.6. Transformation frequencies per surviving C3H 10 T½ cell (a) and per cell at risk (b) as a function of absorbed dose after exposure to 250 kVp X-rays at 2 Gy min^{-1}; [98M2].

Exposure to neutrons resulted in a higher transformation frequency than for low-LET radiation, with no evidence of a dose rate effect. One exception was a study of 5.9 MeV or fission neutrons where an inverse dose-rate effect was reported [93U6]. It is concluded that there are difficulties in interpreting data on cell transformation studies.

Generalised dose-response relationships

The conventional approach to representing the absolute biological effectiveness of a given radiation at low doses is based on the assumption derived from target theory in which the induction I of an effect as a function of dose D can be represented by

$$I(D) = \left(\alpha_1 D + \beta_1 D^2\right) e^{-\left(\alpha_2 D + \beta_2 D^2\right)} \quad (3)$$

in which α_1 and β_1 are single and multihit components for a radiation effect and α_2 and β_2 represent single and multihit components for cell killing. At low doses the incidence from effect is determined by α_1 with the response increasing linearly with dose. It is generally assumed that in this region α_1 will be independent of dose rate. With increasing dose the amount of damage due to multihit effects increases, resulting in a quadratic component in the dose-response curve. At doses above a few gray β_1 and β_2 become significant resulting in a reduction in tumour yield due to the effect of cell killing.

For high-LET radiation (α particles, neutrons) the dose-response curve is generally found to be linear up to the point at which cell killing starts to exert an effect and reduces the tumour yield.

2.2.4 Implications of cellular damage for whole or partial body exposure

The outcome of cell damage in terms of human radiation detriment can be profoundly different according to the exposure conditions. Cellular studies can provide a sound basis upon which to judge these outcomes. After acute exposure to absorbed doses above a few gray, the cells at greatest risk are self-replicating stem cells that supply functional cells. They are programmed to divide so that one daughter cell remains as a stem cell (in order to ensure that stem cell numbers in the tissue remain constant), while the other daughter cell proceeds to specialise (differentiate) by clonal expansion. If sufficient numbers of stem cells in a tissue are killed or are prevented from dividing at the appropriate rate, the tissue loses its ability to function effectively. The consequential effects are referred to as *deterministic.* Studies have established that cell survival is dose and dose-rate dependent for low-LET radiations, and that there is a tissue-specific dose threshold. At high risk are rapidly dividing bone marrow stem cells, and stem cells in the epithelium of the gastrointestinal tract, lungs, thyroid, gonads, skin and lens of the eye.

The effects due to the proliferation of mutated cells at low doses are termed *stochastic.* There is sufficient radiobiological evidence for low-LET radiation to support the general assumption of an increasing risk of an effect with increasing dose at low to intermediate doses, with no threshold. Cellular techniques are providing insight into the way in which radiation can initiate the complex multistage process of carcinogenesis**.** However, there is still much to be learned about the molecular changes that lead to cells with the potential towards malignancy; and most importantly, any advances in knowledge at the cellular level have to be seen in the context of the living organism.

2.3 Deterministic effects

2.3.1 Tissue and organ development

In the space of a few weeks, a single fertilised human egg gives rise to a complex multicellular organism consisting of embryonic cells arranged in a precise pattern, each in its proper place. In the subsequent period of fetal growth, the cells continue to proliferate in the developing tissues and organs. Growth of tissues and organs continues in childhood with increase in cell mass in many tissues, but growth essentially ceases in the adult when cell masses reach a predetermined size.

The majority of cells in tissues of the adult are differentiated, that is, they have developed specific morphology and function which is usually irreversible, but these cells are predestined to die. In many tissues of the body, the rate of death of differentiated cells is rapid and, in a healthy state, must be balanced by proliferation from stem cells. These cells, by definition, are cells that have retained

embryonic characteristics. They are able to divide during the lifetime of the organism, yielding progeny that are destined to differentiate by a process of clonal expansion. Stem cells also retain the ability of self-renewal. These characteristics are illustrated in Fig. 2.7. The number of stem cells compared to differentiated cells varies according to the tissue, but they usually represent, at most, a few percent of the total cell numbers. Furthermore, only a small fraction of the stem cells are active at any one time under normal circumstances. It is not known how the balance between cell proliferation and cell death is achieved, but it is thought that all cells are genetically programmed to die, by apoptosis. When differentiated cells die, a feed-back mechanism is activated to stimulate the stem cells to divide and replenish the population.

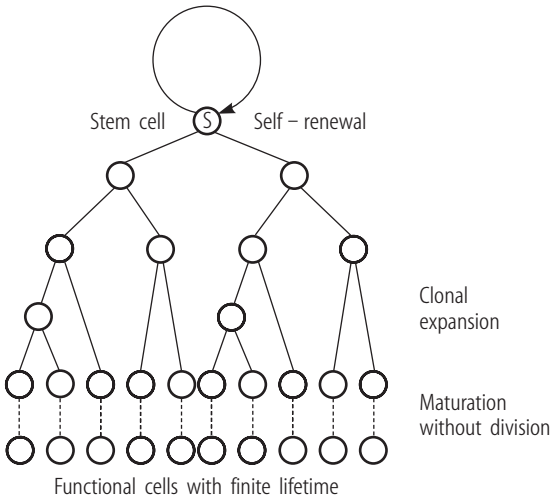

Fig. 2.7. Derivation of differentiated cells from a self-renewing stem cell.

If enough stem cells in a tissue are killed or prevented from undergoing cell division, there will be loss of tissue function; termed deterministic by the International Commission on Radiological Protection (ICRP). The dose-response relationship is characterised by a frequency and severity that increases with dose above a threshold. Most tissues and organs of the body are able to compensate for small reductions in the number of differentiated cells. But if the decrease is large enough, there will be changes seen as loss of tissue or organ function and a consequential response to repair the damage.

2.3.2 Dose-response relationships for radiation damage

The probability of detecting loss of tissue or organ function following exposure to radiation increases steeply above a threshold dose to a maximum. Expressed as a generalised dose-response relationship, the plot of the frequency of the effect versus dose expressed on linear axes is sigmoid (Fig. 2.8, upper panel). Above the threshold dose, the severity of the effect also increases with dose reflecting more cell loss and hence damage to tissue function (Fig. 2.8, lower panel). Protracting the dose results in a lower frequency and less severe symptoms at a given dose compared with acute exposure, demonstrating the importance of stem cell repopulation.

There is individual variation in radiosensitivity in any exposed population. This variation reflects differences in the ability of individuals to cope with radiation-induced cellular damage. Any response is influenced by the age and state of health of the exposed individual.

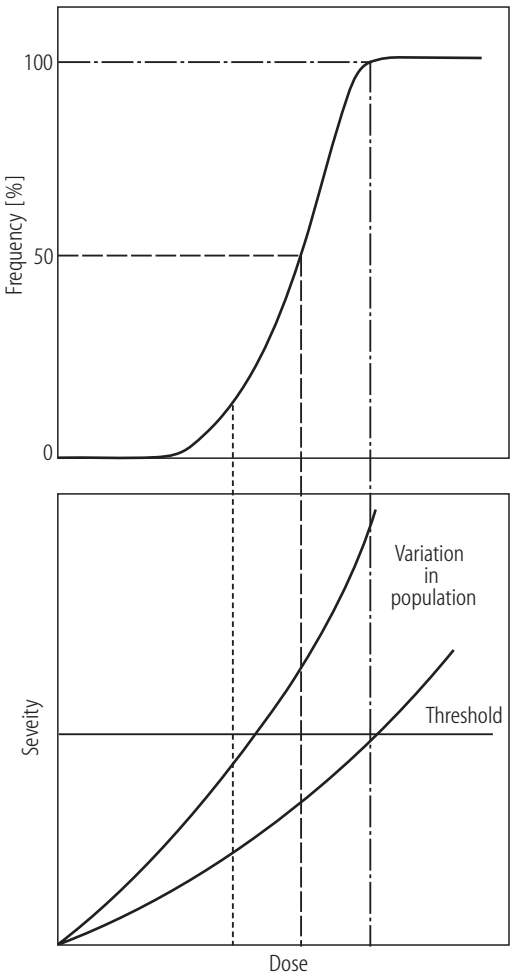

Fig. 2.8. Dose-response relationship for deterministic effects. Variation in frequency and severity; [based on 91I2].

2.3.3 Deterministic effects in humans following acute whole-body irradiation

Evidence of the deterministic effects of radiation comes from several sources. These include retrospective studies on radiotherapy patients, radiologists in the early part of the 20th century, Japanese populations exposed to radiation from atom bombs, and individuals accidentally exposed to high doses following nuclear reactor accidents and radiographic sources. Understanding the effects of acute high doses is important as an aid to prognosis in the treatment of accidental over-exposure, and to ensure that deterministic effects are avoided in normal practices and minimised in accidents. Evidence on deterministic effects also comes from studies with animals.

After exposure to doses of a few Gy, the depression in the numbers of circulating white blood cells (granulocytes) and blood platelets may be so severe as to result in death from septicaemia (infection) and haemorrhage. This is referred to as the haematopoietic syndrome. Recovery depends upon the radiation dose and the ability of the remaining stem cells in the marrow to recover. Loss and recovery of granulocytes and blood platelets follows a similar dose- and time-related pattern.

Depression of the stem cells providing the protective mucosal cells lining the intestinal tract wall results in a denuding of the gut surface. This gastrointestinal syndrome is seen in individuals who have received doses to the gastrointestinal tract in excess of about 5 Gy. Leakage of blood from damaged blood capillaries results in severe anaemia and ingress of intestinal bacteria through the damaged blood vessels results in septicaemia. The haematopoietic syndrome will manifest itself concurrently at these higher doses.

Damage to endothelial cells lining the alveolar air sacs may result in acute inflammation of the lungs (pneumonitis) at doses in the range 5 - 15 Gy. This may occur after radiotherapy or after the inhalation of high specific activity radioactive particles. If the individual survives the pneumonitis, lung fibrosis may later develop which can also be life-threatening through loss of lung function.

At higher whole-body doses (>15 Gy), generalised shock occurs affecting the brain and the cardiovascular system. Coma and death develop rapidly thereafter.

The range of doses associated with death from these syndromes after acute exposure to low-LET radiation is given in Table 2.2. The ranges are based upon human data, supplemented by knowledge of the form of the dose-response relationship derived from animal experiments. No individual would be expected to die after receiving absorbed doses below about 1 Gy. The dose range where half the exposed population would be expected to die without medical treatment is 3 to 5 Gy. Death would be likely at doses between about 6 Gy and 10 Gy, unless they receive treatment to prevent infection and bleeding. Above about 10 Gy death is assumed at present to be inevitable, even after attempts to stimulate the bone marrow or bone marrow transfusion from a suitable donor. These estimates of lethality do not take account of any concurrent radiation-induced damage (e.g. skin burns), or existing debilitating diseases.

Table 2.2. Range of doses associated with acute radiation syndromes in adults exposed to low-LET radiation.

Whole body absorbed dose	Principal effect contributing to death	Time of death after exposure [days]
1-6 Gy	Damage to bone marrow[a]	30-60
5-15 Gy	Damage to the gastrointestinal tract and lungs[b]	10-20
>15 Gy	Damage to nervous system and shock to the cardiovascular system	1-5

a) Dose range considered to result in 50 % of an exposed population dying (LD_{50}) 3-5 Gy.
b) Damage to vasculature and cell membranes especially at high doses is an important factor in causing death.

2.3.4 Deterministic effects following partial body irradiation

2.3.4.1 Tolerance doses in adults after radiotherapy

Extensive experience in the treatment of patients undergoing radiotherapy has provided data upon which to determine the tolerability of healthy tissues and organs to radiation. Called the tolerance dose by clinicians, it is defined as the amount of radiation received during conventional treatment below which unacceptable effects do not occur in more than a few percent of patients within 5 years following treatment. The tolerance doses for some adult tissues are shown in Table 2.3 (children are usually less tolerant to exposure). It is evident that the gonads, lens of the eye and the bone marrow are the most radiosensitive.

2.3.4.2 Threshold doses in radiological protection

The limitations of using data on tolerance doses to derive threshold doses for radiological protection purposes need to be recognised. In contrast to the precise exposure conditions of radiotherapy, exposure of workers to high doses of low-LET radiation is most likely to be non-uniform and resulting from mixed radiations. The tolerance dose therefore can at best be used as a cautious approximation to a threshold dose.

Table 2.3. Tolerance doses for deterministic effects in adults after fractionated radiotherapy treatment

Organ	Effect	Tolerance dose [Gy]
Total bone marrow	Blood cell depletion	1-2
Ovary	Permanent sterilisation	2-6
Testis	Permanent sterilisation[a]	3-4
Eye	Cataract[b]	5-10
Kidney	Nephrosclerosis	23
Liver	Loss of function, ascites	35
Lung	Pneumonitis[c]	40
Heart	Pericarditis	40
Lymph nodes	Hypoplasia, fibrosis	35-45
Thyroid, pituitary	Hypoplasia	>45
Other organs	Hypoplasia, fibrosis	>45

a) A significant but reversible, depression of sperm count occurs after about 0.1 Gy brief exposure.
b) About 2 Gy after a brief exposure.
c) LD_{50} after brief exposure is about 10 Gy.

The threshold doses recommended by the ICRP for the most radiosensitive tissues and organs are summarised in Table 2.4. Thus the threshold dose for temporary sterility in the male for a single absorbed dose in the testes is about 0.15 Sv. Under conditions of prolonged exposure, however, the dose rate threshold is about 0.4 Sv y^{-1}. The corresponding values for permanent sterility are about 3.5 Sv and 2 Sv y^{-1}. The threshold dose for permanent sterility in women for a single absorbed dose is in the range from about 2.5 Sv. For protracted exposure, the dose rate threshold is about 0.2 Sv y^{-1}.

Clinically significant depression of the blood-forming process occurs above a single bone marrow dose of about 0.5 Gy. The dose rate threshold for protracted exposure is about 0.4 Gy y^{-1}. The tolerance dose for death is in the range of 6 to 7 Gy if the radiation is spread over 30 fractions in a period of 6 weeks. Table 2.5 summarises the principal syndromes associated with whole body exposure.

Table 2.4. Estimates of the thresholds for deterministic effects in adults recommended in radiological protection [91I2].

Tissue and effect	Equivalent dose brief exposure [Sv]	Equivalent dose rate protracted exposure [Sv y^{-1}]
Testes		
Temporary sterility	0.15	0.4[a]
Permanent sterility	3.5-6.0	2.0
Ovaries		
Sterility	2.5-6.0	>0.2
Lens		
Detectable opacities	0.5-2.0	>0.1
Visual impairment (cataract)	5.0[c]	>0.15
Bone marrow		
Blood cell depletion	0.5	>0.4[b]

a) This dose is higher because differentiating cells are more radiosensitive than the stem cells so the latter can replenish the differentiating cells at an adequate rate.
b) Supported by evidence of effects after chronic radiation of Beagle dogs.
c) Range 2-10 Sv.

Table 2.5. Summary of acute radiation syndrome

	Syndromes		
	Cerebral	Intestinal	Bone marrow
Critical organ	Brain	Small intestine	Bone marrow
Latent period	20 min	3-5 days	2-3 weeks
Syndrome threshold [Gy]	20	3	1
Death threshold [Gy]	50	10	2
Death occurring within	2 days	2 weeks	3-8 weeks
Cause of death	Cerebral oedema, heart failure	Sloughing of gut, shock	Haemorrhage, infection
Prodromal vomiting	Minutes	1 hour	A few hours
Symptoms	Tremors, cramps, loss of coordination, lethargy, impaired vision, coma	Loss of appetite, vomiting, diarrhoea with bleeding, fever, electrolyte and fluid balance	Fever, breathlessness, internal bleeding, depletion of bone marrow leading to low blood counts
Treatment	Palliative	Barrier nursing, fluid and electrolyte replacement, transfusions of blood cells, bone marrow transplants	
Prognosis	Hopeless	Very poor	Dose-dependent and influenced by treatment

2.3.4.3 Skin irradiation

Based upon extensive experience in the use of fractionated X and gamma radiation in radiotherapy, (typically, 20 to 30 fractions each of 2 to 6 Gy over several weeks), various degrees of skin damage can be observed according to the area and depth of skin involved, the absorbed dose and the duration and frequency of the exposure. The earliest observable change is a transient reddening within a few hours after exposure to doses above about 2 Gy; due to increased capillary permeability. This is followed after moderate doses (about 5 Gy) two to four weeks later by a persistent reddening (the main erythematous reaction) and peeling of skin (dry desquamation). This is due to secondary inflammation resulting from the death of basal (stem) cells of the epidermis. Hair loss also occurs.

At higher doses (about 20 Gy), blistering (moist desquamation) occurs after about four to six weeks due to the inability of basal cells in the irradiated area to divide and for viable basal cells to migrate into the area at a sufficiently rapid rate. It is the health effect to be avoided in both radiotherapy and radiation protection practice. The threshold doses for moist desquamation depends upon the area irradiated and the penetrating powers of the radiation.

Ulceration is the result of infection following moist desquamation and may occur after about 6 weeks. Necrosis due to irreversible damage to the basal cells of the dermis and the underlying blood vessels occurs within two to three weeks after doses of tens of Gy. Late effects developing months to years later include changes in pigmentation; atrophy of the epidermis, sweat glands and sebaceous glands and hair follicles; and fibrosis.

Quantifying the threshold doses for these effects is complicated in practice by the multiplicity of targets at different critical cell depths, which makes it difficult to select a single depth at which to specify the dose to the skin. The depths at which the most serious effects arise are estimated to be in the range of 300 - 500 μm. However, a conservative approach for protection purposes is to use shallower depths (20 - 100 μm, typically 70 μm) for monitoring specifications.

To prevent moist desquamation, the dose must be reduced as the radiation field is increased. To illustrate the importance of field size, the tolerance doses following a single treatment with orthovoltage X-rays was found to be 20 Gy for an area of 6×4 cm, and 11 Gy for an area of 15×20 cm. Following fractionated treatment, the tolerance doses were estimated to be about 50 Gy and 30 Gy respectively for the two field sizes. From experimental studies, the estimated dose threshold following exposure of large areas of skin is about 20 Gy; and no acute tissue breakdown was observed at a dose rate of 0.4 Gy h^{-1} with total doses of about 100 Gy.

Accidental over-exposure of industrial radiographers is a cause for concern in radiation protection. In normal practices, ICRP recommends a limit on effective dose of 20 mSv per year, averaged over 5 years with the further provision that the effective dose should not exceed 50 mSv in a single year [91I2]. This limitation is on effective dose and is assumed to be adequate to prevent deterministic effects. However, an additional annual limit is recommended for localised exposures in order to prevent deterministic effects to the skin. It is 500 mSv averaged over any 1 cm^2 regardless of the area exposed.

2.4 Radiation-induced cancer

2.4.1 Cancer development

The development of cancer is the major late effect resulting from exposure to radiation. Cancer is generally understood to develop in a number of stages. That is, for malignancies to be expressed a series of events must occur in cells and the rate at which they occur is thought to be reflected in the way cancers appear in the population over the course of time.

The development of cancer in tissues is a complex, multi-stage process that can be sub-divided into four phases: neoplastic initiation; neoplastic promotion; conversion and progression. The sub-divisions are necessarily simplifications of the overall process which is, in any event, somewhat variable between different tumour types. However, they do provide a basis from which to interpret the cellular and molecular changes involved [93U6, 00U8].

Neoplastic *initiation* encompasses the essentially irreversible cellular damage, which although not necessarily expressed immediately, provides the potential in cells for the development of cancer. There is good evidence that this initiation process results from damage to DNA leading to gene mutations in single target cells in tissues. The critical damage is likely to be coincident damage to both DNA strands (DNA double strand breaks, Section 2.2.2). Although a proportion of such double strand damage will be repaired, completely error free repair of such damage, even at low doses, is not expected. Neoplastic *promotion* can be seen as a process whereby initiated cells receive an abnormal growth stimulus and begin to proliferate in a semi-independent manner. *Conversion* of these pre-neoplastic cells to a form in which they are committed to become fully malignant is a central feature of the process of neoplastic development. Such changes are now believed to be driven by further gene mutations accumulating within the expanding population of pre-neoplastic cells.

Once the potential for full malignancy has been established, the subsequent *progression* of the disease may depend upon further cellular changes that allow invasion of adjacent normal tissues, the circulation of neoplastic cells in the blood and lymphatic systems and the establishment of metastases (secondary tumour growths) at other sites in the body. It is this invasive process that provides principally for the fatal effects of most common human tumours. On this basis, a single mutational event in a critical gene in a single target cell *in vivo* can create the potential for neoplastic development. Thus, a single radiation track traversing the nucleus of an appropriate target cell has a finite probability, albeit very low, of generating the specific damage to DNA that results in a tumour initiating mutation. These initiated cells can then develop by multistage processes into an overt malignancy. As a consequence, at the level of DNA damage, there is no basis for assuming that there is likely to be a dose threshold below which the risk of tumour induction would be zero. For radiation protection purposes, a progressive increase in risk with increasing dose, with no threshold, is therefore assumed [95C2]. Whilst such a multistage mechanism is considered to be the cause of many human tumours there are likely to be some tumours that may arise in tissues where there has been deterministic damage (fibrosis) for such tumour types a threshold dose may need to be exceeded before the tumour will occur. There are many examples of such tumour types in animals and the development of radiation-induced bone tumours in man may also require a threshold dose to be exceeded [00U8].

Radiation appears to be capable of causing tumours in nearly all tissues of the body, although the frequency of appearance following a unit dose may vary markedly from one tissue to another. Information on the dose related frequency of tumour induction by radiation is gained through follow-up of groups of persons exposed to radiation. The observed tumour frequency can then be compared with an age and sex matched control group, not exposed to radiation, to determine the increase in frequency due to the radiation exposure. Extensive follow-up studies have been carried out on groups of persons exposed to either external radiation or to internally incorporated radionuclides.

Tumours induced by radiation are in general indistinguishable from those occurring spontaneously and since cancer is not uncommon (about one in five die as a result of it in Western Europe and North America), the problem of determining a relatively small excess due to radiation exposure is difficult. In general, large exposed populations are necessary to obtain statistically meaningful results.

The chief sources of information on the risks of radiation-induced cancer are the A-bomb survivors exposed to whole-body irradiation in Hiroshima and Nagasaki, patients with ankylosing spondylitis and other patients who were exposed to partial-body irradiation therapeutically, either from external radiation or internally incorporated radionuclides, and various occupationally exposed populations, such as uranium miners and radium-dial painters. Some quantitative information on thyroid cancers may also be obtained following the Chernobyl accident. Increasingly information is becoming available from epidemiological studies on groups of persons occupationally exposed to radiation. In general, however, the radiation exposures in these populations is relatively low and there is limited power in the studies to obtain quantitative estimates of risks of radiation-induced cancer. Reports by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) provide a comprehensive review of the data available [94U7, 00U8].

In it's 1990 recommendations, the ICRP re-assessed the epidemiological data and this resulted in an increase in estimates of the lifetime risk of radiation-induced cancer. Partly, this arose as a result of revised dosimetry for the A-bomb survivors and a longer follow-up of the population, but mainly it was attributed to a change in the model now used to project lifetime risks [91I2]. Similar calculated values of lifetime risk have been published by UNSCEAR [94U7, 00U8].

2.4.2 Dose-response relationships

2.4.2.1 Assessment of lifetime risk

There is always a minimum period of time between irradiation and the appearance of a radiation-induced tumour. This period is termed the latent period and its length varies with age and from one tumour type to another. Some types of leukaemia and bone cancer have latent periods of only a few years but many solid tumours have latent periods of ten or more years. For leukaemia and bone cancer there is fairly good evidence that the risk is almost completely expressed within about twenty-five years following exposure. For solid tumours of longer latency, such as those of the GI tract , liver and lung it is not yet clear whether the incidence of these tumours passes through a maximum and declines with time following exposure, whether the risk levels out, or alternatively increases indefinitely during the remainder of life.

To project the overall cancer risk for an exposed population, it is therefore necessary to use models that extrapolate over time data based on only a limited period of the lives of the individuals. Two such projection models have generally been used:

(a) the additive (absolute) risk model which postulates that radiation will induce cancer independently of the spontaneous rate after a period of latency, variations in risk may occur due to sex and age at exposure as well as the tissue exposed.

(b) the relative (multiplicative) risk model in which the excess (after latency) is given by a constant (or time-varying) factor applied to the age dependent incidence of natural cancers in the population.

In most cases the spontaneous risk of cancer increases with age and therefore the relative risk model will predict an increasing incidence of radiation-induced cancer with age. This model also gives different risks of radiation-induced cancer in different populations, depending on the national cancer incidence. Data available from the A-bomb survivors in Japan and from studies on uranium miners suggest the relative risk projection model gives a better fit to the data, at least for some of the most common cancer types. Despite this there are indications from a number of exposed groups that the risk of cancer starts to decline many years after exposure. This has been well documented for leukaemia, but has also been

observed in the case of bone cancers (patients in Germany given ^{224}Ra), thyroid cancers (US follow-up study after thymus irradiation), solid cancers (patients treated for ankylosing spondylitics) and possibly lung cancers in the uranium miners exposed to radon and its decay products [88U5; 00U8]. These results suggest that for the Japanese population the excess risk may ultimately decrease with time and thus relative risk projection models applied over a lifetime could result in an overestimate of the cancer risk.

2.4.2.2 Effects of dose and dose rate

The total radiation dose and the dose rate both influence cancer induction and are linked to the form of the dose-response relationship. For radiological protection purposes tumour induction is generally assumed to increase with increasing dose, with no threshold, as indicated above. However, studies using cells in culture reveal that for many endpoints, including mutation, the dose-response for exposure to low-LET radiation is not linear, but that the effectiveness of radiation, per unit dose, increases as the dose increases. At very low doses, where there is a low probability of more than one radiation event occurring in a cell nucleus it may be expected that the effect is linearly related to dose. At higher doses, where multiple ionising events within a single cell are commonplace, damage arising from interactions between two or more events becomes more probable. Ultimately, at high doses cell killing will progressively reduce the risk of tumour induction. For single (acute) radiation exposures cell killing starts to become significant at doses of a few gray. The generalised dose-response is given in Equation 3 (Section 2.2.3.2).

The difficulty in assessing risks of cancer following exposures to low-LET radiation at low doses and dose rates is illustrated in Fig. 2.9. This gives, schematically, data points and possible dose-response curves for cancer induction. Frequently, as in this example, information is only available at relatively high doses. An approach commonly used in risk assessment is to fit a linear dose-response relationship to the data (curve B) a procedure usually considered to give an upper limit to the risk at low doses. This will be the case unless significant cell killing has occurred. If this linear relationship is due to single tracks acting independently then the effect per unit dose would be expected to be independent of dose magnitude and dose rate. In practice, however, this is not generally observed and the linear quadratic relationship (curve A) frequently gives a better fit to the data at low to intermediate doses implying that at higher doses damage is the result of both single and multiple tracks. At still higher doses cell killing becomes significant with a consequent reduction in tumour yield.

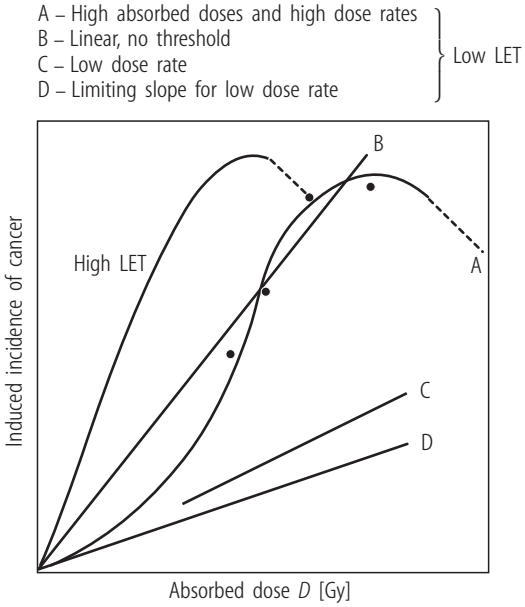

Fig. 2.9. Dose-response relationship for radiation-induced cancer: possible inferences are illustrated in extrapolating data available at high doses and high dose rates to response at low doses and dose rates for low-LET radiation; [based on 90N2].

With a progressive lowering of the dose and the dose rate, allowing more opportunity for repair of damage, curve C might be obtained. A point may ultimately be reached at which multiple track events make a negligible contribution to tumour incidence and damage is produced only as a result of single tracks acting alone giving a linear response (curve D) with the effect directly proportional to dose (slope α_1, the risk coefficient). A similar response would be obtained by lowering the dose rate alone as even with high total doses the rate of build up of lesions would be slower and the opportunity for multiple track events would decrease. Hence in the limit, curve D, could be achieved either by reducing the dose to very low values so that effects are independent of dose rate or by reducing the dose rate to very low values. The approach used for assessing risks at low doses and low dose rates of low-LET radiation is described in Sections 2.4.5 and 2.4.6. For high-LET radiation it is assumed that there is no dose rate effect and the response is proportional to dose for doses below those at which there is cell killing.

The data on the A-bomb survivors provide information on risks of cancer in a range of tissues, although to date no quantitative information is available for radiation-induced cancers of the liver, cells on bone surfaces, thyroid and skin. Information on radiation-induced cancer in these tissues is, however, available from other epidemiological studies summarised in Table 2.6. The principal studies used to quantify the effects of both external radiation and internally incorporated radionuclides are summarised below.

Table 2.6. Human populations available for risk estimation

Atomic bombs	Japanese survivors[a]
	Marshall islanders[a,b]
Medical diagnosis	Multiple fluoroscopies (breast)[a]
	Prenatal irradiation[a]
	Thorotrast injections[c]
Medical therapy	Pelvic radiotherapy (cervix)[a]
	Spinal radiotherapy (ankylosing spondylitis)[a]
	Neck and chest radiotherapy (thyroid)[a,b]
	Scalp radiotherapy[a]
	Radium treatment[c]
Occupational exposure	Uranium miners[c]
	Radium ingestion (dial painters)[c]
Radiation accidents	Radiation workers[a,b,c]
	Chernobyl[a,b]

a) Exposure to external radiation
b) Internal exposure to β/γ internal emitters
c) Internal exposure to α emitters

2.4.3 Exposures to external radiation

2.4.3.1 The A-bomb survivors in Japan

The mortality experience of the Hiroshima and Nagasaki A-bomb survivors has been the single most important source of information on the risk of radiation-induced cancer. This population has been the subject of a comprehensive follow-up since 1950. Information is available on the exposure of individuals to whole body radiation at a range of ages. Data on mortality from radiation-induced cancer that became available in the 1980s on the population of more than 90,000 people in the Life Span Study (LSS) necessitated a revision of previous risk estimates [87P3, 90S3]. There were a number of components to this change. The first was a revision of the dosimetry (termed DS86) to allow, amongst other factors, for the high humidity in the air over the cities which has substantially reduced the neutron dose at Hiroshima from the earlier 1965 (T65) estimates which were based on measurements in the dry atmosphere of the Nevada desert. Improved estimates were also made of the yield of the Hiroshima bomb (increased from 12.5 to 15 ktonnes), the shielding provided by buildings and of tissue and organ doses. The second was

that the number of excess fatal cancers in the population increased due to the longer period of follow-up (to 1985) and an estimate of the cancers occurring in the period 1945-1950 was made. The third, and most significant change, was that relative risk, rather than additive risk models appeared to provide a better basis for assessing lifetime risk of most solid cancers (Section 2.4.2.1).

UNSCEAR [88U5] in a report to the General Assembly provided the first information on radiation-induced cancer risks for a number of tissues in the Japanese population based on relative risk projection models. The total cancer risk in the population, at high dose and high dose rate, was then estimated to be 7-11 $\times 10^{-2}$ Sv^{-1} using age-averaged and age-specific constant relative risk models. This compared with the Committee's 1977 assessment of 2.5 $\times 10^{-2}$ Sv^{-1} [77U2] at high dose rate using the additive model. Because children and young persons are more sensitive to radiation than adults. The application of age specific risk coefficients therefore increases the predicted numbers of radiation-induced cancers in the whole population compared with that for a working population (Section 2.4.6).

These risk estimates for whole body radiation exposure were based on an extrapolation into the future which is somewhat uncertain for solid cancers because two-thirds of the Japanese survivors were still alive and two-thirds of the cancer risk had still to be expressed. Up to 1985 about 80 excess leukaemias and 260 excess solid cancers had occurred in the LSS population for whom DS86 doses were available out of a total of about 6000 cancer deaths [87P3]. The risk of radiation-induced leukaemia is more certain than that for solid cancers, however, as few more excess cases are now expected. There remain uncertainties in extrapolating the cancer risks based on the Japanese population exposed to radiation at high dose rates to the low doses and dose rates relevant for radiological protection purposes (see Section 2.4.5).

In a more recent report on the LSS, Pierce *et al* [96P1] reported on five more years of follow-up (1986-1990). Their analysis included an additional 10,500 survivors (86,572 in total). During 1950-1990 there have been 7827 cancer deaths, of which it is estimated there are 87 excess leukaemias and 334 solid cancers. The mortality curve for all solid cancers combined shows essentially a linear dose-response in the range 0-3 Sv, whereas for leukaemia the trend in dose is non-linear with an upward curvature. The radiation-induced leukaemia risk seems to have been almost completely expressed during the follow-up period, and the lifetime excess absolute risk of leukaemia associated with an acute dose of 1 Sv has been estimated as being about 1 %. However, in contrast to leukaemia, nearly a quarter of the radiation-induced solid cancers are estimated to have arisen in the most recent five-year period of the mortality follow-up, i.e. 1986-90 [96P1]. Since most of the A-bomb survivors exposed at young ages are still alive, the future pattern of cancer risks in this group will be important in determining lifetime risks. A significant increase in the risk of solid cancers is now seen at doses down to about 50 mSv [00U8].

2.4.3.2 Thyroid cancer

A number of epidemiological studies provide information on cancer risks in individual tissues. Groups of children and young persons who received thyroid irradiation, and who can be used to derive risk coefficients for thyroid cancer, include children who received X-ray treatment for thymic enlargement, patients treated in US hospitals for thyrotoxicosis and other benign lesions of the neck and patients who received X-ray treatment for thyroid disease [85N1, 85S4, 00U8]. In the majority of cases, particularly in the young, thyroid cancer is not fatal. The mortality from radiation-induced thyroid cancer is expected to be about 10 % of the incidence. There is also evidence that the risk in adults is about half that in children and that the risk in females is about twice that in males. For a population uniformly exposed to external radiation the risk of fatal thyroid cancer is estimated to be 8.0 $\times 10^{-4}$ Sv^{-1} assuming a 5 year latent period [91I2]. In human populations given iodine-131 for non-therapeutic reasons, and who received doses well below 2 Gy, no significant excess of thyroid cancers has been observed. This suggests a risk coefficient 3 to 4 times less than that obtained following external radiation at high dose rates [85N1]. Data on thyroid cancer incidence in children in areas of the former Soviet Union that were contaminated with fall-out from Chernobyl indicate an increased risk of thyroid cancer in some areas. To date the data are insufficient to provide quantitative risk estimates [00U8]. Thyroid cancer risks from exposures to radioiodine are considered further in Section 2.4.4.

2.4.3.3 Skin cancer

An ICRP Task Group [91I3] reviewed data on the risks of skin cancer. Most of the data came from groups given partial body irradiation in the course of medical treatment, although some data were also available from occupationally exposed groups, in particular radiologists and radiation technicians and uranium mining populations. Little information is available from the A-bomb survivors. On the basis of a relative risk model, the Task Group calculated a risk of fatal skin cancer for exposure of a general population of 2×10^{-4} Sv^{-1} at low doses, on the assumption that 0.2 % of cases would be fatal. They stressed the uncertainty in assessing the temporal pattern of radiation-induced skin cancers.

2.4.3.4 Breast cancer

Data are available on radiation-induced breast cancer from follow-up studies on the A-bomb survivors as well as from studies of patients in North America given fluoroscopy examinations for tuberculosis or treated for acute postpartum mastitis. Risks calculated from either population are little different, based on additive projection models. ICRP has based its risk estimate of 2×10^{-3} Sv^{-1}, for a mixed population of men and women, on the data on the A-bomb survivors. The risk of breast cancer also varies considerably with age at exposure. Thus, for exposure in the first decade of life, the risk is about 4 times that at ages 40-50 years [93M4].

2.4.4. Exposure to internally incorporated radionuclides

Human data on cancer induction from internally incorporated radionuclides are available for only a few radionuclides and have been reviewed by UNSCEAR [94U7, 00U8]. Quantitative data for risk estimation are available only for alpha particle emitting radionuclides.

Limited data are available on humans exposed to β/γ emitters. A number of epidemiological studies have followed groups exposed to ^{131}I. These studies cover a wide range of doses, varying from very high doses delivered in the treatment of hypothyroidism to the low doses received by patients exposed to diagnostic procedures or exposed to radiation from fallout in the Marshall Islands. The information available provides little evidence that exposure to ^{131}I is associated with a risk of thyroid cancer, although in some cases the follow-up is relatively short. This lack of effect, compared with the effect of external radiation, may be due to an effect of dose rate or to differences in the distribution of dose within the gland. There may also be differences due to ages at exposure. As in the case of external radiation the groups were predominantly young persons. The extent to which exposures to ^{131}I has contributed to the increased risk of thyroid cancer following the Chernobyl accident is still uncertain.

Some very sparse data on tumour induction are available on a few individuals given ^{32}P, ^{35}S and ^{59}Fe for medical reasons and there is some information on persons in the Southern Urals exposed to ^{90}Sr who used water from the Techa River for drinking and irrigation [94K1]. A number of studies have also considered the effects of radionuclides in weapons fallout or in discharges to the environment from other nuclear facilities. These data do not at present provide a basis for assessing risks from intakes of β/γ emitting radionuclides.

The available information on α-particle emitters covers groups exposed to radium isotopes (^{224}Ra, ^{226}Ra, ^{228}Ra) where bone tumours are the predominant late effect, and Thorotrast (colloidal $^{232}ThO_2$) which principally results in irradiation of the liver, spleen and bone marrow, with tumours arising mainly in the liver and bone marrow (leukaemia). Information is also available in man on lung cancer following occupational exposure to radon and its decay products. A number of epidemiological studies of domestic exposure to radon have been published and others are presently under way, to date the data are generally consistent with risks obtained from worker studies although exposures are lower and have a reduced sensitivity for obtaining quantitative risk estimates. Twenty-six men who worked with plutonium in North America on the Manhattan project during the Second World War have also been studied (estimated body

contents 52-3180 Bq). Seven individuals had died by 1991. The causes of death were lung cancer (2 cases), myocardial infarction, arteriosclerotic heart disease, accidental injury, respiratory failure due to pneumonia/congestive heart failure and osteosarcoma of the sacrum. Three men also had a history of skin cancer [91V3]. There is a high probability that the bone cancer was caused by exposure to plutonium as the spontaneous risk is about 1 in 2000.

ICRP [91I2] has recommended the use of radiation weighting factors w_R for calculating the equivalent dose to tissues and thus interpolating between the effects of high and low-LET radiation. The w_R for α-particle irradiation is taken to be 20.

2.4.4.1 Radium-226/228 luminisers

An increased incidence of bone cancer and of head sinus carcinoma has been observed in persons in the USA exposed to long-lived radium, particularly in painters of luminous dials, but also radium chemists or persons treated with radium salts for a possible therapeutic effect [86R2, 94R1]. These persons became internally contaminated with pure ^{226}Ra ($t_{1/2}$ = 1,600 years) in some cases, and in other cases with various mixtures of ^{226}Ra and ^{228}Ra ($t_{1/2}$ = 5.8 years). Bone cancers and head sinus carcinomas have arisen in these populations. The majority of these cancers had appeared by 1969, although three bone tumours have appeared since then and more recently head cancers have appeared at a greater rate than bone cancers. The radium isotopes deposit principally in the skeleton and the bone sarcomas appear to have been induced by α particles from either the ^{226}Ra or ^{228}Ra decay series. The head sinus carcinomas are thought to be caused mainly by the accumulation of decay products of radon (^{222}Rn) gas in the frontal sinuses and mastoid air cells. This radon is produced by the decay of ^{226}Ra in the bone.

Except for the bone sarcomas and head sinus carcinomas no definite excess in other types of malignancy, including leukaemia, is presently ascribed to the internal deposition of long-lived radium. The follow-up study on this population was essentially discontinued in the USA in the mid 1990s.

2.4.4.2 Radium-224 patients

The effects of intakes of radium has also been studied in German patients injected with ^{224}Ra shortly after World War II. The study group consists of a population of 682 adults and 218 juveniles (age at first injection varied between 1 and 20 years) who received weekly or twice weekly intravenous injections of ^{224}Ra, mainly for the treatment of bone tuberculosis or ankylosing spondylitis [86M1, 94S5]. The last bone tumour occurred in 1988, 41 years after the injection of ^{224}Ra into a three-year-old boy and is the only bone sarcoma reported in this series since 1974. Very few new tumours are now expected and follow-up of the population is now limited.

Based on the information on the incidence of bone cancers following intakes of ^{224}Ra and average bone dose from its deposition in the skeleton, ICRP [91I2] has adopted a total risk estimate for fatal cancer of 5×10^{-4} Sv^{-1} (assuming a radiation weighting factor w_R for α-particle irradiation of 20).

2.4.4.3 Miners exposed to radon

An increased mortality from lung disease has been observed in under-ground miners working in Czechoslovakia, Canada, United States of America and Sweden exposed to radon (^{222}Rn) and its decay products [88B3, 98B5].

The increase in mortality from lung cancer has been correlated with air concentrations of radon in different mines and the duration of exposure. Bronchial stem cells and secretory cells in the airways are considered to be the main target cell for the induction of lung cancer resulting from radon exposure. There are many difficulties in calculating the radiation dose to these cells as a result of exposure to radon

decay products (expressed in working level months[1]). The radiation dose over the working life must be taken into account and the dust loading of the atmosphere known as it determines the extent of the uptake of radon decay products onto the respirable particles. In addition to any possible synergistic effects between smoking and radon exposure, the presence of dust, diesel fumes and other possible carcinogens in the mine atmosphere causes some uncertainty as to whether an excess of cancer can be attributed to radiation alone. The BEIR VI Committee [98B5] recommended two models for estimating radon risks based on its analysis of the data on radon-exposed miners, without expressing a preference for either. One of the BEIR VI models takes account of factors such as total exposure, age and average radon concentration. Risks predicted under the latter model are about 50 % greater than those based on the former model. The BEIR VI Committee also considered both multiplicative and submultiplicative versions of these models. The risk predicted for smokers under the submultiplicative form of each model is only slightly smaller than that based on the multiplicative version. In contrast, the risk for non-smokers under the submultiplicative assumption is about twice that under the multiplicative version of the corresponding model.

Based on the various combinations of the BEIR VI models, the lifetime risk of lung cancer for smokers in the UK would lie in the range 10 %-15 %, while that for non-smokers would be in the range 1 %-3 %. For a general population of smokers and non-smokers, the range in lifetime risks would be about 3 %-5 %. The BEIR VI model can also be used to calculate total risks of lung cancer in a population in absolute terms. Thus in the UK population lung cancers attributable to the mean domestic radon concentration of 20 Bq m^{-3} would be in the range of 2000-3300 per year, based on the above models. Taking into account the proportion of non-smokers in the population, it can be estimated that about 500-1300 of radon-associated deaths would arise among non-smokers.

For a working population, ICRP [91I2] have adopted a risk factor for lung cancer of 0.68×10^{-2} Sv^{-1} based on data from the the A-bomb survivors.

2.4.4.4 Thorotrast patients

Thorotrast is colloidal thorium dioxide. In the late 1920s it began to be injected into the arteries of patients for use in diagnostic radiology as an X-ray contrast material. The average dose of about 25 ml of Thorotrast contained 5 g of thorium with an activity (from α-particles) of about 20 kBq ^{232}Th with additional radioactivity from its decay products. The colloidal Thorotrast was cleared from the bloodstream by uptake into phagocytic cells depositing about 60 % in liver, 30 % in spleen and 10 % in red marrow. Extensive epidemiological studies in Portugal, Sweden, Denmark, the United States, the Federal Republic of Germany and Japan have shown that retention of thorium dioxide particles in the liver and in the bone marrow resulted in an increased risk of liver tumours and leukaemias as well as liver cirrhosis and other cardiovascular diseases [84V1, 94V2]. On the basis of an injected dose of 25 ml the dose to the liver is estimated to be 0.25 Gy y^{-1} (high-LET). Present estimates, based on a latent period of 20 years, suggest a lifetime risk of liver cancer following exposure to Thorotrast of about 0.15×10^{-2} Sv^{-1} (assuming a w_R for α-particle irradiation of 20), about half this risk is expected to be expressed by 40 years after exposure [88B3, 91I2].

[1] 1 WL is any combination of the short-lived decay products of radon per litre of air which will result in the ultimate emission of 1.3×10^5 MeV of α particle energy. A WLM results from exposure to a concentration of decay products in air of 1 WL for an average working month of 170 hours.

2.4.5 Dose and dose rate effectiveness factors (DDREFs)

Risk coefficients for radiation-induced cancer are based mainly on population groups exposed at high doses and high dose rates as described above. Studies at the molecular, cellular, tissue and whole animal level have demonstrated that radiation damage increases with dose and that, at least for low-LET radiation, at high dose rates it is often greater per unit of exposure than at low dose rates. Thus, although the assumption normally made for radiation protection purposes is that the dose-response curve for cancer induction is linear, with the risk proportional to dose, in practice a dose and dose rate effectiveness factor (DDREF) has commonly been used to allow for a reduced effectiveness of radiation in inducing cancer in man at low doses and low dose rates. The choice of a suitable DDREF has caused considerable debate with relevant data being available from cellular and animal studies, as well as human epidemiology.

ICRP in its 1990 recommendations based estimates of DDREF principally on an analysis by Pierce and Vaeth [89P2] of the data from the Japanese survivors. This analysis shows that the data do not allow for a reduction factor of much more than about 2. Other epidemiological data showed little evidence of dose rate effects although studies on thyroid cancer incidence [85S4] and breast cancer mortality [89M3] indicate possible reduction factors of up to 3 or 4. As a consequence ICRP adopted a DDREF of 2, recognising that 'the choice is somewhat arbitrary and may be conservative'. In practice, the DDREF would be expected to vary with tissue and with exposure conditions although a single value had to be assigned for protection purposes. A better understanding of the mechanisms involved will be essential for improving understanding of the effects of both dose and dose rates on radiation-induced tumour induction in man. A summary of values of DDREF recommended by national and international bodies is given in Table 2.7. No DDREF is recommended for high-LET radiation (i.e. DDREF = 1).

Table 2.7. Summary of dose and dose rate effectiveness factors for radiation-induced cancer

Source	Reference	DDREF
ICRP 1977	77I1	2
NCRP 1980	90N2	2-10
UNSCEAR 1986	86U4	up to 5
UNSCEAR 1988	88U5	2-10
BEIR 1990	90B4	2
ICRP 1991	91I2	2
UNSCEAR 1993	93U6	<3
UNSCEAR 2000[a]	00U8	<3

a) 3 for hereditary disease

2.4.6 Risk coefficients for protection

In the last few years a number of reports have been published which have calculated risks of radiation-induced cancer for different populations. They have been based predominantly on information derived from the A-bomb survivors but supplemented by data from other epidemiological studies as summarised above. Most risks have been calculated for the general population, although a number of reports have also given risks for workers. These tend to be lower (by about 20-40 %) because of the greater risk to children and young persons calculated using the relative risk projection model for most solid cancers.

The assumption made for protection purposes is that the incidence of radiation-induced cancer increases with the dose, with no threshold. Thus they are stochastic in nature. Tables 2.8 and 2.9 summarise the information on risks of radiation-induced cancer at high doses and high dose rates published in recent years by UNSCEAR [88U5, 00U8], BEIR [90B4], NRPB [93M4] and ICRP [91I3], using mainly relative risk projection models for most solid cancers. In the majority of studies lifetime risks of cancer have been calculated, although NRPB also gave risks to 40 years after exposure (the then period of follow-up of the A-bomb survivors). UNSCEAR [88U5] calculated risks based on both an age-

averaged and an age-specific constant relative risk models. BEIR V [90B4] calculated risks to a US population and gave values for a number of tissues using time-varying relative risk models for some cancers (leukaemia, respiratory tract, breast cancer in females). It is noteworthy that BEIR V, unlike UNSCEAR, calculated excess cancer deaths, not early deaths. The former risk is about 20-25 % less than the latter reflecting the baseline cancer rate in the population. ICRP [91I2] calculated risks for a 'world' population based on an average value for five populations (Japan, UK, USA, Puerto Rico, China) and on transferring both absolute and relative risks across populations.

Table 2.8. Estimated lifetime fatal cancer risks in populations (all ages, both sexes) associated with exposure to low-LET radiation at high doses and high dose rates, based on a multiplicative projection model

Source	Reference	Population	Fatal cancer risk [10^{-2} Sv^{-1}]
UNSCEAR 1977	77U2	-	2.5[a]
UNSCEAR 1988	88U5	Japan	7-11[b]
BEIR V 1990	90B4	USA	7.9[c]
ICRP 1991	91I2	Five nations	10.0[d]
Muirhead 1993	93M4	UK	4.9 - 11.80

a) additive model
b) range based on age-averaged and age-specific constant relative risks
c) see text (Section 2.4.6)
d) average value based on US, UK, Japan, Puerto Rico and Chinese populations. Risk for workers 8.0×10^{-2} Sv^{-1}
e) risk calculated to 40 years after exposure and lifetime assuming age-specific relative risks. Risk for workers 5.9-10.1 $\times 10^{-2}$ Sv^{-1}.

Note: These values are for acute doses only and do not include an adjustment for dose rate.

Table 2.9. Lifetime fatal cancer risks given by UNSCEAR 2000 [00U8].

	Fatal cancer risk	
	1 Sv	0.1 Sv
Leukaemia	1 %	0.05 %
Solid Cancers		
Males	9 %	0.9 %
Females	13 %	1.3 %

NOTE: These values are for acute doses only and do not include an adjustment for dose rate

Overall the lifetime risks calculated in recent years are not too different for the various studies, the lowest value being for UNSCEAR [88U5] using age-averaged risk coefficients. ICRP [91I3] adopted a rounded value of 10×10^{-2} Sv^{-1} for the risk coefficient for fatal cancer at high doses and high dose rate following exposure of a mixed population of all ages. Applying a DDREF of 2 gives a risk of 5×10^{-2} Sv^{-1} for radiation protection purposes. Risk coefficients for individual tissues are given in Table 2.10. For workers the risk coefficient adopted for radiation protection purposes is 4×10^{-2} Sv^{-1}. These risk coefficients have been used by ICRP in developing the dose limits given in the 1990 recommendations [91I3] and provide the basis for the International Basic Safety Standards [96I5] and the European Basic Safety Standards [96E2].

Table 2.10. Risk coefficients for fatal cancer adopted by ICRP

	Fatal cancer risk coefficient [10^{-2} Sv^{-1}]		
		ICRP 1991[b]	
Organ or tissue	ICRP 1977[a]	Population	Workers
Bladder		0.30	0.24
Red bone marrow	0.20	0.50	0.40
Bone surface	0.05	0.05	0.04
Breast	0.25	0.20	0.16
Colon		0.85	0.68
Liver		0.15	0.12
Lung	0.20	0.85	0.68
Oesophagus		0.30	0.24
Ovary		0.10	0.08
Skin		0.02	0.02
Stomach		1.10	0.88
Thyroid	0.05	0.08	0.06
Remainder	0.50	0.50	0.40
Gonads (hereditary disease)	-	-	-
Total	1.25	5.0	4.0

a) 77I1
b) 91I2

2.4.7 Low dose studies

The majority of studies on which risk estimates for radiation-induced cancer are based are for populations exposed at high doses and high dose rates. Studies of low dose rate exposure generally involve low doses and because of the likely low excess risks are hampered by lack of statistical power and possibly also by confounding factors. However low dose rate studies can provide a check on the risks derived by extrapolation from high dose rate studies. The main studies of interest are on workers who are occupationally exposed although some data are also available on risks in children following exposures *in utero* and on persons from areas of high natural background.

2.4.7.1 Occupational exposures

Several studies have been conducted of nuclear industry workers. In the USA, Gilbert *et al*, [89G1] performed a joint analysis of data for about 36,000 workers at the Hanford site, Oak Ridge National Laboratory and Rocky Flats weapons plant. Neither for the grouping of all cancers nor for leukaemia was there an indication of an increasing trend in risk with dose.

In 1976 NRPB set up the National Registry for Radiation Workers (NRRW). The NRRW was designed to investigate the effects of occupational exposures to ionising radiation by direct epidemiological observations. The first analysis of the NRRW was published in l992 [92K2]. The main findings were:

- a strong “healthy worker effect”,
- a statistically significant trend in leukaemia risk with dose, and
- weaker evidence of a trend with dose for solid tumours.

A “healthy worker effect” means that death rates in the group of workers studied are lower than in a group of the general population of the same age and sex. This is a common finding in epidemiological studies of working populations. The observation of a healthy worker effect in the NRRW cohort was reassuring, but not unexpected. The more important findings were a trend with dose for leukaemia and a (non-significant) trend for solid tumours. The risk factors in the first NRRW analysis were compatible with those recommended by the ICRP but the confidence intervals were wide.

To obtain more precise information on the risks of radiation work NRPB carried out a second analysis of the NRRW with a larger cohort and a longer period of follow-up [99M6]. A comparison of the main features of the two studies is shown in the box.

Comparison of NRRW cohorts for the first and second analyses

	First	Second
No. of Workers	95,217	124,743
Collective dose [man Sv]	3,198	3,810
Mean dose [mSv]	33.6	30.5
Person-years	1.2 million	2 million
Total deaths	6,660	12,972

The second NRRW analysis provided further information on mortality among UK radiation workers. As in the first analysis, there was a strong healthy worker effect, with mortality from all causes and all malignancies less than that expected from national rates. The 90 % confidence intervals for the trend in cancer risk with external dose are tighter than before, and they now exclude values more than four times those seen among the Japanese A-bomb survivors, although they are also generally consistent with no raised risk. For leukaemia excluding chronic lymphatic leukaemia (CLL) there is evidence, of borderline statistical significance, of an increasing risk with dose and, as with solid cancers, the data are consistent with the A-bomb findings. Further analyses should provide more information on risks in relation to occupational radiation exposure.

A combined analysis of mortality among 95,673 workers (85.4 % men) in the US, the UK and Canada has been published [95C1]. The combination of the data from the various studies increases the overall power to study associations between radiation and specific cancers. The combined analysis covered a total of 2,124,526 person-years (PY) at risk and 15,825 deaths, 3,976 of which were due to cancer. As with the NRRW, mortality from leukaemias, excluding CLL was significantly associated with cumulative external radiation exposure. There was no evidence of an association between radiation dose and mortality from all cancers. It was concluded that the results of the study did not suggest that current radiation risk estimates for cancer at low levels of exposure are appreciably in error.

2.4.7.2 Background radiation

Studies of exposure to natural radiation (other than radon) have generally involved looking for any geographical correlation with cancer rates. Such studies are difficult to interpret, however, owing to the effect of confounding factors such as socio-demographic variables and other factors that vary geographically.

2.5 Hereditary disease

Radiation damage to the male and female germ cells, resulting in an increase in hereditary disease, is the other main late effect resulting from exposure to ionising radiation. Only very limited data on genetic damage are available from human populations and estimates of risk have to be derived mainly from animal studies.

2.5.1 Categories of genetic damage

Inheritance is the process by which the genetic information carried by the DNA in the cell nucleus is passed from one generation to the next. This is essentially an orderly process but mutations do arise spontaneously giving a positive background level of genetic damage. Hereditary effects may occur by changes arising in the base sequence in the DNA of a single gene leading to gene mutation, or by rearrangement of collections of genes within and between chromosomes causing chromosomal aberrations. Both may be produced by radiation.

There are three main types of gene mutation namely dominant, recessive and X-linked. Every individual receives a set of genes from each parent. If dominant, a gene mutation in one set of genes but not in the other can express itself in spite of its counterpart from the other parent being normal. A recessive gene mutation cannot be expressed unless the genetic material from both parents carries the same mutation. Females have two X chromosomes and males one X and one Y, the Y chromosome being virtually inert apart from factors for maleness. An X-linked gene mutation can readily express itself in the male whereas in the female X-linked mutations will not express themselves unless both X chromosomes carry the same mutation.

The normal chromosome number in man is 46. Chromosomal mutations are due to alterations in chromosome numbers or structure. If the number of chromosomes is increased or decreased in the fertilised egg this produces such profound effects that, except in a few instances, death is likely to occur soon after conception; if a child survives it is likely to have severe physical and/or mental defects. There is at present no good evidence for radiation-induction of diseases of chromosomal origin [82U3, 88U5].

The genetics of some inherited diseases are more complicated because some relatively common chronic diseases have a genetic element but additional factors such as environment play a part in their expression. Changes in the mutation rate will also alter the incidence of these 'multifactorial' diseases. Examples of various categories of hereditary diseases have been reviewed by UNSCEAR [77U2]; examples are given in Table 2.11.

Most live-born children with inherited chromosomal mutations exhibit mental and/or physical abnormalities. There is little or no chance of sufferers who reach adulthood reproducing and so passing these defects on to their children. These conditions are therefore maintained in the population by new mutations arising either spontaneously or induced by an environmental insult such as radiation. Dominant mutations show up in the first generation after exposure as do X-linked mutations in males and may occur in subsequent generations if they do not prevent childbearing. Recessive mutations, however, tend to occur in later generations. When assessing the risks of radiation it is therefore necessary to allow for hereditary effects which may not appear for several generations.

Table 2.11. Examples of hereditary diseases [77U2].

Dominant disorders
Congenital cataract
Cystic kidney disease
Huntington's chorea (progressive mental retardation)
X-linked diseases
Haemophilia
Albinism
Colour blindness
Heart valve defects
Autosomal recessive diseases
Cretinism
Disorders of amino acid metabolism
Aplastic anaemia
Muscular dystrophy
Multifactorial diseases
Ankylosing spondylitis
Varicose veins
Cleft palate
Diabetes mellitus
Schizophrenia
Asthma
Chromosome anomalies
Down's syndrome

2.5.2 Risk coefficients for hereditary disease

So far no hereditary effects at levels that are statistically significant have been observed in human populations exposed to radiation [88U5]. Neel *et al* [89N4] have reviewed all the genetic studies in Hiroshima and Nagasaki on the children born to irradiated survivors. The 'end points' considered were congenital defect, survival of liveborn infants, sex-chromosome aneuploidy and balanced chromosomal exchanges, cancer with onset below age 20, mutations altering protein charge or activity, sex ratio, and physical growth and development. The average conjoint parental gonad exposures for the parents was about 0.5 Gy (based on DS86 dosimetry), the exact figure depending on the radiation histories of the parents whose children formed the basis for a specific end point. No statistically significant effects were observed. Taken together, the data suggest a lower limit for the doubling dose for genetic damage following acute irradiation of approximately 1.4-1.8 Sv. This compares with a value of 0.3 Sv in the mouse for acute exposure and 1 Sv for chronic exposure. The assumption made in calculating risks for radiation protection purposes is that the incidence of radiation-induced hereditary disease increases with the dose, with no threshold. Thus they are stochastic in nature.

In the absence of direct quantitative human data, animal studies have been used by UNSCEAR [88U5] to assess the risk of radiation-induced hereditary disease in human populations. Tables 2.12 and 2.13 gives some estimates of the incidence of hereditary diseases in a population recommended by UNSCEAR and ICRP in recent years. They are based on a doubling dose for hereditary disease of 1 Gy derived from animal studies. In the most recent report by UNSCEAR [01U9] the risk of radiation-induced hereditary disease has been appreciably reduced compared with its previous advice.

Table 2.12. Incidence of genetic disease at equilibrium from parental exposure.

Disease classification	Incidence (low-LET)[a] [10^{-2} Gy^{-1}]				
	UNSCEAR, 1977 [77U2]	ICRP, 1977 [77I1]	UNSCEAR, 1982 [82U3]	UNSCEAR, 1988 [88U5]	ICRP, 1991 [91I2]
Chromosomal anomalies	0.4		0.04	0.04	0.04
Dominant and X-linked	1.0		1.0	1.0	1.0
Recessive	-		-	0.15	0.15
Multifactorial	0.45		0.45	-	3.5[b]
Total	1.85	2.0	1.49	1.19	2.4

a) Assuming doubling dose of 1 Gy.
b) Severity less than other genetic diseases, weighted by factor of 1/3.

Table 2.13. Incidence of genetic disease from one-generation exposure to low-LET, low dose rate or chronic radiation [01U9].

Disease class	Baseline frequency per 10^6 live births	Incidence (low-LET)[a] [10^{-2} Gy^{-1}]	
		1st generation	2nd generation
Chromosomal anomalies	4,000	-	-
Dominant and X-linked	16,500	0.075-0.15	0.05-0.10
Recessive	7,500	-	-
Multifactional			
Chronic multifactional	650,000	~0.025-0.12	~0.025-0.12
Congenital anomalies	50,000	~0.2	~0.04-0.10
Total	738,000	~0.3-0.47	0.11-0.32

a) Assuming doubling dose of 1 Gy

In its most recent recommendations ICRP [91I2] gives a risk of hereditary disorders of 2.4×10^{-2} Sv^{-1} expressed over all generations following exposure of either parent (Table 2.12). This risk factor includes a risk factor for multifactorial diseases. At present the information on such diseases is very limited and only a tentative value is available. ICRP [91I2] have assessed the risk as 3.5×10^{-2} Sv^{-1} following exposure of either parent. The severity of multifactorial diseases are considered to be not as great as other hereditary diseases so they are weighted by a factor of three, giving a risk factor of 1.2×10^{-2} Sv^{-1}. The genetically significant exposure in a population will be less than this because a proportion of the population are older than child bearing age. If the mean age of child bearing is 30 years and average life expectancy is 75 years then the probability of genetic harm resulting from exposure of the entire population is 30/75 ($= 0.4$) $\times 2.4 \times 10^{-2}$ $Sv^{-1} \approx 10^{-2}$ Sv^{-1} [91I2] (Table 2.14).

For a working population the reproductive fraction is less than the entire population. For a working population, the reproductive fraction is (30-18)/(65-18) = 0.25. The risk factor for workers is thus about 0.6 of that for an entire population (0.25/0.4) giving a risk factor for workers of 0.6×10^{-2} Sv^{-1} (60 % of 1×10^{-2} Sv^{-1}) (Table 2.14).

2.6 Irradiation *in utero*

For the developing embryo and fetus there is evidence that deterministic effects, severe mental retardation and cancer induction may occur following irradiation *in utero*. The risk of hereditary disease may be taken to be the same as after birth.

2.6.1 Deterministic effects

Evidence of the deterministic effects of radiation on the embryo and fetus is derived almost entirely from animal experiments. It is necessary to extrapolate the results of these studies to predict the consequences of radiation exposure in man.

The effects of radiation on the embryo depend on the time of exposure relative to its development. When the number of cells in the embryo is small (i.e., in the first few days after fertilisation) and they are not yet specialised, damage is frequently seen in animals as failure of the conceptus to implant or loss of embryos, which would be seen in humans as miscarriage. However, recent evidence from *in vitro* human embryo research has shown that the survival of even one cell in the early embryo before implantation can allow normal development of cells to occur, since all the necessary genetic components are present in each cell of the embryo at this early stage of development. The consequences of any of these cells carrying a point mutation are unquantified, but the possibility of stochastic effects occurring cannot be dismissed.

Malformations have been observed in rodent embryos at a stage when organs such as the brain, skeleton, eyes and heart are developing. Congenital abnormalities are commonly found in the offspring of rodents but any attempts to project the results to predict effects in man are fraught with difficulties.

With this cautionary note and bearing in mind, proposed human threshold doses for radiological protection purposes for low-LET radiation: 0.05 Gy for reabsorption of pre-implantation embryos; 0.05 Gy for minor skeletal abnormalities; 0.2 Gy for functional disorders of the central nervous system; and between 0.2 and 0.5 Gy for serious skeletal abnormalities and growth retardation, such information provides a basis for guidelines to ensure that pregnant women are adequately protected [03I1]. Protraction of the dose will reduce any effect.

2.6.2 Brain function

The human brain is probably the most complex organ in the body and its proper development and function depend upon an elaborate sequence of events which must be coordinated temporally and spatially. Any disturbance of this sequence could lead to abnormality since the normal function of the nervous system depends upon the proper location of the neuronal cells.

A study of about 1600 children exposed *in utero* at Hiroshima and Nagasaki to various radiation doses and at various developmental stages has shown about 30 cases of clinically severe mental retardation with a greater incidence than expected in the higher dose groups. Excess mental retardation was not observed following exposure up to 8 weeks from conception, was at a maximum between 8 and 15 weeks and then was somewhat lower between 16 and 25 weeks. No effect was observed following exposures later than 25 weeks [84O2; 88O3].

The period of maximum sensitivity (8-15 weeks) corresponds with the timing of both of the major waves of neuronal proliferation and migration within the cerebral cortex. Although the number of cases is small, the data indicate an excess probability of 40% at 1 Sv received during the 8-15 weeks after conception. The current results of IQ tests amongst those children exposed *in utero* indicates a general downward shift in the distribution of IQ with increasing dose. A coefficient of about 30 IQ points Sv^{-1} relates to *in utero* exposure between 8-15 weeks after conception. A smaller shift is identified in the 16-25 week period [88S1].

This downward shift in IQ of 30 points Sv^{-1} shown schematically in Figure 2.10 is consistent with the observation of an incidence of 0.4 for a dose of 1 Sv. At doses of the order of 0.05 Sv, no effect would be detectable in the general distribution of IQ, but at somewhat larger doses the effect might be sufficient to show an increase in the numbers classified as seriously mentally retarded. The net result is that the end point of serious mental retardation would appear to demonstrate a threshold, which is reasonably consistent. The ICRP now believes that the phenomenon is deterministic with a threshold related to the minimum shift in IQ that can be measured. It is not therefore included in the definition of radiation detriment used for protection purposes.

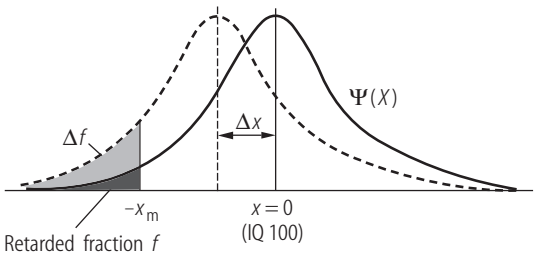

Fig. 2.10. The shift to the left from $\psi(x)$ by Δx (30 IQ points) increases the background retarded fraction f by Δf. $-x_m$ denotes the number of standard deviations below IQ 100 to classify an individual as mentally retarded [91I2].

2.6.3 Risk coefficients for cancer

Information on the risk of cancer following irradiation *in utero* has been reviewed by UNSCEAR [72U1, 77U2] and by the BEIR-III Committee [80B2]. Current risk estimates for radiation-induced childhood cancer are based mainly on data collected in the Oxford Survey of Childhood Cancers (OSCC) concerning obstetric radiography [75B6]. This study contains information on over 150,000 childhood cancer deaths in Great Britain during 1953-81 and the same number of matched control children [87K3]. The OSCC, in common with other, smaller, case-control studies, indicates a relative risk of about 1.4 (40 % increase in risk) for childhood cancer associated with prenatal irradiation [89B7]. Concerns about possible bias and confounding in these case-control studies have been raised – for example, by Boice and Miller [99B8] – in view of issues such as the lack of evidence for a raised risk from cohort studies, and the similarity of the relative risks for leukaemia and other cancers in the OSCC. In their review of these issues, Doll and Wakeford [97D2] concluded that there is strong evidence against bias and confounding as alternative explanations for the raised risks seen in the OSCC and other case-control studies. The doses received by the fetus are uncertain; based on estimated average doses of about 10-20 mGy. Based on data from the OSCC and information from UNSCEAR [72U1] on doses received *in utero* from obstetric radiography the number of excess cancer cases (to 15 years of age) following irradiation *in utero* is calculated to be about 6×10^{-2} Gy^{-1} [93M4]. Since slightly less than 50 % of childhood cancers consist of leukaemia and other lymphatic/haematopoietic cancers [81O1] and the relative risks are similar for these and other cancers, a risk of 2.5×10^{-2} Gy^{-1} is calculated for leukaemia and 3.5×10^{-2} Gy^{-1} for solid cancers. As approximately half of all childhood cancers are fatal [81O1], the number of excess cancer deaths is calculated to be 3×10^{-2} Gy^{-1} (low-LET), comprising 1.25×10^{-2} Gy^{-1} for leukaemias and 1.75×10^{-2} Gy^{-1} for solid cancers. These risks are derived principally from follow-up studies on children irradiated *in utero* with radiation doses up to a maximum of 10-20 mGy (low-LET). They are therefore applicable for estimating risks at low doses and dose rates. There is also likely to be an additional risk of cancer that will appear late in life but the information is very limited. In addition, follow-up of persons exposed to A-bomb radiation *in utero* in Hiroshima and Nagasaki indicates that the raised cancer risk continues into adulthood, although quantification of this risk is difficult [88Y1, 97D1].

2.6.4 Hereditary disease

Hereditary disease is considered in Section 2.5. Genetic studies in the offspring of atomic bomb survivors have not shown any significant radiation-related increases in any measure of genetic damage employed. In experiments in mice the sensitivity of fetal gonads was comparable to that of adult gonads or a little lower [74S2]. It is therefore assumed that the risks of hereditary disease from *in utero* irradiation are the same as after birth (2.4×10^{-2} Sv^{-1}) following exposure of either male or female germ cells. It may be the risk will be lower in early embryogenesis and fetogenesis prior to the establishment of germinal tissues.

2.7 Summary of risk factors for cancer and hereditary disease

The ICRP, in its most recent 1990 recommendations [91I2], considers four components of the detriment (health effects) due to irradiation of the tissues and organs of the body at low doses when assessing the overall effects of radiation. These include the probability of fatal cancer; the probability of non-fatal cancer and the probability of severe hereditary disease, both weighted for severity relative to fatal cancer; and the time scale of appearance of these detrimental effects. The risk factors developed by ICRP for protection purposes are summarised in Table 2.14. The overall weighted severity values assigned to the non-fatal cancers and severe hereditary diseases (including multifactorial diseases) each amount to about one-fifth of the detriment associated with fatal cancer. In summary the aggregated detriment amounts to 7.3×10^{-2} Sv^{-1} for a nominal population. It is somewhat less (5.6×10^{-2} Sv^{-1}) for a population aged 18-64 years who are occupationally exposed, when account is taken of the omission of younger persons who are more radio-sensitive and the shorter mean potential period of reproduction. The temporal pattern of fatal cancer risk is such that the period of maximum risk occurs in the seventh and eighth decades of life if the multiplicative projection model is used to calculate the lifetime expression of the cancers in persons exposed continuously to small annual doses at or below the dose limits.

Table 2.14. Risk factors for protection [10^{-2} Sv^{-1}] [77I1, 91I2]

		ICRP 1991	
	ICRP 1977	Public	Workers
Fatal cancer	1.25	5.0	4.0
Hereditary defects	0.4[a]	1.0[b]	0.6[b]
Total	1.65	6.0	4.6
Total (weighted)[c]	-	7.3	5.6

a) Two generations
b) All generations
c) To allow for non-fatal cancers and years of life lost for cancers and hereditary disease.

2.8 Conclusions

Deterministic effects in tissues and organs are the result of the loss of substantial numbers of stem cells, thereby cutting off the supply of functional cells. The consequence can be a temporary or permanent loss of tissue function which may be life threatening. A characteristic of the dose-response relationship for deterministic effects is that they are avoidable below a dose threshold. This is a reflection of sufficient numbers of stem cells maintaining functional cell populations. Knowledge of dose thresholds has been derived from the tolerance doses observed in radiotherapy. The tolerance doses vary with the tissue - the gonads, the bone marrow, the gastrointestinal and the lens of the eye being the most sensitive. It is the opinion of the ICRP that deterministic effects can be avoided if the presently recommended effective dose limits (based upon limiting stochastic effects) and the annual equivalent doses for the lens of the eye and the skin are not exceeded.

There are a number of important questions that remain to be answered in the assessment of the risks of radiation-induced cancer in human populations. Very limited information is available at the low doses and low dose rates that are important for radiation protection purposes and the risks have to be assessed from populations exposed at high doses and dose rates by applying an appropriate dose and dose rate effectiveness factor. Increasingly, however, epidemiological studies on groups of workers in the nuclear industry are providing information on exposures at low doses and dose rates although at present any estimates of risk have large uncertainties associated with them. With the development of these national studies and by pooling them internationally these uncertainties should be progressively reduced.

Continued follow-up of exposed populations, in particular the A-bomb survivors in Japan is needed for validating current lifetime projection models. It seems unlikely that epidemiological studies will be able to answer all the questions concerned with the effects of dose, dose rate, radiation quality and individual sensitivity to cancer induction. Ultimately this must depend on a much better understanding of the response of tissues to radiation. This will come increasingly from cellular and molecular studies designed to understand the fundamental mechanisms involved in cancer induction.

The assumption made for protection purposes is that the incidence of radiation-induced cancer and hereditary disease increases with the dose, with no threshold. Thus it is not possible to completely prevent any risks. Protection standards must, therefore, be set to keep any risk to an acceptable level.

Table 2.15 gives a chronology of the first century of radiation protection.

Table 2.15. Chronology of the first century of radiation protection

Year	Event	Investigator
1895	Discovery of X-rays (November 8)	Roentgen
1896	X-ray report made public (January 3)	
	Discovery of radioactivity (February)	Becquerel
	First reports of possible X-ray injury;	Edison
	Damage to eyes (March 3)	Morton
	Skin effects first noted (April 18)	Stevens
1901	X-ray lethality to mammals demonstrated experimentally	Rollins
1904	First death in X-ray pioneer attributed to cumulative overexposure (October)	Dally
1906	Law of radiosensitivity of tissues put forth	Bergonie Tribondeau
1911	International radium standard and Curie unit	Curie
1915	British Roentgen Society adopts radiation protection recommendations	
1920	First Standing X-ray Protection Committee	ARRS
1921	British X-ray and Radium Protection Committee issues first memorandum	
1925	First “tolerance dose” proposed	Mutscheller
1927	Genetic effects of X-rays shown (drosophila)	Müller
1928	Roentgen unit formally adopted, International X-ray and Radium Protection Committee formed (forerunner of ICRP)	
1929	US Advisory Committee on X-ray and Radium Protection formed (forerunner of NCRP)	
1931	USACXRP publishes first recommendations - 0.2 R/day	
1932	Concept of greater permissible dose for partial body irradiation (hands) introduced	Failla
	Discovery of neutrons	Chadwick
1934	ICXRP recommends permissible dose of 0.2 R/day	
1936	USACXRP recommends reduction in permissible dose to 0.1 R/day	
1941	USACXRP recommends adoption of maximum body burden of 0.1 μCi for radium	
	Suggested maximum permissible dose of 0.02 R/day	Taylor
1944	Maximum permissible concentration for inhaled radioactivity introduced	Parker
	Rem and Rep introduced	Parker
1950	ICRP set up	
1991	Publication of 1990 Recommendations of ICRP	

Please Note: Work on preparation of this Chapter was completed in March 2002. Readers should note that ICRP is planning to issue new recommendations on radiological protection in 2005. This will take into account more recent information on health effects published since its 1990 recommendations [91I2].

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