INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION

Committee 1 Task Group Report: C1 Foundation Document (FD-C-1)

Biological and Epidemiological Information on Health Risks Attributable to Ionising Radiation: A Summary of Judgements for the Purposes of Radiological Protection of Humans

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The *following summary statements relate largely to the health effects of radiation in the dose range up to a few tens of mSv for the purposes of radiological protection.*

- **For cancer and hereditary disease at low doses/dose rates the use of a simple proportionate relationship between increments of dose and increased risk is a scientifically plausible assumption.**

- **A dose and dose-rate effectiveness factor (DDREF) of 2 recommended in *Publication 60* should be retained for radiological protection purposes; the effect of introducing the uncertain possibility of a low dose threshold for cancer risk is judged to be equivalent to that of an uncertain increase in the value of DDREF.**

- **Proposed changes in radiation weighting factors for protons and neutrons are noted; these judgements are fully developed in the ICRP Committee 2 Foundation Document. *"Basis for dosimetric quantities used in radiological protection"(FD-C-2).***

- **New radiation detriment values and tissue weighting factors have been proposed; the most significant changes from ICRP 60 relate to breast, gonads and treatment of remainder tissues.**

- **Detriment adjusted nominal probability coefficients for cancer are $5.9\ 10^{-2}\ Sv^{-1}$ for the whole population and $4.6\ 10^{-2}\ Sv^{-1}$ for adult workers; the respective ICRP60 values are $6.0\text{-}10^{-2}\ Sv^{-1}$ and $4.8\ 10^{-2}\ Sv^{-1}$.**

- **Detriment adjusted probability coefficients for hereditary disease up to the second generation are $0.2\ 10^{-2}\ Sv^{-1}$ for the whole population and $0.1\ 10^{-2}\ Sv^{-1}$ for adult workers; the respective ICRP60 values are $1.3\ 10^{-2}\ Sv^{-1}$ and $0.8\ 10^{-2}\ Sv^{-1}$ but these relate to risks at a theoretical equilibrium and no longer seem justified**

- **Cancer risk following *in-utero* exposure is judged to be no greater than that following exposure in early childhood.**

- **Knowledge of the roles of induced genomic instability, bystander cell signalling and adaptive response in the genesis of radiation–induced health effects is insufficiently well developed for radiological protection purposes; in many circumstances these cellular processes will be incorporated in epidemiological measures of risk.**

- **Genetic susceptibility to radiation-induced cancer involving strongly expressed genes is judged to be too rare to appreciably distort**

estimates of population risk; the potential impact of common but weakly expressing genes remains uncertain.

- **Dose responses for radiation-induced tissue reactions (deterministic effects) in adults and children are, in general, judged to have true dose thresholds which result in the absence of risk at low doses; a reduction in the dose threshold for cataract induction (visual impairment) is proposed.**

- **Dose responses for *in-utero* radiation-induced tissue reactions, malformations and neurological effects are also judged to show dose thresholds above a few tens of mGy; uncertainty remains on the induction of IQ deficits but at low doses the risk is judged to be insignificant.**

- **Risks of non-cancer disease at low doses remain uncertain and no specific judgement is possible.**

1. Introduction

Since the publication of the 1990 Recommendations of the ICRP (*Publication 60*, ICRP 1991), ICRP Committee 1 has continued to maintain broad surveillance on scientific developments regarding the quantification of health effects attributable to radiation exposure and the biological mechanisms that underlie these effects. Much of the output of Committee 1 is represented in ICRP Task Groups reports and Committee 1 working parties have reviewed data in other relevant areas.

The purpose of the present Task Group report is to summarise all post-1990 Committee 1 judgements relating to the health effects of radiation in order to support the development by the Commission of its new Recommendations. In many of the areas considered in the present report, Committee 1 had already provided specific judgements, eg on the risk of multifactorial diseases *(Publication 83)* and on radiation weighting factors *(Publication 92*). However, the revision of a) judgements on the induction of tissue reactions; b) nominal risk coefficients for risks of cancer and heritable disease; c) the transport of cancer risk between different populations; and d) the choice of tissue weighting factors required much additional work from the Task Group. For this reason the above topics are covered in detail in this report.

An additional feature of the present report is the extent to which the accumulation of epidemiological and biological knowledge since 1990 has served to strengthen some of the judgements made in *Publication 60* or, in some cases, has led to a revision in procedures for risk estimation. In spite of the detailed nature of these gains in knowledge, the principal objective of this report is the provision of broad judgements for practical purposes of radiological protection. Accordingly, much of the work of the Task Group centres on the continuing use of effective dose as a radiological protection quantity for prospectively estimating risks in the population and to demonstrate compliance with dose limits. The application of the concept of effective dose is discussed in the Committee 2 Foundation Document (FD-C-2).

The report is structured in the following way. Section 2 provides a brief summary of the gains in knowledge since 1990 on the biological processes that underlie the health effects of radiation exposure. Section 3 provides updated judgements on the mechanisms and risks of radiation-induced tissue reactions. Section 4 considers the mechanisms and genetics of cancer induction, summarises previous judgements on radiation weighting factors and details new epidemiologically-based judgements on nominal risk coefficients, transport of risk, radiation detriment and tissue weighting factors; Section 4 also summarises an earlier judgement on cancer risk *in-utero*. Section 5 briefly considers non-cancer diseases after radiation. In Section 6, the Task Group details a newly developed approach to the

estimation of risks of heritable disease and provides a revised estimate of this risk. Finally, in Section 7, a simple tabular format is used to summarise the principal recommendations from the Task Group and to map these judgements to the appropriate sections of the report.

2. Interactions of Radiation with Cells and Tissues

The purpose of this section is to summarise knowledge on the interactions of radiation with cells and tissues in the body with emphasis on the information and concepts that have developed since 1990. The intention is to provide a biological framework for the judgements to be developed in subsequent sections of the report. Although some of these biological data and concepts are complex, much of this report is intended for the non-specialist reader. Consequently the report will not enter into the detail of many of the biological and biophysical debates but rather seeks clarity and simplicity on the judgements made. Details of these debates may be found in earlier ICRP publications and other reviews.

2.1 Biophysical aspects of radiation action on cells

ICRP has not specifically reviewed the broad topics of radiation biophysics and microdosimetry since 1990 but important advances and judgements are given in *Publication 92* (ICRP 2003) and in a new ICRP Task Group report on Low Dose Risks (Publication LDR-C-1). The understanding of the early post-irradiation biophysical processes in cells and tissues has advanced substantially and the following paragraphs briefly highlight some major points of development. Further information is available in *Publication 92*, *Publication LDR-C-1* and Goodhead et al 1996.

Knowledge of the fine structure of energy deposition from radiation tracks in DNA dimensions has grown, largely through the further development of Monte-Carlo track structure codes. Coupled with radiobiological information, track structure data have impacted greatly on thinking in respect of the nature of biologically critical damage to DNA.

In particular, it has been recognised that a high proportion of radiation induced damage in DNA is represented in complex clusters of chemical alterations. Such clustered damage can arise via a combination of damages induced by the main tracks, secondary electrons and secondary reactive radical species. Double and single strand breaks in the DNA sugar-phosphate backbone (DSB and SSB) plus a variety of damaged DNA bases can combine together in clusters with a substantial fraction of total damage being closely spaced. There is also evidence that both the frequency and complexity of complex clustered damage depends upon the linear energy transfer (LET) of the radiation.

When DSB, SSB and base damages are considered together, complex clustered damage may constitute as much as 60% and 90% of total DNA damage after low and high LET radiations respectively. These data highlight a major difference between DNA lesions induced by radiation and those arising spontaneously via oxidative attack by reactive chemical radicals. Whereas the former are predominantly complex and clustered

the latter are randomly distributed and simple in their chemical structure. As described in *Publication LDR-C-1* and noted in 4.1.2, the different repair characteristics of simple and complex DNA lesions is an important factor in the development of judgements on health effects after low doses of radiation.

In addition to improvements in our understanding of the induction of complex DNA damage by radiation there have been other advances in radiation biophysics. For example radiation induced damage has been investigated at the level of chromosome structure and this work has been paralleled by the biophysical modelling of the induction of gene/chromosomal mutations. There has also been valuable technical innovation including the development of single particle irradiation systems (microbeams) and of imaging methods for the cellular vizualization of DNA-protein interactions during DNA damage-response (see *Publication LDR-C-1*; Churubini et al 2001).

2.2 Chromosomal DNA as the principal target for radiation

In addition to the biophysical information outlined in Section 2.1, there is more direct evidence that implicates chromosomal DNA as the principal cellular target for biological effects. Much of the early evidence on this issue concerned the greater radiobiological effectiveness of radionuclides incorporated into DNA in the cell nucleus as compared with cellular proteins in general (UNSCEAR 1993). More recently the use of microbeam irradiation facilities capable of delivering a defined dose to different parts of the cell has fully confirmed the radiosensitivity of the cell nucleus. However as noted in Section 2.5 these microbeam techniques have also provided evidence of the potential complexity of cellular radiation response.

In addition, since 1990 the critical importance of DNA damage for radiobiological effects, including cancer induction, has been emphasised by a large number of studies with cells and animals that are genetically deficient in DNA damage response – many of these specific genetic deficiencies increase the frequency of radiobiological effects (UNSCEAR 1993, 2000; *Publication 79*, ICRP 1998). Finally the rapidly developing concordance noted in 2.1 between biophysical predictions on radiation action, the biological importance of complex DNA damage and the characteristics of radiation induced gene and chromosomal mutations add weight to the conclusion that certain forms of DNA damage are critically important to radiobiological effects.

2.3 DNA Damage response and repair

2.3.1 DNA repair, apoptosis and cellular signalling

Advances in knowledge of the mechanisms and consequences of post-irradiation processes in cells arguably represent the most profound change in our understanding of radiobiology. Much of this advance can be ascribed to the greatly improved technology and knowledge base that is now characteristic of modern cell/molecular biology and genetics. The UNSCEAR 2000, NCRP 2001 and *Publication LDR-C-1* reports deal with these issues in detail and only a few key conclusions are given here.

- The isolation and characterisation of critical DNA damage response genes, eg for ATM, NBS and DNA PK_{cs} proteins, have provided insights into the structure and function of the most important biochemical pathways that operate to recognise and signal the presence of DNA damage.
- There is now good understanding of many of these pathways and this leads to the view that error-prone repair of chemically complex DNA double strand lesions best explains the cellular radiobiological responses known for many years ie. the induction of chromosome aberrations, gene mutation and cell killing.
- The potential for error-free, recombinational repair of DNA double strand lesions is recognised but, since it is thought to be restricted to the later phases of the cell cycle, its impact overall is not likely to be great.
- Coupled with earlier cellular studies, molecular and biochemical data add weight to the view that the activity of DNA damage response and repair processes are major determinants of dose/dose rate and radiation quality effects in cells.
- Post-irradiation programmed cell death (apoptosis) and delaying effects on the passage of cells through their reproductive cycles are now much better understood at the molecular and biochemical levels.
- In terms of protective effects, apoptotic elimination of radiation damaged cells may be viewed as an alternative to repair ie apoptotic death reduces the frequency of viable cells carrying mutations.
- The imposition of cell cycle checkpoints in irradiated cells has been biochemically linked with the complex network of DNA damage signalling and may serve to maximise opportunities for repair or as points where the cell decides its fate (life or death) on the basis of biochemical balance.
- New highly sensitive techniques for studying the induction of DNA double strand breaks in single cells and post-irradiated cellular signalling show great promise for gaining knowledge of DNA damage response at low doses.

A critical element in the advances that underpin the above judgements is the now compelling evidence that perturbation of DNA damage response/repair and apoptotic/cell cycle control are often closely associated with tumorigenic development. This concept gives increased confidence that these cellular activities are integral to the cellular defences mounted against post-irradiation tumour development. This in turn means that the characteristics of these cellular processes are important elements in the development of judgements in radiological protection.

2.3.2 Adaptive responses

The relatively high level of knowledge gained on post-irradiation DNA repair, apoptosis and cellular signalling may be contrasted with the continuing uncertainty on the mechanisms and significance of so called adaptive responses. Typically, in some experimental systems, adaptive responses are seen in cells conditioned by a priming dose of radiation. In some way this conditioning dose allows cells to develop increased resistance to a second radiation challenge.

Data relating to adaptive responses of various types have been reviewed extensively (UNSCEAR 1994, 2000; NCRP 2001; *Publication LDR-C-1*). The principal conclusions from these reviews may be summarised as follows:

- There is evidence that adaptive responses are not a universal feature of cells *in vitro* nor *in vivo.*
- Even in the most well studied cellular system (cytogenetic response in human lymphocytes) there is a) no evidence that adaptive responses may be triggered by doses of a few tens of milligray and b) there is considerable donor variation in the expression of the response.
- Although some studies support an association with more general stress response mechanisms, chemical radical scavenging and/or more efficient DNA repair, mechanistic knowledge of adaptive responses remains fragmentary.
- Although there are some positive results, animal studies on tumour induction (and immune response) do not provide consistent evidence of adaptive responses that reduce health effects.

2.4 The induction of gene and chromosomal mutations

As noted earlier there are now strong links between the biophysical processes that determine the induction of complex DNA double-strand lesions, error-prone DNA damage response/repair processes and the forms of gene and chromosomal mutations (DNA sequence loss or rearrangement) characteristic of ionising radiation exposure. Much of the available quantitative dose-response data for cells pre-date *Publication 60* and the specific forms of mutational dose-response recorded depend upon

the biological system, the mutational endpoint, radiation quality (LET) and dose-rate (Thacker 1992; UNSCEAR 1993, 2000).

In general, however, mutational dose-responses are linear-quadratic for low LET and tend towards linearity as LET increases. For low LET radiations, reduction in dose-rate usually reduces the frequency of induced gene/chromosomal mutations in mammalian somatic and germ cells. The maximum dose-rate reduction factor is usually 3-4 but it can be somewhat higher for chromosome aberration induction in human lymphocytes. A reasonably consistent relationship between RBE and LET for mutation induction has also been recorded with maximum values for RBE of around 10-20 usually being seen in the LET range 70-200 keV μm^{-1}.

A novel feature of recent studies involving 'chromosome painting' techniques is that complex chromosome exchanges involving the interaction of >2 breakpoints are infrequent at low doses of low LET radiation but can be a significant fraction of high LET induced events at all doses. Advances in the understanding of radiation action on cellular DNA has included modelling of the formation of chromosomal exchanges but contention remains on whether these exchanges demand the interaction of two damaged sites or whether a significant fraction derives from the interaction of damaged and undamaged sites (UNSCEAR 2000). Since 1990 considerable effort has been made to investigate the induction of gene and chromosomal mutations at low doses. There are many technical factors that limit the resolution of such low dose effects but two studies are notable.

First, a large scale investigation of chromosome aberration induction by x-rays in human lymphocytes provided evidence of a linear dose-response at low doses with a limit of resolution of around 20 mGy. Second, the use of a highly sensitive *in vivo* mutation system relating to pigment-producing cells in mouse skin showed linearity of mutational dose response down to the lowest x-ray doses of around 50 mGy (see UNSCEAR 2000, *Publication LDR-C-1)*.

There have also been valuable developments in the use of chromosomal aberration not only as biomarkers of radiation exposure but also for the purposes of establishing relationships between *in vivo* cellular response, dose/dose rate effects and potential health outcomes (Tucker et al 1997; Tawn et al 2004).

2.5 Epigenetic responses to radiation

A major feature of radiobiological research since 1990 has been a range of studies that provide evidence of post-irradiation cellular responses that appear to result in genomic change and/or cellular effect without an obvious requirement for directly induced DNA damage (see Churubini et 2001, *Publication LDR-C-1*). In a broad sense these processes may be

termed epigenetic and they contrast with the well established radiobiological concept of direct DNA targeting by ionising radiation tracks which has underpinned much of the post 1990 developments in biophysics and DNA damage response. Although there are elements of overlap, these epigenetic effects may be placed in two categories a) radiation induced genomic instability; b) post-irradiation bystander signalling between cells.

2.5.1 Radiation induced genomic instability

Whereas conventional DNA damage response is known to result in the expression of genomic damage within the first or second post-irradiation cell cycles, the term induced genomic instability broadly describes a set of phenomena whereby genomic damage and its cellular consequences are expressed persistently over many post-irradiation cell cycles (Little 2003; Morgan 2003). This instability, as expressed in cultured cells, can take the form of increased frequencies of chromosome aberrations, gene mutations and apoptosis/cell death; other manifestations have also been recorded. *Publication LDR-C-1* has reviewed the recent evidence concerning induced genomic instability including the examples given below.

Much of the *in vitro* cellular work on induced genomic instability has been performed using chromosomal endpoints. Although persistent chromosomal instability has been reproducibly demonstrated in mass cultures of established cell lines there have been fewer studies of clonal cell populations and normal diploid cells. In this context a recent cytogenetic study with human diploid fibroblasts using mass culture and clonal techniques was particularly revealing in that it found no evidence of instability phenomena.

This negative result raises the possibility that induced genomic instability is preferentially expressed in abnormal or genetically altered cells and this would be consistent with the difficulties experienced in clearly demonstrating the phenomenon *in vivo*. After *in vivo* exposure of humans and mice to high and low LET radiations cytogenetic results have been negative or showed inconsistent evidence of persistent instability in haemopoietic cells. Nevertheless there are positive results in certain mouse strains and further work is called for. In addition, there are indications that in mice the expression of induced genomic instability varies with genetic background and, in some cases, it may associate with deficiency in DNA damage response.

The biological basis of induced genomic instability in its various forms is not well understood. Some biochemical data suggest the involvement of cellular stress and oxidative processes; other cytogenetic studies implicate potentially unstable DNA segments encoding DNA repeat sequences .

2.5.2 Post-irradiation bystander signalling

The so called bystander effect relates to the expression of cell death/apoptosis, gene/chromosomal mutation, genomic instability and/or changing patterns of protein abundance in cells not directly intersected by radiation tracks (see Little 2003, Morgan 2003, Mothersill and Seymour 2001). These bystander cells are believed to be responding to signals from their irradiated neighbours via intercellular communication mediated by molecules passing through gap junctions in adjoining cell membranes or via diffusion of these signalling molecules through the cell culture medium. Data relating to the bystander effects of radiation are reviewed in *Publication LDR-C-1* and only a few points are noted here.

Experimental studies on the bystander effect in cultured cells have been greatly facilitated by the development of microbeam irradiation facilities which allow the delivery of defined numbers of radiation tracks to cells or their nuclei. In this way cellular effects arising in unirradiated cells may be specifically determined. Alternatively cells may be irradiated in mass culture with a fluence of particles that allow for only a fraction of cells/cell nuclei to be intersected. The expression of bystander signalling is then evidenced by a frequency of cellular effects that exceeds the number of track intersections.

The majority of bystander studies relate to cellular irradiation with high LET alpha particles and protons although some low LET studies, particularly on signalling through the growth medium, are available. The biological mechanisms involved in bystander signalling are probably diverse and remain to be adequately elucidated. Some data point towards induction of oxidative stress and modulation of DNA damage response pathways. In the case of effects mediated through the culture medium, there is some evidence for the release of chromosome-damaging (clastogenic) factors from irradiated cells and the mobilisation of intracellular calcium together with increased reactive oxygen species in recipient cells.

Thus, the phenomena of induced genomic instability and bystander effects when expressed *in vitro* may show some common stress-related mechanisms. There are, however, few data and some controversies on the relative contribution of bystander signalling to cellular effects overall and the extent to which this is dose-dependent. Studies on bystander effects *in vivo* are in their infancy although there are some positive data relating to clastogenic factors.

2.6 Tissue Reactions

There have been no profound changes in scientific views on the quantitative aspects of radiation-induced tissue reactions (deterministic effects) since 1990. However, there have been some developments

concerning the mechanisms through which these reactions may be modified (see also section 3).

An increasing number of studies on early tissue reactions has shown the ability to modify these using various cytokines and growth factors, primarily to stimulate regeneration of progenitor cells. Other biological response modifiers can be used for late reactions, in particular vascular modifying agents that delay the expression of organ damage induced in experimental animal systems. This ability to modify the response of tissues and organs has prompted consideration of a change in the term 'deterministic effects' to tissue and organ reactions, because the effects are not necessarily pre-determined in quantitative terms.

It has been recognised more since the 1990 recommendations that the structure of tissues and organs plays a major role in their response to irradiation. Paired organs, or organs where the functional subunits (FSU) are arranged in parallel, rather than in series, can sustain inactivation of many FSU without clinical signs of injury, because of a substantial reserve capacity and compensation by the remainder of FSU. This is one of the major reasons for the presence of a threshold dose for overt injury, and in particular for a high tolerance to partial-body irradiation, where a critical part of such organs may be spared.

Late tissue reactions not only have a long and dose-dependent latency period before expression, but also they have a long progression period, with the incidence in many cases still rising well past 10 years after irradiation. Late reactions can be 'generic', which means arising in the responsible target tissue, and other late reactions can be 'consequential', meaning arising as a consequence of a severe early reaction affecting the target tissue for late reactions to exacerbate the latter.

There has been a consolidation of the use of the linear-quadratic formalism for describing the changes in iso-effective dose resulting from changes in the pattern of dose delivery, i.e. acute single doses, multifractionated doses, or continuous exposures. In general, the ratio of the linear and quadratic constants is higher for early reactions and consequential late reactions, and lower for generic late reactions.

2.7 Mechanisms of Radiation Tumorigenesis

The technical and academic developments in biology since 1990 have also had a major impact on our understanding the complex process of multistage tumorigenic development (eg. UNSCEAR 1993, 2000; NCRP 2001; *Publication LDR-C-1*).

In brief both lympho-haemopoietic and solid tumours are believed to originate from single stem-like cells in their respective tissues. Certain gene and chromosomal mutations which are often tissue-specific can

confer cellular properties which allow these target stem cells to partially escape from their normal constraints of growth and development. In some cases these cells acquire novel properties via gain of function mutations in so called oncogenes; in others, it is loss of function of so called tumour-suppressor genes that applies. On current hypotheses, the full potential for malignancy in these tumour-initiated cell clones is then developed in a step-wise fashion via the appearance of other gene/ chromosomal mutations or in some cases the non-mutational silencing of key genes. In this way, over time, tumours develop increasing malignant potential by growth selection and the bypass of cell senescence. In some cases the rate of tumour development may be increased following the acquisition of mutations that result in the de-stabilisation of DNA and chromosomes. This process of accelerated mutation rate can be a major drive for tumorigenesis in some tissues but, given its clear mutational basis, tumour-associated genomic instability is distinct from the phenomenon of radiation induced genomic instability noted in Section 2.5.

Tumour development is however far more complex than the stepwise accumulation of clonal mutations. There is good evidence that the micro environmental interaction of tumorigenic and normal cells is a critical element in cancer development and the recruitment of a blood supply to an evolving solid tumour is one important example of this.

Since 1990 there has been good progress in understanding the mechanistic basis of radiation tumorigenesis using animal models and by undertaking genetic analysis of certain radiation-associated human tumours (see UNSCEAR 1993, 2000; NCRP 2001; *Publication LDR-C-1*).

2.7.1 Animal models of radiation tumorigenesis

A combination of cellular, cytogenetic, molecular and histopathological techniques has been employed to investigate experimentally multistage radiation tumorigenesis. Much of the most informative work has been undertaken in rodent models with some of these models having a genetic basis which has been informed by studies with human counterpart tumours. In brief for leukaemia and solid tumours of the skin, bone, brain, lung, breast and gastro-intestinal tract there is evidence on the process of multistage tumorigenesis after radiation and the identity of some of the critical mutations involved. Many of these mutations are present in the human counterpart tumours and also in the same rodent tumours arising spontaneously or after exposure to other carcinogens. Overall a key message from these studies is that radiation tumorigenesis appears to proceed in an unremarkable multistage manner with no obvious features that distinguish radiation as an unusual carcinogen. In particular, although data remain sparse, there are as yet no indications that the epigenetic process of induced genomic instability makes a consistent and major contribution to radiation tumorigenesis. By contrast, in those animal models where it has proved possible to associate radiation

exposure with a specific gene or chromosomal mutation, radiation appears to be acting at a very early stage (initiation) in tumorigenesis via a gene loss mechanisms that is consistent with the principal mechanism of *in vitro* somatic cell mutagenesis noted in Section 2.4.

Data from quantitative animal studies on radiation tumorigenesis are important for the development of some critical judgements in radiological protection. The implications of such data for consideration of the effects of dose, dose-rate and radiation quality effects are noted later in this report.

2.7.2 Radiation-associated human tumours

There are limited opportunities for mechanistic investigations with human tumours which have a high probability of radiation causation. The cytogenetic and molecular studies undertaken with radiation-associated tumours of lung, liver, thyroid, skin and bone marrow have tended to focus on particular gene or chromosomal mutations and the relationship between these mutations and initial radiation damage remains unclear (UNSCEAR 2000). However, in general accord with the results of animal studies, the human data developed since 1990 do not suggest that radiation tumorigenesis proceeds in an unusual fashion; evidence for the presence of specific mutational signatures of radiation is currently lacking. The involvement of induced genomic instability in radiation tumorigenesis has been found to be lacking or is viewed as controversial (Nakanishi et al 2001; Cox and Edwards 2002; Lohrer 2001).

2.7.3 Genetic susceptibility to cancer

The issue of inter-individual genetic differences in susceptibility to radiation-induced cancer was noted in *Publication 60* and reviewed in *Publication 79* (ICRP 1998) and UNSCEAR (2000, 2001). Since 1990 there has been a remarkable expansion in knowledge of the various single gene human genetic disorders where excess spontaneous cancer is expressed in a high proportion of gene carriers – the so called high penetrance genes. There is also a growing recognition and some data on variant genes of lower penetrance where gene-gene and gene-environment interactions determine a far more variable expression of cancer.

Studies with cultured human cells and genetically altered laboratory rodents have also contributed much to knowledge and, with more limited epidemiological/clinical data, suggest that a high proportion of single gene, cancer-prone disorders will show increased sensitivity to the tumorigenic effects of radiation.

Recently, good progress has been made in demonstrating experimentally the complex interactions that may underlie the expression of cancer-predisposing genes of lower penetrance; this work is however in its infancy.

2.8 Heritable diseases

Views on the risks of induction of heritable diseases by radiation exposure of the gonads were developed in *Publication 60* by extrapolating quantitative data on dose-response for germ cell mutations in experimental animals (predominantly mice) to humans. Although extended follow-ups of mortality and cancer incidence in the offspring of the Japanese A-bomb survivors have been published (Izumi et al 2003a, 2003b) these data do not alter the conclusions of previous analyses. In addition, few new quantitative data on mutation induction in mice have become available. However, since 1990 there have been significant developments in our understanding of the mutational process and new concepts for genetic risk estimation in human populations (UNSCEAR 2001).

The application of molecular genetic techniques has provided detailed knowledge of the molecular basis of naturally-occurring mutations that cause heritable diseases in humans; also of radiation-induced gene (specific locus) mutations in mouse germ cells. There is now strong evidence that large multi-locus deletions of the genome constitute the predominant class of radiation-induced mutation. It is judged that only a proportion of such multi-gene loss events will be compatible with embryonic/fetal developmental and live birth. These findings have led to the concept that the principal adverse genetic effect in humans is likely to take the form of multi-system developmental abnormalities rather than single gene diseases.

Another conceptual change based upon new human genetic information is the development of methods to assess the responsiveness of the frequency of chronic multifactorial diseases (eg coronary heart disease and diabetes) to an increase in mutation rate. This has allowed an improved estimate to be made of the risks associated with this large and complex class of disease where expression requires the interaction of genetic and environmental factors.

These human genetic, experimental and conceptual advances have been integrated to form a new and more robust framework for the estimation of genetic risks (UNSCEAR 2001).

There have also been developments on the estimation of radiation-induced mutation rates in mice and humans using expanded simple tandem DNA repeat (ESTR) loci in mice and minisatellite loci in humans. These DNA repeats are highly mutable with the mutations manifesting as changes in the number of tandem repeats. This increased mutability is expressed spontaneously and after radiation and attention has been given to the mutational mechanisms involved, including the untargeted and transgenerational effects of radiation (UNSCEAR 2000, 2001; CERRIE 2004). However, since on current knowledge mutations at these DNA

repeat sequences are only rarely associated with genetic disorders, the Task Group judges that there is no good reason to include quantitative mutational data for these loci in the estimates of genetic risk given in Section 6 of this report.

3. Risks of Tissue Injury

3.1 Revision of judgements given in Publication 60

3.1.1 Definition of stochastic effects and tissue reactions

The deposition of energy by ionising radiation is a random process. Even at very low doses it is possible that sufficient energy may be deposited into a critical volume within a cell to result in cellular changes or cell death. The killing of one or a small number of cells will, in most cases, have no consequences in tissues, but modifications in single cells such as genetic changes or transformations leading ultimately to malignancy, may have serious consequences. These effects resulting from damage in a single cell are termed stochastic effects. There is a finite probability of the occurrence of such stochastic events even at very low doses, so there will be no threshold dose unless all such events can be repaired up to some level of dose. As the dose is increased the frequency of such events increases, but in the absence of other modifying factors, the severity of the resultant effects is not expected to increase, in contrast to the case for tissue reactions (see below).

With larger doses there may be a substantial amount of cell killing, sufficient to result in detectable tissue reactions. These reactions may occur early or late after irradiation. The depletion of renewing parenchymal cell populations, modified by stromal influences, plays a crucial role in the pathogenesis of early tissue reactions. In order to reach the level of detection, a given proportion of cells must be depleted. This constitutes a threshold, which depends on the specified level of injury.

When the term stochastic was introduced, effects caused by injury in populations of cells were called non-stochastic (*Publication 41* (ICRP 1984)). This was later considered an unsuitable term, and in *Publication 60* (ICRP 1991) it was replaced by the term deterministic, meaning "causally determined by preceding events". Now it is recognised that both early and late tissue reactions are not necessarily predetermined, and they can be modified after irradiation by the use of various biological response modifiers. Hence it is considered preferable to refer to these effects as early or late tissue or organ reactions. These reactions are distinct from the stochastic effects in tissues, which are the induction of cancers from irradiated somatic cells and genetic diseases in offspring following parental germ cell irradiation.

3.1.2. Tissue and organ reactions

Early tissue reactions (hours to a few weeks) can be inflammatory-type reactions as a result of cell permeability changes and histamine release

e.g. erythema, and subsequent reactions as a consequence of cell loss e.g. mucositis, and epidermal desquamation.

Late tissue reactions (months to years) are called "generic" if they occur as a result of injury directly in the target tissue e.g. vascular occlusions leading to deep tissue necrosis after protracted irradiations, or "consequential" if they occur as a result of early reactions, e.g. dermal necrosis as a result of severe epidermal denudation and chronic infection, and intestinal strictures caused by severe mucosal ulceration (Doerr and Hendry, 2001).

3.1.3 Cell survival curves

Cell depletion plays a major role in the early desquamatory reactions in tissues after irradiation. In a few cell types and tissues, rapid cell loss after irradiation is mediated by apoptosis, as exemplified by lymphocytes and salivary glands. In other tissues, cell death is caused by reproductive failure of regenerative stem cells, which may undergo apoptosis before or after attempted mitoses, or of proliferating transit (differentiating) cells. The majority of nonproliferating mature cells do not die from irradiation, but from natural senescence. For a given level of tissue damage, it has been shown that dose modifying factors for different irradiation conditions are the same for survival of tissue target cells and for a given level of early tissue reactions, demonstrating the importance of target cell survival for these types of reaction (Hendry and Thames, 1987).

The survival of cells as a function of dose (Figure 3.1) is commonly described using the linear-quadratic equation:

$$S = \exp-(\alpha D+\beta D^2)$$

The constant α describes the linear component of cell sensitivity to killing on a semi-log plot of survival (log) versus dose (linear), and β describes the increasing sensitivity of cells to higher radiation doses. The ratio α/β is the dose at which the linear and quadratic components of cell killing are equal. This ratio is a measure of the curvature of the survival curve. The α/β ratio is lower and the curve on a semi-log plot is more pronounced for homogeneous, slowly proliferating cell populations, such as in slow-renewing organ systems like kidney and spinal cord. The α/β ratio is higher and the survival curve is straighter for heterogeneous, rapidly proliferating cell populations, such as the regenerative target cell populations in oral mucosa and intestine. One possible contributor to this straightening is the presence of subpopulations with different sensitivities as a function of cell-cycle phase. The α/β ratio is generally in the range 7-20 Gy for early reactions in tissues (10 Gy is commonly used) and 0.5-6 Gy for late reactions (3 Gy is commonly used).

When dose rates are lower than around 0.1 Gy/hour there is repair of cellular radiation injury during the irradiation. This causes the β component to decrease and to reach zero at very low dose rates. The α component is not modifiable by changing dose rate. A special feature for some cell types is hypersensitivity to doses less than 0.5 Gy, typically at 0.2-0.3 Gy (Joiner et al 2001), but not at higher doses. This causes a deviation from the smooth linear-quadratic cell survival curve. It is considered by some to be due to stimulation of repair processes at doses above 0.2-0.3 Gy. The deviation has been detected for early skin reactions in humans, and for skin reactions and kidney injury in experimental animal systems.

With high LET irradiations, there is less repairable injury and hence the β component and dose rate effects are small or absent. There is also no hypersensitivity component to the survival curve.

3.1.4 Early and late reactions in tissues and organs

Early desquamatory reactions in epithelia, and depression of the haemopoietic system, are caused by the sterilisation of stem and progenitor cells in the tissues, resulting in a transitory or permanent lack of mature cells depending on the level of dose. Such reactions are characteristic of the radiation response of renewing cell lineages, such as epidermis, mucosa, haemopoiesis and spermatogenesis. The time course of expression and restoration of tissue components generally depends on their normal rate of renewal, and is dose-dependent at low doses but not at high doses. Complete denudation of such tissues after high doses occurs at a time equivalent to the lifetime of new mature cells plus those produced by any radioresistant progenitor cells. The stroma produces a variety of growth factors that induce the repopulation and differentiation needed to restore particular tissue components. The time course can be advanced and the restoration made more complete by the application of exogenous growth factors that further stimulate the reparative processes.

Late reactions in tissues are due in part to the slow rate of renewal and death of component cell populations, where the cells are functional as well as capable of division (Michalowski, 1981; Wheldon et al. 1982). Late reactions are also due to dysfunction of a complex system of inter-cellular signalling pathways which normally regulate the various tissue and organ functions (Rubin et al 1998). In some tissues it has been shown that different types of damage appear after different latency periods. For example, in spinal cord, there is an early demyelination effect within a few months, then a second phase of demyelination and necrosis of the white matter after 6-18 months, and a later phase after 1-4 years that is mostly a vasculopathy (van der Kogel 2002).

In most tissues, responses are greater when irradiated volumes are larger. With early skin reactions, the volume effect is due largely to the

decreasing ability to heal large areas mainly because of limited cell migration from the margins. With late reactions the volume effect relates to organ architecture. In spinal cord the critical elements are arranged in series, so that when more elements are irradiated there is a greater chance of inactivating one of them to cause paralysis. There is also less benefit from cellular migration from the edges of the radiation field when irradiated volumes are larger. By contrast, in for example kidney and lung, the tissue functional subunits (FSU, respectively nephrons and alveoli) are arranged in parallel (Withers et al 1988). In these cases, there can be inactivation of some FSU without causing a decrease in organ function, until a critical number of FSU is reached. Late tissue injury is progressive and strongly dose dependent, and it has been shown that the incidence of late morbidity after radiotherapy in humans continues to increase gradually to 10 years and beyond (Jung et al 2001). There are various procedures that have been shown in experimental animal systems to delay the onset and development of late radiation morbidity (see below).

Tissues vary not only in their temporal responsiveness, but also in their radiosensitivity. Among the most radiosensitive tissues are the ovary and testes, bone marrow, and the lens of the eye. In general, the dose-incidence relationship for these tissues will be sigmoid in shape when plotted on linear axes, the effect becoming more frequent as the dose increases (Figure 3.2a). Tissue and organ reactions vary with the dose, in severity as well as in incidence. The upper panel in Figure 3-3 illustrates how the incidence of a particular reaction, defined as a clinically recognisable pathological condition, increases as a function of dose in a population of individuals of varying sensitivities. The lower panel in Figure 3.3 represents the dose-severity relationship for a population of individuals with various sensitivities. The severity of the pathological condition increases most markedly in those individuals in a subgroup who are most sensitive (curve a), reaching the threshold of detectability at a lower dose than in the less sensitive groups (curves b and c). The range of dose over which the different subgroups cross the same threshold of severity is reflected in the upper panel of Figure 3.3, which shows the frequency of the pathological condition in the total population, and which reaches 100% only at that dose which is sufficient to exceed the defined threshold of severity in all members of the population.

In reality, substantially less than 1% of an average population is very radiosensitive because of inherited mutations in important damage-sensing or repair genes. The remainder has a spectrum of sensitivities, and this has a flattening influence on the slope of the dose-incidence curve. This modification of the slope is in addition to primary contributions from inherent target-cell sensitivity and from features of tissue architecture discussed above. It is not yet possible to determine accurately the sensitivity of individuals within this spectrum of radiosensitivities, using cellular or molecular tests.

Threshold doses for some tissue and organ reactions in the more radiosensitive tissues in the body are shown in Table 3.1. These have been deduced from various radiotherapeutic experiences and accidental exposure incidents. In general, fractionated doses or protracted doses at low dose rate, are less damaging than are acute doses.

3.1.5 Mortality after whole body exposure

Mortality after irradiation is generally the result of severe cell depletion in tissues of, or other major dysfunction of, one or more vital organs of the body. After partial body irradiation, or inhomogeneous whole body irradiation, the probability of death will depend on the particular organs exposed, the volume irradiated, and the dosage level. After whole body irradiation which is fairly homogeneous, for example with penetrating photon beams above about 1 MeV energy, death may occur from one of several distinct syndromes which are characteristic of particular dose ranges, and which are due to injury in specific organ systems.

For a specific syndrome potentially leading to death, the relationship between the percentage of survivors and the dose is sigmoid in shape on a linear plot, whereas for a transformed probability-linear plot the shape is approximately linear (Figure 3.2b). The survival-dose relationship is often described by its midpoint, the LD_{50} i.e. the dose that is lethal for half of the individuals, and the slope of the curve. The slope can be characterised by the probit width, which is the standard deviation of the distribution, or by other parameters in other transformations of the data. Values of $LD_{5\text{-}10}$ and $LD_{90\text{-}95}$ are helpful in assessments of the dose that will result in the death of only a few or of many.

For a normal healthy adult human, the $LD_{50/60}$ i.e. within 60 days, is around 4 Gy midline dose, but there are estimates in the literature ranging from 3 to 5 Gy. Estimates of LD_{10} are around 1-2 Gy, and around 5-7 Gy for LD_{90} (UNSCEAR, 1988 Annex G; NUREG, 1997). The cause of death is haemopoietic failure, resulting primarily from a lack of progenitor cells that produce functional short-lived granulocytes, as well as from haemorrhages without the replacement of radioresistant red cells. It is possible to improve the chances of survival of individuals exposed to doses around or even above the $LD_{50/60}$ by appropriate medical care such as fluid replacement, antibiotics, antifungal drugs, and barrier nursing (UNSCEAR, 1988 Annex G), by infusing platelets and concentrates of isologous blood stem cells, and by injecting growth factors such as granulocyte-macrophage colony-stimulating factor. Some experts have considered that supportive medical treatment may increase the $LD_{50/60}$ to around 5 Gy, and possibly to around 6 Gy if growth factors are also employed (NUREG, 1997). In experimental animal systems these procedures have been shown to significantly increase the LD_{50} values (Table 3.2). Growth

factors have been used for many years in the treatment of humans following whole body irradiation for haematological diseases. However, in the few cases of accidental radiation exposures where they have been used, they did not save the individuals who were considered at risk of death, possibly because of the delay in starting the growth factor treatment. However, the growth factors were reconsidered to be of some benefit.

At doses in excess of about 5 Gy, additional effects occur, including severe gastrointestinal (stem cell and endothelial capillary cell) damage which, when combined with haemopoietic damage, causes death in 1-2 weeks. There are few human data to assess accurately the LD_{50} for this syndrome, but it may be approaching 10 Gy acute dose (UNSCEAR, 1988 Annex G; NUREG, 1997), and supportive medical treatment and growth factors are expected to increase this approximate value. If some marrow and most of the gut have been spared because of inhomogeneous irradiation, then at acute doses above 10 Gy to the lungs, acute inflammation (pneumonitis) may occur leading to death. Renal damage also occurs in the same dose range, if the kidneys have been irradiated. All these effects potentially can be alleviated to some extent, as evidenced by the success of growth factors and other molecules in reducing tissue and organ injury in animal systems after irradiation (Table 3.2). At even higher doses towards 50 Gy and above, there is acute damage in the nervous and cardiovascular systems and the individual dies of shock after a few days (NCRP, 1974). Approximate doses for death at different times are given in Table 3.3. These are for high dose, low LET radiation given over a few minutes.

If the dose is given over a period of hours or more it requires a greater whole body dose for these effects to occur. For example, if the dose-rate is about 0.2 Gy per hour, LD_{50} values may be increased by around 50% (NUREG, 1997). If the dose is delivered over a month, the $LD_{50/60}$ may be doubled (UNSCEAR, 1988 Annex G). At low (chronic) radiation dose rates, there is evidence of a chronic radiation syndrome affecting in particular the haemopoietic, immune and neural systems (Guskova et al 2002; AFRRI, 1994,1998; Akleyev et al 2002). The threshold doses for depression of the immune system is about 0.3-0.5 Gy per year (Akleyev et al, 1999), and estimated threshold doses for effects in other organs are given in Table 3.1. Severe reactions do not occur in most body tissues of adults or children after annual doses below 0.1 Gy over many years. Red bone marrow, reproductive cells, and the lens of the eye, show the greatest sensitivity.

Tissue and organ reactions resulting from exposure to high LET irradiation are similar to those from low LET exposure, but their frequency and severity are greater per unit absorbed dose of high LET irradiation. These differences are expressed in terms of the relative biological effectiveness (RBE) for the effect under consideration. The RBE of high versus low LET

radiation is defined as the ratio of the absorbed dose of the reference low LET radiation to cause the same level of the same biological effect as that of a dose of high LET radiation.

RBE values for tissue and organ reactions are higher at lower doses and when low doses per fraction are given repeatedly to accumulate the total dose (*Publication 58*, ICRP 1989). RBE values tend to be smaller for early effects in haemopoietic and reproductive tissue, larger for gastrointestinal tract and skin, and even larger for late reactions in for example lung and kidney.

The effective maximum RBE will be that value which applies at the threshold dose for the particular effect under consideration. This will be less than the value RBE_m, which is defined as the ratio of such doses at very low doses. This is the ratio of the linear components of the linear-quadratic fittings to data at higher doses. Hence it represents an extrapolation to dose levels below the threshold dose, which is of theoretical but not of practical interest. It also ignores the possibility of occult hypersensitivity at very low doses. RBE_m values for neutrons are 2-5 times lower, and effective maximum RBE values are even lower, than values of RBE_M values for stochastic effects in corresponding tissues. Thus the use of Q or w_R values in cases where tissue effects are over-riding, would result in an overestimate of the contribution to the risk from high LET radiation.

3.1.6 Summary of projected estimates of dose-thresholds for morbidity and mortality

For the purposes of developing judgements for the forthcoming ICRP *Publication PPRA-MC*, the Commission requested the Task Group to update and summarise threshold estimates of the acute absorbed doses for 1% incidences of morbidity and mortality involving adult human organs and tissues after whole body gamma ray exposures. These 1% incidence estimates, derived by the Task Group from publications which utilise mathematical projections of dose-response data, are given in Table 3.4 together with estimates of development times for the effects in question.

3.1.7 Dose limits for specific tissues

Publication 60 (ICRP 1991; paragraph 194 and Table 6) describes the need to provide dose limits for exposure of the eye and localised areas of the skin because these tissues are not necessarily protected against radiation-induced reaction/injury by the limit on effective dose which, in these circumstances, protects against cancer development.

Information available since 1990 has not provided evidence necessitating a change of view in the tumorigenic radiosensitivity of the skin or relevant sub-cutaneous tissues. It is judged therefore that the occupational and

public dose limits for the skin and hands/feet given in Table 6 of *Publication 60* remain applicable. However, recent studies have suggested that the lens of the eye may be more radiosensitive than previously considered. In particular, among both A-bomb survivors (Minamoto et al 2004) and a group of children treated for skin haemangioma (Hall et al 1999), there is evidence of excesses of both cortical and posterior subcapsular cataract at doses somewhat lower than expected. In the assignment of a dose threshold for cataract, uncertainties are recognised on the mechanisms of cataract development; also, on the relationship between the detection of lens opacity and the expression of visual impairment. Nevertheless the recent data noted above led the Task Group to judge that the dose threshold for cataract (visual impairment) induction by acute dose, low LET radiation should be lowered to ~1.5 Gy (see Table 3.4). The Task Group is also aware of unpublished data that also tend to support a lowering of this threshold dose. Until these new data are available for review it is recommended that the dose limit for the lens of the eye (annual equivalent dose) given in *Publication 60* (Table 6) is retained, ie 150 mSv for occupational exposure and 15 mSv for the public.

A secondary issue that emerges is whether equivalent dose (Sv) or radiation weighted dose (Gy) should be used to express dose limits for these specific tissues. Given that these dose limits are required for operation of the general system of protection they may be regarded as a special case. On this basis it is recommended that in this special case the use of equivalent dose is retained for use by ICRP.

3.2 Effects in the embryo and fetus

The risks of tissue injury and developmental changes (including malformations) in the irradiated embryo and fetus have been reviewed recently in ICRP *Publication 90* (2003). In the main, this review reinforced the judgements on *in utero* risks given in *Publication 60* although, on some issues, new data allow for clarification of views. On the basis of *Publication 90*, the following conclusions can be summarised on the *in-utero* risks of tissue injury and malformation at doses up to a few tens of mGy low LET.

The new data from animal studies confirm embryonic sensitivity to the lethal effects of irradiation in the pre-implantation period of embryonic developments. At doses of a few tens of mGy such lethal effects will be very infrequent and the data reviewed provide no reason to believe that there will be significant risks to health expressed after birth.

In respect of the induction of malformations, the animal data strengthen the view that there are gestation age-dependent patterns of *in-utero* radiosensitivity with maximum sensitivity being expressed during the period of major organogenesis. On the basis of these animal data it is judged that there is a dose-threshold of around 100 mGy for the induction

of malformations; therefore, for practical purposes, risks of malformation after low dose *in-utero* exposure may be discounted. ICRP *Publication 90* reviews the experimental data on neurodevelopment following *in utero* irradiation for which dose thresholds generally apply; it also considers human epidemiological data as summarised below.

The review of human A-bomb data on the induction of severe mental retardation after irradiation in the most sensitive pre-natal period (8-15 weeks post-conception) now more clearly supports a dose-threshold of at least 300 mGy for this effect and therefore the absence of risk at low doses. The associated data on IQ losses estimated at around 25 points per Gy are more difficult to interpret and a non-threshold dose response, cannot be excluded. However, even in the absence of a true dose-threshold, any effects on IQ following *in-utero* doses of a few tens of mGy would be undetectable and therefore of no practical significance. This judgement accords with that developed in *Publication 60*.

Table 3.1: Estimates of the thresholds for deterministic effects in the adult human testes, ovaries, lens and bone marrow (from ICRP, 1984[1])

Tissue and effect	Threshold		
	Total dose received in a single brief exposure (Gy)	Total dose received in highly fractionated or protracted exposures (Gy)	Annual dose rate if received yearly in highly fractionated or protracted exposures for many years (Gy y^{-1})
Testes			
Temporary sterility	0.15	NA[2]	0.4
Permanent sterility	3.5-6.0[3]	NA	2.0
Ovaries			
Sterility	2.5-6.0	6.0	>0.2
Lens			
Detectable opacities	0.5-2.0[4]	5	>0.1
Visual impairment (Cataract)[5]	5.0[5]	>8	>0.15
Bone marrow			
Depression of hematopoiesis	0.5	NA	>0.4[6]

[1] For further details consult *Publication 41* (ICRP, 1984)
[2] NA denotes Not Applicable, since the threshold is dependent on dose rate rather than on total dose.
[3] See UNSCEAR, 1988.
[4] See also Otake and Schull, 1990
[5] Given as 2-10 Sv (NCRP, 1989) for acute dose threshold.
See Table 3.4 and Section 3.1.7 for revised judgements by the Task Group.
[6] Possible reduction to 0.3 Gy y^{-1}, on the basis of the Mayak and Techa River populations developing chronic radiation syndrome; judgement contingent on the bone marrow criterion used.

Table 3.2: Dose-modifying factors (DMF) reported in mice or other species where stated. Updated from Hendry, 1994.

Organ	Agent	DMF[a]
Bone Marrow:		
Early reactions		
	Antibiotics	1.2 – 1.8 (rodents and monkeys)
	Granulocyte-Macrophage Colony-Stimulating-Factor	
Intestine:		
Early reactions	Antibiotics	1.1 – 1.4 (rats)
	Interleukin-1	1.1
	Angiogenic Growth Factors	1.1 (mice)[b]
	Interleukin-11, Transforming Growth Factor-β3	>1.0
Late reactions	Low molecular weight diet	>1.0 (rats)
	Antiplatelet Clopidogrel	>1.0 (rats)[c]
Skin:		
Alopecia	Prostaglandin E2	1.2 – 1.5
Early reactions	γ-linolenic acid	1.1 –1.2 (pigs)
Late reactions	γ-linolenic acid	1.1 –1.2 (pigs)
	Blood-cell modifiers	1.4
	Cu/Zn/Mn-SOD	>1.0 (pigs)[d]
Oral mucosa:		
Early reactions	Keratinocyte Growth Factor	about 2.0
Lung:		
Pneumonitis	Interleukin-1,	>1.0
	Tumour Necrosis Factor-α	>1.0
Spinal cord:		
Late reactions	Vasoactive agents	1.1 (rats)
Kidney:		
Late reactions	Captopril, Angiotensin II blockers	>1.0 (rats)

[a] DMF = ratio of radiation doses with or without the protective agent, causing the same level of effect. >1.0 indicates that the observed protection was not quantified in terms of a DMF value.

[b] Okunieff et al (1998)

[c] Wang et al (2002)

[d] Lefaix et al (1996)

Table 3.3: Range of doses associated with specific radiation induced syndromes and death in human beings exposed to acute low LET uniform whole body radiation.

Whole body absorbed dose[a] Gy	Principal effect contributing to death	Time of death after exposure (days)
3-5	Damage to bone marrow ($LD_{50/60}$)	30-60
5-15	Damage to the gastrointestinal tract	7-20
5-15	Damage to the lungs and kidney	60-150
>15	Damage to nervous system	<5, dose-dependent

[a] Some dose range data include judgements from outcomes of partial body irradiations.

Table 3.4: Projected threshold estimates of the acute absorbed doses for 1% incidences of morbidity and mortality involving adult human organs and tissues after whole body gamma ray exposures

Effect	Organ/tissue	Time to develop effect	Absorbed dose (Gy)[e]
Morbidity:			*1% Incidence*
Temporary sterility	Testes	3-9 weeks	~0.1[a,b]
Permanent sterility	Testes	3 weeks	~6[a,b]
Permanent sterility	Ovaries	< 1week	~3[a,b]
Depression of blood-forming process	Bone marrow	3-7 days	~0.5[a,b]
Main phase of skin reddening	Skin (large areas)	1-4 weeks	<3-6[b]
Skin burns	Skin (large areas)	2-3 weeks	5-10[b]
Temporary hair loss	Skin	2-3 weeks	~4[b]
Cataract (visual impairment)	Eye	Several years	~1.5[a,c,f]
Mortality:			
Bone marrow syndrome:			
- without medical care	Bone marrow	30-60 days	~1[b]
- with good medical care	Bone marrow	30-60 days	2-3[b,d]
Gastro-intestinal syndrome:			
- without medical care	Small intestine	6-9 days	~6[d]
- with conventional medical care	Small intestine	6-9 days	>6[b,c,d]
Pneumonitis	Lung	1-7 months	6[b,c,d]

[a] ICRP (1984)
[b] UNSCEAR (1988)
[c] Edwards and Lloyd (1996)
[d] Scott and Hahn (1989) Scott (1993)
[e] Most values rounded to nearest Gy; ranges indicate area dependence for skin and differing medical support for bone marrow.
[f] Minamoto et al 2004; Hall et al 1999; see text in Section 3.1.7.

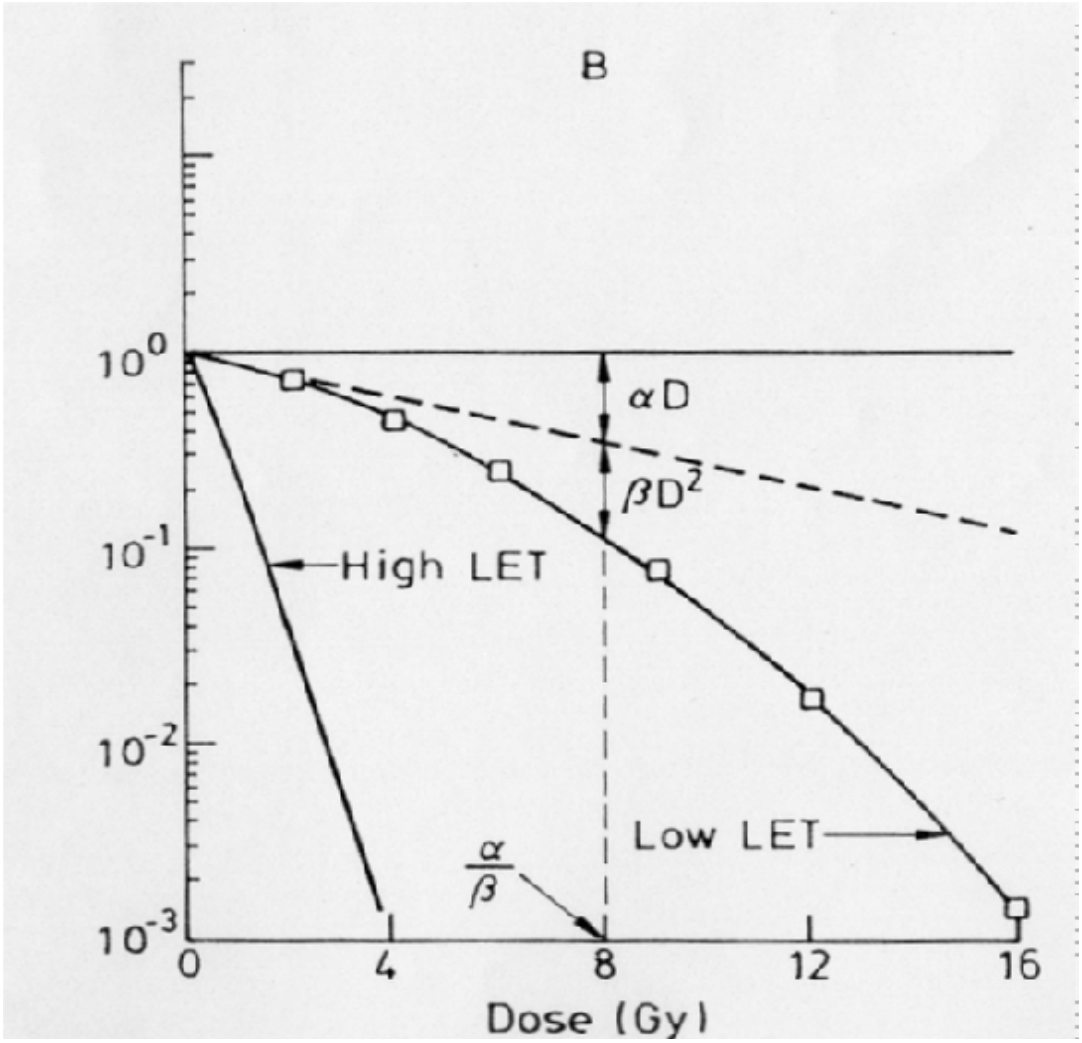

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Figure 3.1: Dose-response for cell survival (S) on a semi-log plot described by the linear quadratic equation $S = \exp - (\alpha D + \beta D^2)$.

From ICRP (1991).

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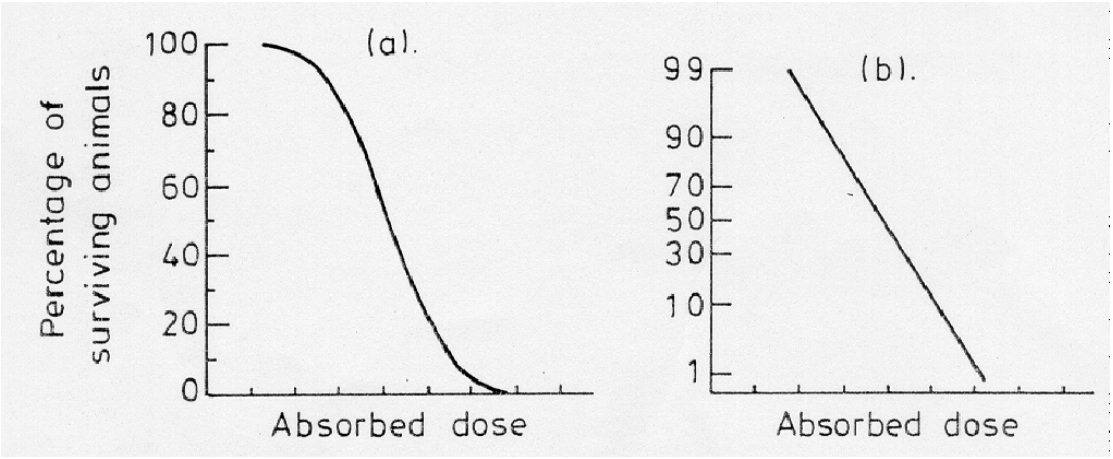

Figure 3.2: Relationship between mortality and dose
a) sigmoid relationship on a linear-linear plot
b) linear relationship on a transformed probability – linear plot.

From ICRP (1991).

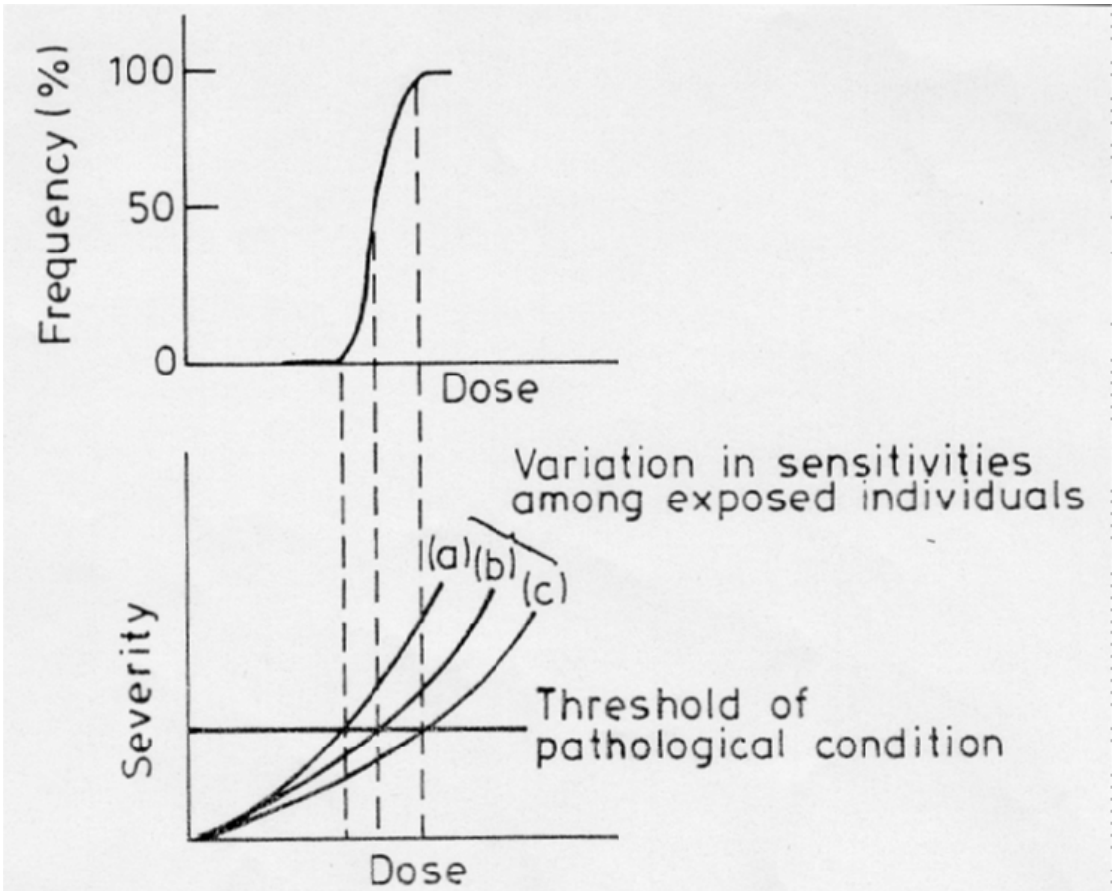

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Figure 3.3: Relationships between dose and the frequency and severity of tissue reactions.

Upper panel - expected sigmoidal increase in frequency in a population of individuals with varying sensitivities.

Lower panel – expected dose-severity relationships for three individuals with different sensitivities.

From ICRP (1991).

4. Risks of Radiation Induced Cancer

In the development of judgements on the risk of radiation induced cancer in the dose range between a few mSv and a few tens of mSv, the Task Group have given attention to a:) the implications of fundamental data on radiation response; b) quantitative aspects of animal tumorigenesis; and c) direct epidemiological observation of cancer risk in humans, albeit at doses generally greater than a few tens of mSv. The conclusions reached by the Task Group on the implications of fundamental and animal data are used to guide the projection of higher dose epidemiological data for the purposes of estimating cancer risk in the low dose region of interest. Also, to consider the application of a dose and dose rate effectiveness factor (DDREF) that would apply to human exposures at low doses and low dose rates. Judgements developed in Section 6 on heritable effects are brought forward in order to provide new estimates of detriment and the nominal probability coefficients for risk in a single section of the report.

4.1 Fundamental data on radiation response

In formulating recommendations for protecting humans against the carcinogenic effects of radiation ICRP are required to consider a very broad span of biological data and concepts; many of these are subject to ongoing debate and, in some cases, contention. There is, however, general agreement that epidemiological methods used for the estimation of cancer risk do not have the power to directly reveal cancer risks in the dose range between a few mSv and a few tens of mSv. Accordingly there is a growing role for biological data in the development of ICRP recommendations and where there is uncertainty and/or contention there is a need to arrive at a scientifically balanced judgement based upon peer reviewed data.
The principal criteria used by the Task Group in seeking a balanced view of biological data are captured in the questions given below.

- How relevant to *in vivo* human tumorigenesis are the radiobiological end points in question?
- Is the design, methodology and statistical strength of a given study sufficient to support the published conclusions?
- Do these published conclusions accord with those of similar studies and take adequate account of other relevant experimental data?

Where there are conflicting data and concepts:

- Which of the conflicting elements show greatest coherence with fundamental knowledge of the cancer process in general and, where possible, with epidemiological data?
- How critical is the issue for the broad purposes of radiological protection?

These questions have been applied to a large set of published cancer-related fundamental data considered by ICRP Committee 1 and by other committees with interests in radiation cancer risk (eg. UNSCEAR 2000; NCRP 2001; *Publication LDR-C-1).* From this evaluation the following judgements have been developed by the Task Group.

4.1.1 Dose response relationships for gene and chromosomal mutations

On the basis that the induction, by radiation, of gene and chromosomal mutations is of direct importance to the cancer process, the majority of relevant data from cellular studies is compatible with a simple relationship between dose and effect. A linear-quadratic form generally describes the full dose-response for low LET radiations. The most informative data, although sparse, suggest linearity down to doses of a few tens of mGy and there is no good reason to suggest a departure from this simple proportionality in the dose range down to a few mGy. At low LET radiation doses of a few mGy and below, linearity of response for targeted events in cells is expected because the fluence of tracks becomes equal to or less than the number of cells in the radiation field (see Section 2.1). If, however, bystander effects were to be shown to contribute substantially to low dose cellular effects in general then this expectation might not be met.

4.1.2 DNA damage-response in cells

There is much data to support the view that the activity of DNA damage response processes in cells is closely coupled with both cellular radiobiological effects and cancer development. On this basis the fidelity of post-irradiation DNA repair is expected to be a critical determinant of low dose response. Current data point towards the predominance of an inherently error-prone repair process for the chemically complex DNA double-strand lesions that are characteristic of radiation action. Error prone DNA repair at doses down to a few tens of mGy is consistent with the approximate linearity of cellular dose-response for gene/chromosomal mutations and implies a simple proportionality between dose and the cancer risk associated with such mutations. The possibility of biochemical changes in DNA repair fidelity at doses below a few tens of mGy cannot be excluded but there are no specific reasons to predict such changes.

A challenge to this conventional scientific view has come from proposals based upon the capacity of cells to sustain and repair a relatively high flux of spontaneously arising oxidative damage to DNA (see UNSCEAR 2000; *Publication LDR-C-1).* The question posed is that if cells can deal adequately with this relatively high level of spontaneous DNA damage then a small number of additional DNA lesions resulting from exposure to a few tens of mGy (~ 2 DNA double strand lesions or ~1 complex cluster per cell at ~50 mGy low LET) would be of little or no consequence for cancer risk.

This challenge might have some strength if spontaneously arising and radiation-induced DNA lesions were to be of the same type. However, as noted in 2.1 and 2.3 there is good reason to believe that the clustered and chemically complex DNA lesions characteristic of radiation action arise very infrequently from spontaneous oxidative processes in cells; these oxidative processes tend to result in simple and readily repairable damage to the single strands of DNA. Since complex DNA lesions are inherently difficult to repair correctly, the challenging argument loses, therefore, much of its scientific strength.

These issues have been addressed in detail by UNSCEAR (2000) and ICRP *Publication LDR-C-1* and for the reasons summarised above the Task Group concludes that the balance of evidence weighs against challenges to simple proportionality in low dose response that is based upon the relative abundances of spontaneous and radiation-induced DNA damage.

It has also been proposed that simple proportionality between dose and radiobiological effect may not apply in all circumstances because of the activity of the adaptive DNA damage response processes noted under 2.3. The Task Group recognises that the data on adaptive responses in human lymphocytes is reasonably reproducible but even these data show that this form of response is not consistently expressed in cell strains and has a poorly understood mechanistic basis. Other forms of adaptive response, eg. immunological stimulation, considered by UNSCEAR (1994, 2000) and that seen in some recent animal studies on tumorigenesis (Mitchel et al 1999, 2003) are also judged to have most uncertain biological bases.

Overall, the Task Group concludes that the concept of adaptive responses to radiation lacks adequate biological support and the available data fail to provide good evidence of robust protective effects for cancer. The integration of the concept of adaptive response into a biological framework for radiological protection is therefore judged to be unjustified at this time.

4.1.3 Epigenetic responses to radiation

Although the Task Group is well aware that research is proceeding at a good pace the available data do not provide good evidence of a robust causal association between cancer risk and the epigenetic phenomena of induced genomic instability and bystander signalling. It seems likely that diverse stress-related cellular processes underlie the expression of both types of response but there is much uncertainty on dose-response characteristics, the extent to which *in vivo* expression occurs and how this might influence cancer risk. On this basis the Task Group suggest that, at present, it is not possible to meaningfully integrate data on these processes into the low dose judgements necessary for radiological protection. Indeed, since direct human epidemiological data at low LET doses of above around 100 mGy provide the principal means for estimating nominal cancer risk coefficients, at these doses cancer risk

estimates will incorporate all relevant biological processes including the epigenetic factors noted in this report. The critical issue of uncertainty is therefore not simply whether such epigenetic factors influence cancer risk per se but rather whether the *in vivo* dose response characteristics might provide for differential contributions to risk at say 200 mSv compared with say 10 mSv. Similar conclusions on these epigenetic responses were drawn by the majority of members in the recently published report of the CERRIE Committee (CERRIE 2004).

4.2 Animal Data on Tumour Induction and Life Shortening

Animal data, largely from rodent studies, were included in consideration of relative biological effectiveness (RBE) in ICRP *Publication 92* and have been reviewed in *Publication LDR-C-1* in respect of dose-response and judgements on the dose and dose-rate effectiveness factor (DDREF). The relationship between RBE and radiation weighting (w_R) is adequately summarised in *Publication 92* and further developed in *Publication FD-C-2.*

In respect of dose response, the most reliable animal data are generally compatible with a simple proportionate relationship between dose and risk but there are examples of highly curvilinear threshold-like responses for the induction of thymic lymphoma and ovarian cancer in mice. The processes that underlie the induction of these tumour types have a high degree of dependence upon cell killing and for this reason these responses are judged by the Task Group to be atypical (see *Publication LDR-C-1*).

When mouse data for thymic lymphoma and ovarian cancers are excluded from analyses the values for DDREF from animal studies are generally compatible and at doses at or below around 2 Gy a DDREF value of 2 or less is implied.

4.3 Relative Biological Effectiveness (RBE) and Radiation Weighting (w_R)

The relationships between RBE and w_R were reviewed in *Publication 92*. The outcome of this review, which involved input from Committees 1 and 2, was a recommendation that although the w_R values for protons and neutrons required revision. w_R values for other radiations given in *Publication 60* remained appropriate.

For protons of energy >2 MeV it was judged in *Publication 92* that the w_R value of 5 given in *Publication 60* is a significant overestimate of their biological effectiveness and for incident protons of practical importance (> 10 MeV) a w_R of 2 was proposed. For neutrons, *Publication 92* proposed that ICRP continues the use of w_R values that depend upon the energy of the incident neutrons. However, a continuous function as given in *Publication 92* (Figure 1 of page 3) was recommended rather than the step function given in *Publication 60*. *Publication 92* noted that for

practical purposes this procedure will reduce problems of computation of effective dose but should not be taken to imply precise knowledge of the underlying biological effectiveness. The issues of w_R for neutrons and photons/electrons have been considered further by Committee 2 and detailed judgements are given in *Publication FD-C-2*.

Those Auger emitting radionuclides and compounds, which have the potential to localise to the cell nucleus and bind to DNA, were recognised in *Publication 60* as a special case for low LET radiation. The Task Group support the view given in *Publication 92* that Auger emitters will continue to need special attention in radiological protection and that specific physiological and biophysical data would be needed in order to consider Auger emitting compounds on a case by case basis.

4.4 Estimation of Cancer Risk from Epidemiological Data

The Task Group was specifically charged by the Commission with developing nominal risk coefficients for cancer risk and providing recommendations on the transport of risk, radiation detriment and tissue weighting factors. This was a major new element of work for Committee 1 and required input from Committee 2 and the Commission. The outcome of this work is summarised below.

4.4.1 Nominal risk coefficients, radiation detriment and tissue weighting factors

Nominal risk coefficients are derived by averaging gender and age at exposure-specific lifetime risk estimates in representative populations. The lifetime risk estimates are computed using risk models specific to various cancer sites. Because of the uncertainty in applying risk models generated from one population to another population with different cancer patterns, population-specific nominal risks are averages of risk estimates from alternative models. These nominal risks are computed for each site of interest and summed to give the population total nominal risk. The overall site-specific and total nominal risks are computed by averaging the population-specific average risks.

Radiation detriment is a concept used to quantify the harmful effects of radiation exposure in different parts of the body. It is determined from nominal risk coefficients, taking into account severity of the disease in terms of lethality and years of life lost. Total detriment is the sum of the detriment for each part of the body (generally tissues or organs).

The concept of "effective dose" associated with a given exposure involves weighting individual tissues of interest, in some useful partition of the human body, by the relative detriments for these parts of the body. In such a system, the weighted sum of the tissue-specific dose equivalents, called the effective dose, should be proportional to the total estimated detriment from the exposure, whatever the distribution of equivalent dose

within the body. The components of detriment are essentially the same for cancer and hereditary disease and, if desired, these detriments may be combined.

For generality, the estimates summarised here are derived as averages across Asian and Euro-American populations. An attempt was made to choose an appropriate model to use for transferring risks across various populations whenever there is sufficient evidence to favour one model over another. The risk modelling was conducted principally with the data from the Japanese Life Span Study of A-bomb survivors (LSS), but the broader radiation epidemiology literature was examined for compatibility with the LSS-derived estimates. For several tissues it was possible to use a group of data sets to estimate cancer risk.

The following text briefly outlines the general models of risk and the sources of data used; methodological aspects of the risk estimates; and the detriments associated with a range of tissues. Estimated numerical values and recommendations that derive from this work are summarised in Tables 4.1, 4.3 and 4.4.

4.4.1.1 Risk modelling

Within a given exposed population, comparable descriptions of the radiation-associated risk can be made using either excess relative risk (ERR) or excess absolute risk (EAR) models, so long as the models allow for variation in the excess risk with factors such as gender, attained age, and age-at-exposure. While suitably data-rich multiplicative (ERR) or additive (EAR) models lead to virtually identical descriptions of the excess risk in the population used to develop the risk estimates, they can lead to markedly different excess risk estimates when applied to populations with different baseline rates.

Both ERR and EAR models were developed for oesophagus, stomach, colon, liver, lung, breast, ovary, bladder, thyroid and leukaemia (bone marrow). As noted below, ICRP 60 nominal risks were used for bone surface and skin cancers (ICRP, 1991). Because the data for other human tissues and organs are insufficient to individually judge the magnitude of their radiation risk, they were consigned to a "remainder" category (called other solid). ERR and EAR models also were developed for this group.

In general, the parameters in these risk models were estimated using incidence data from the studies of the Japanese atomic bomb survivors with follow-up from 1958 through 1998 for solid cancers (Preston et al, in preparation). For solid cancers these models involved a linear dose response allowing for modifying effects of gender, exposure age, and attained age. These effects were constrained to equal the value seen for all solid cancers as a group unless there were indications that these

constraints resulted in a marked reduction in the goodness of fit. Leukaemia risk estimates were based on an EAR model with a linear-quadratic dose-response that allows for effect modification by gender, exposure age, and time following exposure (Preston et al, 1994). Model parameters are given in Appendix 1.

While the LSS studies do provide some information on skin cancer risks (Ron et al, 1998), it was judged that they may not be adequate for a general population because of differences in risk related to skin pigmentation. Therefore, the Task Group used the nominal skin cancer risk estimate of 0.1 per Gy from ICRP Publication 59 (ICRP, 1992). This estimate was also used in ICRP Publication 60 (ICRP, 1991). The nominal risk estimate for bone surface also was taken from ICRP 60 because the LSS atomic bomb studies provide no data and other data sources were extremely limited. The low-LET estimate used in ICRP 60 was 0.00065 per Gy.

The risk models described above were used to compute gender-specific lifetime risk estimates for a range of ages at exposure (0 to 85 years in 5 year intervals) in the Asian and Euro-American composite populations (see Appendix 1). Lifetime risks for exposure ages were then averaged using weights reflecting the age distribution of the full population or for a working age (18-64 year old) population.

In ICRP Publication 60, nominal cancer risks were computed based on mortality data; however, in the current report, risk estimates are based principally on incidence data. The reason for the change is that incidence data provide a more complete description of the cancer burden than do mortality data, particularly for cancers that have a high survival rate. In addition, cancer registry (incidence) diagnoses are more accurate and the time of diagnosis is more precise. It is recognised, however, that incomplete coverage of the A-bomb population because of migration from Hiroshima or Nagasaki introduces a factor of uncertainty on risk estimates based on these cancer incidence data. At the time of ICRP Publication 60, comprehensive incidence data were not available. Since then, a thorough evaluation of cancer incidence in the Life Span Study (LSS) of Japanese atomic bomb survivors has been published (Thompson et al 1994; Preston et al, 1994), and new analyses regarding the latest A-bomb cancer incidence data are expected soon (Preston et al, in preparation). Site-specific risk estimates were taken from the most recent solid cancer incidence analyses of the atomic bomb survivor LSS, with follow-up from 1958 through 1998, and adjusted to reduce bias in risk estimates due to uncertainty in individual dose estimates (Pierce et al, 1990). The newly implemented atomic bomb dosimetry system, DS02, is a considerable improvement over DS86. On average, the DS02 dose estimates are slightly greater than the DS86 estimates. Risk estimates using the two systems differ by less than 10% (Preston et al, 2004).

Although the primary estimates are based on models derived from the LSS data, information from other radiation-exposed populations was also considered. Such information is available from studies of:

- Patients with therapeutic or diagnostic exposures to radiation;
- Workers exposed to radiation in course of their job, eg. uranium miners;
- Persons with environmental exposures, eg. from fallout or from natural radiation.

These studies have been reviewed in detail by UNSCEAR (2000) and the International Agency for Research on Cancer (IARC, 2001, 2002). Some of these studies are more informative than others about radiation risks. The LSS is particularly valuable in estimating radiation risks for a general population, because of the very long, mainly prospective follow-up, the large size of the cohort, and the inclusion of persons of all ages and both genders who received a wide range of doses. Other studies, however, can provide information on the effects of exposure received under different circumstances, such as exposure to high-LET rather than low-LET radiation, exposures received in a chronic or fractionated manner rather than acutely, or risks in countries other than Japan. For example, for thyroid cancer, data from four populations exposed to radiation for medical reasons in various countries were considered in addition to the LSS (Ron et al., 1995). As mentioned earlier, the nominal risk estimates for bone surface and skin are those used in ICRP Publication 60 (ICRP, 1991). These estimates are largely based on studies of groups with medical exposures (eg. intakes of radium-224 in the case of bone surface).

For cancers at some sites there is reasonable compatibility between the data from the LSS and those from other sources. However, it is recognised by the Task Group that there are significant differences in radiation risks for a number of sites, e.g., lung when compared with radon-exposed miners (UNSCEAR 2000). In general, when the LSS cancer incidence risks were compared to those from medically or occupationally-irradiated populations exposed to low-LET external radiation, the risk estimates were broadly compatible. In ICRP 60, the liver cancer risk estimate was based on estimates derived from studies of patients injected with the radioactive contrast medium Thorotrast, for which generalisations to low-LET radiation exposures are problematic, although this estimate is highly relevant when estimating risks for high-LET exposures. In the current report, the LSS liver cancer risk estimate was preferred. This estimate, however, was substantially higher than that of other groups exposed to x- or gamma-radiation (UNSCEAR 2000), probably because of a reported strong interaction between hepatitis virus and radiation in the LSS (Sharp et al, 2003), which would not be expected to occur in populations with lower rates of hepatitis virus infection. Accordingly a

nominal 50% reduction was applied in the transfer of liver cancer risk from the LSS.

Cancer Risk in Different Tissues

Nominal cancer risks and tissue weights were developed for 12 tissues and organs (oesophagus, stomach, colon, liver, lung, bone surface, skin, breast, ovary, bladder, thyroid, bone marrow) with the remaining tissues and organs grouped into one "remainder" category. These individual tissues and organs were selected because it was deemed that there was sufficient epidemiological information on the tumorigenic effects of radiation to make the judgements necessary for estimating cancer risks. Leukaemia, excluding chronic lymphocytic leukaemia (CLL) and multiple myeloma were included in the bone marrow category. The remainder category also includes all other tissues not explicitly evaluated as individual cancer sites.

Composite Populations

Composite baseline rates were computed using incidence rates averaged across six populations for cancers of the oesophagus, stomach, colon, liver, lung, female breast, ovary, bladder, thyroid, leukaemia (excluding CLL) and solid cancers combined. Population-based cancer incidence rates were obtained from the 8th edition of Cancer Incidence In Five Continents (Parkin et al, 2003) and population size data were obtained from the WHO international mortality statistics database. The cancer rates used are for selected Asian (Shanghai, Osaka, Hiroshima and Nagasaki) and Euro-American (Sweden, United Kingdom, U.S SEER) populations and then an unweighted average was calculated to form a composite population.

Gender-specific, all-stage relative survival statistics from the U.S. SEER program for 1994-1999 (5-year survival) and 1979-1999 (20-year survival) were averaged to compute overall relative survival rates for different cancer sites. Although the SEER relative survival rates are higher than those found for many other European and Asian countries, reducing the survival rates did not change estimates of relative detriment appreciably.

Hereditary risks

The estimate of genetic (hereditary) risk from radiation has been substantially revised since the ICRP 60 report as a result of new information that has become available and the work of ICRP during the interim. These revised estimates and their derivation are given in Section 6. Several factors have led to this revision of genetic risk estimates, in brief:

- Most radiation-induced mutations are large multi-gene deletions, which are more likely to cause multi-system developmental abnormalities rather than single gene (i.e., Mendelian) diseases. Importantly, only a fraction of these are likely to be compatible with live births.

- Nearly all chronic diseases have a genetic component, but because most of these are multi-genic and multi-factorial, the mutation component (i.e., the responsiveness of these diseases to an alteration in mutation rate) is small, so that chronic diseases respond only minimally to a radiation-induced increase in mutation rate.

- The ICRP 60 report made the implicit assumption that all genetic diseases should be treated as lethal. In view of the range of severity and lethality for the various types of genetic disease, the lethality fraction for genetic diseases now has been explicitly designated as 80%.

- New genetic risk coefficients recommended by ICRP consider exposure and genetic risk for two generations only – the equilibrium value used in ICRP 60 is judged to be of limited scientific validity because of the unsupported assumptions necessary on selection coefficients, mutation component and population changes over hundreds of years.

As a result, the risk of heritable effects in the whole population associated with gonadal dose is now estimated to be around 20 cases per 10,000 people/Sv, rather than around 100 cases per 10,000/Sv in ICRP 60 (see Section 6, Table 6.6). The corresponding relative contribution of the gonadal dose to the total detriment is now estimated as 3-4%, versus the former ~18%.

4.4.1.2 Methodological Aspects

Uncertainty and sensitivity analyses

The estimated risk of radiation-related cancer is uncertain, and the sources of this uncertainty are many. The most familiar is statistical uncertainty, represented by confidence limits or statistical likelihood distributions. For a chronic or low-dose exposure, the estimate and its statistical uncertainty are divided by an uncertain dose and dose-rate effectiveness factor (DDREF), a process that both reduces the estimate and further increases its uncertainty (see below).

When an estimate based on a particular exposed population is applied to other populations or to other radiation sources, further uncertainty is introduced. Differences between radiation sources can produce uncertainty due to random or systematic error in dose estimates in either the original or secondary population.

Risk-based radiological protection depends heavily on the assumption that estimates based on studies of informative exposed populations, such as the Life Span Study cohort of atomic bomb survivors, can be applied to other exposed populations. Combined analyses of dose-response data from different populations (e.g., Preston et al, 2002) provide valuable information relevant to that assumption. Unfortunately, such information is available for very few site-specific cancers. Transfers of risk estimates

between populations pose a particularly difficult problem for cancer sites for which baseline rates differ widely between the two populations. This problem is discussed in more detail below.

Other major sources of uncertainty include possible interaction of radiation exposure with other cancer risk factors, notably including smoking history in the case of lung cancer, and reproductive history in the case of female breast cancer. This problem is similar to that of transfer of risk estimates between populations, in that the interaction can be represented as an uncertain linear combination of an additive and a multiplicative model. However, there is epidemiological evidence favouring an additive or sub-multiplicative interaction in the case of lung cancer and smoking (Pierce et al, 2003; Travis et al, 2002; Lubin et al, 1995), and a multiplicative interaction in the case of breast cancer and reproductive history (Land et al, 1994).

Another uncertain factor is the relative biological effectiveness, relative to high-energy photons, of radiations of different qualities including medical x-rays in the 30-200 keV range, electrons, neutrons, protons, and alpha particles. Quantification of such uncertainties has been discussed in detail elsewhere eg NCI/CDC (2003). The use of central values is preferred by ICRP for radiological protection purposes, but it should be kept in mind that RBE values for specific radiations are intrinsically uncertain. Other aspects of uncertainty associated with the possible existence of a low dose threshold for cancer risk are summarised in Section 4.4.5. Uncertainties associated with dose estimates for internal radionuclides (eg CERRIE 2004) are noted in *Publication FD-C-2*.

Dose and dose-rate effectiveness factor

For reasons related to statistical power, the dose-specific statistical estimates of radiation-related risk upon which this report is based reflect observed cancer excesses at equivalent doses greater than about 200 mSv, mainly delivered acutely. However, many of the more contentious issues in radiation protection involve risks from continuous exposures, or fractionated exposures with acute fractions of a few mSv or less. Experimental investigations tend to show that fractionation or protraction of dose is associated with reduced dose-specific risk, suggesting that dose-specific estimates based on high-dose, acute exposure data should be divided by a dose and dose-rate effectiveness factor (DDREF) for applications to low-dose, continuous, or fractionated exposures. The magnitude of DDREF is uncertain, and has been treated as such in a number of recent reports based on quantitative uncertainty analysis (eg NCRP (1997) EPA (1999), NCI/CDC (2003). However, the mean of the probabilistic uncertainty distribution for DDREF employed in those analyses differs little from the value of 2 recommended by the ICRP (1991) and UNSCEAR (1993). A DDREF of 2 is also generally compatible with the animal data noted in 4.2. For these reasons the Task Group recommends that a DDREF of 2 continues to be used by ICRP.

Gender averaging

Some radiation-related cancers are sex-specific, and for many others gender is a major modifier of radiation-related risk. In accordance with current ICRP procedures, intermediate and final numerical risk estimates presented here are gender-averaged. Radiation risks were also calculated by retaining gender specificity of intermediate results and gender-averaging only at the final stage. The final results were similar, within acceptable limits, for the two methods of calculation and gender-specific data are not recommended for the general purposes of radiological protection.

Transfer of risk between populations

If two populations differ with respect to prevalence of known modifiers of radiation-related risk, their responses to radiation exposure might be expected to differ. However, even in the absence of such information, it is problematic to transfer site-specific estimates of radiation-related risk from one population to the other if the corresponding baseline rates differ. For (an extreme) example, the LSS population provides by far the most usable estimates available of radiation-related gastric cancer risk, but age-specific baseline rates differ by a factor of 12 between Japan and the United States. There is rough equivalence between dose-specific excess absolute risk (EAR_{LSS}) and the product of excess relative risk (ERR_{LSS}) and baseline rates for the population of Japan, but the relationship

$$EAR_{LSS} = ERR_{LSS} \times baseline_{Japan}$$

corresponds approximately to

$$EAR_{LSS} = 12 \times ERR_{LSS} \times baseline_{US}.$$

Thus, a multiplicative model estimate of excess risk for stomach cancer in the US population based on an ERR model ie.

$$ERR_{mult} = ERR_{LSS,}$$

is about one twelfth as high as the estimate based on directly transferring the EAR_{LSS}:

$$ERR_{add} = EAR_{LSS}/baseline_{US} = ERR_{LSS} \times (baseline_{Japan}/baseline_{US})$$

Assuming that ionising radiation exposure acts primarily as a cancer initiator, multiplicative transfer would be plausible if the difference in population rates were associated with differential exposure to cancer promoters, and additive transfer would be plausible if the rate difference could be ascribed to differential exposure to competing cancer initiators. Given little or no information about radiation-related stomach cancer risk in the US population, or about modification of radiation-related risk by whatever factors are responsible for the 12-fold difference between gastric cancer rates in the two countries, it would not be unreasonable to consider all estimates of the form

$$ERR_{US}(p) = p \times ERR_{add} + (1\text{-}p) \times ERR_{mult},$$

for $0 \leq p \leq 1$, as being equally likely. With this approach, the overall uncertainty is high, and the mean value, $ERR_{US}(1/2)$, does not really represent the range of (presumably) equally likely transfer estimates.

For most sites, the difference between Japanese and US rates is considerably less than 12-fold, which means that inability to discriminate between the additive and multiplicative transfer models is less consequential. However, among the sites considered for the present report, only for lung, breast, and thyroid was it considered that there was sufficient information to justify a representative value other than $ERR_{US}(1/2)$.

Because a recent pooled analysis of radiation effects on breast cancer risk (Preston et al, 2002) provides strong evidence against the use of common ERR models, breast cancer risks were based solely on an EAR model, namely that based on the A-bomb data. The use of EAR models for predicting thyroid cancer risks is problematic because variation in screening intensity will have a marked effect on the rate of radiation-associated thyroid cancers. Therefore, thyroid cancer risks were based solely on the ERR model developed from the pooled analysis of radiation-associated thyroid cancer risks (Ron et al, 1995).

Therefore, the population risks were defined as weighted averages of the additive (absolute) and multiplicative excess risk estimates with weights based on judgements concerning the relative applicability of the two risk estimates. Weights of 0.5 were used for all tissues except breast and bone marrow in which only an EAR model was used, thyroid and skin for which only an ERR model was used, and lung for which the ERR model was given a weight of 0.3 because of suggestions in the atomic bomb survivor data that the radiation-associated excess rate is more comparable across sexes than the ERR and also that radiation dose and smoking history interact additively as lung cancer risk factors.

Computation of radiation detriment

As in ICRP Publication 60, the detriment for a tissue, T, is defined as

$$D_T = (R_{F,T} + q_T R_{NF,T}) l_T$$

where R_F is the nominal risk of fatal disease, R_{NF} is the nominal risk of non-fatal disease, q is a non-fatal weight (between 0 and 1) reflecting the reduced quality of life associated with living with a serious illness, and l is the average life lost due to the disease relative to normal life expectancy, expressed relative to the average over all cancers. As discussed below, the quality of life factor is a function of the lethality (k) of the disease and a subjective judgement accounting for pain, suffering, and adverse effects of treatment.

Since incidence data are being used here, the nominal risk coefficients are R_I ($= R_F + R_{NF}$) and the detriment is computed as

$$(k_T R_{I,T} + q\ (1\text{-}k_T)\ R_{I,T})\ l_T = R_{I,T}\ (k_T + q\ (1\text{-}k_T))\ l_T$$

The computations in ICRP 60 were based on nominal mortality risk coefficients, R_F, and q was taken to be equal to the lethality fraction k. Thus, the ICRP 60 cause-specific detriment is $(R_F + k\ (1\text{-}k)\ R_F / k)\ l$ which is equal to $R_F\ (2\text{-}k)\ l$ (cf pages 134-136 and Table B20 in ICRP 60), where $R_{NF} = (1\text{-}k)\ R_F / k$.

Quality of life detriment:

Since there are quality-of-life detriments resulting from cancer in addition to lethality detriments, the Task Group judges that cancers should be weighted by both lethality and a smaller added component to account for pain, suffering and any adverse effects of cancer treatment. To achieve this, a factor termed q_{min} is applied to the non-lethal fractions of cancers to produce an adjusted lethality fraction termed q_T. The formula used to calculate q_T with an adjustment for non-lethal detriment is:

$$q_T = q_{\min} + k_T\,(1 - q_{\min})$$

where k_T is the lethality fraction and $q_{\min}$ is the minimum weight for non-lethal cancers.

The value of $q_{\min}$ was set equal to 0.1 (in most instances the result is not highly sensitive to the value chosen). In effect, the $q_{\min}$ adjustment has an impact upon detriment calculations in proportion to the fraction of cancers that are non-lethal. Accordingly, highly lethal cancers such as lung and stomach cancer are little affected by $q_{\min}$ whereas relatively non-lethal cancers such as breast or thyroid are. For example, if the lethality of a cancer type was 0.30, the adjusted q_T would be 0.37. However, the $q_{\min}$ adjustment was not used for skin cancer because radiogenic skin cancer is almost exclusively of the basal cell type which is usually associated with very little pain, suffering or treatment sequelae.

Relative life lost:

Relative life lost is an important component of the detriment computation. Average life lost for a given cause was computed for each gender in each composite population as the average over ages at exposure and subsequent attained ages of the residual lifetime. The weights were equal to the number of deaths from the cause of interest in each age group. These were converted to relative values by division by the average life lost for all cancers.

Table A1 in Appendix 1 presents the lethality factors, non-fatal case weights, and relative life lost values used in the current computations. ICRP 60 values are shown for comparison.

4.4.1.3 Principal features of new estimates of cancer risk

In ICRP 60 the ERR and EAR models were given equal weights for various tissues, except for bone marrow. In the present assessment, the relative weights assigned to the ERR and EAR models were allowed to depart from 50:50 when warranted by the available data. This made a more realistic model for the inter-country transfer of radiogenic breast cancer risks and largely prevented the potential problem of thyroid cancer or skin cancer risk estimates being affected by differing degrees of cancer screening.

The present relative detriments (Table 4.1) are similar to the values calculated in ICRP 60 except for four tissue groups: breast, bone marrow, remainder tissues and gonads. There appear to be several reasons why the relative detriment for breast cancer has increased from 0.05 to 0.081. Those exposed as juveniles in the LSS cohort now make a larger contribution to the overall breast cancer risk, whereas the mortality data used for the ICRP 60 analysis only partially reflected this contribution. Furthermore, in the current incidence analyses (Preston et al, in preparation), the ERR estimates for women exposed over age 40 years are higher than those used in ICRP 60. In the 1958-1987 LSS Tumour Registry report on radiation and solid cancer incidence (Thompson et al, 1994), breast cancers contributed about 11% of the total excess solid cancers as averaged over males and females. In the current analyses, breast cancers account for about 18% of the radiation-associated solid cancers. Studies of other exposed populations have confirmed the substantial breast cancer risk from radiation (Preston et al, 2002). On the other hand, the lethality fraction for breast cancer has decreased in the past 15 years, probably reflecting increased early detection and improved treatments, but this appears to have little impact on the relative detriment estimates.

Improved description of the temporal diminution of leukaemia risk has contributed to a reduction in the relative detriment for bone marrow from 0.143 to 0.101. The reduction of gonadal risk has already been explained above and pertains to new information and a revised approach for assessing risks of hereditary disease.

The further accumulation of LSS data in the period following ICRP 60 has significantly influenced the "remainder tissues" category. There is now evidence for excess radiation risk, in the aggregate, among a variety of other tissues, although the degree of risk for any single tissue is unclear. Since the risk in the remainder category is spread over a large number of tissues and organs, the judgement of the Task Group is that any given tissue should receive a small weight. This judgement is consistent with

LSS and/or other evidence suggesting the risk is probably very small or that evidence is lacking.

In order to provide additional supporting information on factors that influence detriment estimates, the Task Group computed site-specific, lethality adjusted nominal risks and detriment values using various methods. The methods used were: 1) the current incidence-based estimates; 2) mortality-based computations using risk models based on the most recent LSS mortality data (Preston et al, 2003) applied to the current composite populations together with the current lethality and life lost factors (ie. the same as (1), but using risk models derived from current mortality rather than incidence data); 3) mortality-based computations using ICRP 60 ERR models (Table 1, Land and Sinclair, 1991) applied to the current composite populations together with the current lethality and life lost factors (ie. the same as (1), but using the ICRP 60 relative risk models for mortality in place of the models based on current incidence data) and 4) the actual ICRP 60 values. Results of these computations are shown in Table 4.2. Parameter estimates for the risk models used in method 2 are given in Appendix 1. It can be seen that the values of relative detriment using incidence- and mortality-based risk models (i.e. approaches (1) and (2) above) are generally similar. There are, however, greater differences for some tissues in respect of the application of ICRP60 methodology to current data (Current ICRP60) and the specific published ICRP60 values. (ICRP-60 actual).

During the computation of gender-averaged values for detriment based on cancer incidence and mortality data the Task Group was required to compute male-and female specific data. These data (not shown) do not contribute specifically to the formulation of the ICRP tissue weighting scheme, but can act to inform related judgements by ICRP Committee 2 and the Commission.

For the purposes of judgements developed by ICRP Committee 2 *(FD-C-2)* the gender-specific relative detriments computed for breast, ovary, thyroid and gonads (heritable effects only) are given in the table of Appendix 2.

Table 4.1: Summary of Gender-Averaged Nominal Risks and Detriment[a]

a) Whole population

Tissue	Nominal Risk Coefficient (cases per 10,000 persons per Sv)	Lethality fraction	Lethality-adjusted nominal risk* (relating to column 1)	Relative cancer free life lost	Detriment (relating to column 1)	Relative detriment+
Oesophagus	17	0.93	17	0.87	15.0	0.025
Stomach	90	0.83	88	0.88	77.5	0.127
Colon	121	0.48	92	0.97	88.8	0.146
Liver	19	0.95	19	0.88	16.7	0.027
Lung	101	0.89	100	0.8	80.1	0.131
Bone surface	7	0.45	5	1	5.1	0.008
Skin	1000	0.002	4	1	4.0	0.007
Breast	69	0.29	38	1.29	49.1	0.081
Ovary	13	0.57	11	1.12	11.7	0.019
Bladder	43	0.29	23	0.71	16.4	0.027
Thyroid	24	0.07	7	1.29	9.2	0.015
Bone Marrow	42	0.67	38	1.63	61.5	0.101
Other Solid	189	0.49	145	1.03	148.9	0.244
Gonads (Hereditary)	20	0.80	19	1.32	25.4	0.042
Total	***1755***		***605***		***609.5***	***1.000***

b) Working age population (18-64 y)

Tissue	Nominal Risk Coefficient (cases per 10,000 persons per Sv)	Lethality fraction	Lethality-adjusted nominal risk* (relating to column 1)	Relative cancer free life lost	Detriment (relating to column 1)	Relative detriment+
Oesophagus	13	0.93	13	0.91	12.0	0.025
Stomach	88	0.83	85	0.89	76.1	0.162
Colon	62	0.48	47	1.13	53.2	0.113
Liver	15	0.95	15	0.93	14.1	0.030
Lung	109	0.89	108	0.96	103.7	0.220
Bone surface	7	0.45	5	1	5.1	0.011
Skin	1000	0.002	4	1	4.0	0.008
Breast	59	0.29	33	1.20	39.4	0.084
Ovary	9	0.57	7	1.16	8.4	0.018
Bladder	40	0.29	21	0.85	18.1	0.039
Thyroid	5	0.07	1	1.19	1.7	0.004
Bone Marrow	46	0.67	41	1.17	48.1	0.102
Other Solid	97	0.49	74	0.97	71.9	0.153
Gonads (Hereditary)	12	0.80	12	1.32	15.3	0.032
Total	***1562***		***468***		***471***	***1.000***

* Defined as $R*q + R*(1-q)* ((1 - q_{min}) q + q_{min})$, where R is the nominal risk coefficient, q is the lethality, and $(1 - q_{min}) q + q_{min}$ is the weight given to non-fatal cancers. Here q_{min} is the minimum weight for nonfatal cancers. The q_{min} correction was not applied to skin cancer (see text).

+ The values given should not be taken to imply undue precision but are presented to 3 significant figures to facilitate the tracibility of the calculations made.

[a] The values in the Table differ from these in the corresponding table in Annex A of the draft 2005 Recommendations as a consequence of an internal ICRP review of the calculations initially made.

2009 **Table 4.2: Comparison of Gender-Averaged Nominal Risks and Detriment**
2010 **in Whole Population based on Different Methods of Calculation**

Tissue	Method of calculation	Nominal risk (cases per 10,000 persons per Sv)			Lethality adjusted nominal risk*	Detriment	Relative detriment+
		Total	Fatal	Non-fatal			
Oesophagus	Current Incidence	17.3	16.1	1.3	17.2	15.0	0.025
	Current Mortality	29.1	27.0	2.1	29.0	25.2	0.039
	Current ICRP-60	26.7	25	1.9	26.6	23.2	0.032
	ICRP-60 actual	31.6	30	1.6	31.5	24.3	0.033
Stomach	Current Incidence	90.4	75.0	15.5	88.1	77.5	0.127
	Current Mortality	72.0	59.7	12.3	70.1	61.7	0.095
	Current ICRP-60	56.2	47	9.6	54.7	48.1	0.067
	ICRP-60 actual	122.2	110	12.2	121.0	100.8	0.139
Colon	Current Incidence	121.3	58.0	63.4	91.5	88.8	0.146
	Current Mortality	71.8	34.3	37.5	54.2	52.6	0.081
	Current ICRP-60	245.3	117	128.1	185.1	179.5	0.249
	ICRP-60 actual	154.5	85	69.5	123.3	102.7	0.142
Liver	Current Incidence	19.0	18.2	0.9	19.0	16.7	0.027
	Current Mortality	37.7	36.0	1.7	37.2	32.8	0.050
	Current ICRP-60	15.8	15	0.8	15.7	13.8	0.019
	ICRP-60 actual	15.8	15	0.8	15.8	15.8	0.022
Lung	Current Incidence	101.3	90.1	11.2	100.2	80.1	0.131
	Current Mortality	110.8	98.6	12.2	109.6	87.7	0.135
	Current ICRP-60	70.3	63	7.8	69.5	55.6	0.077
	ICRP-60 actual	89.5	85	4.5	89.3	80.3	0.111
Bone Surface	Current Incidence	7.0	3.2	3.9	5.1	5.1	0.008
	Current Mortality	7.0	3.2	3.9	5.1	5.1	0.008
	Current ICRP-60	7.0	3	3.9	5.1	5.1	0.007
	ICRP-60 actual	6.9	5	1.9	6.4	6.4	0.009
Skin	Current Incidence	1000.0	2.0	998.0	4.0	4.0	0.007
	Current Mortality	1000.0	2.0	998.0	4.0	4.0	0.006
	Current ICRP-60	1000.0	2.0	998.0	4.0	4.0	0.006
	ICRP-60 actual	1000.0	2.0	998.0	4.0	4.0	0.006
Breast	Current Incidence	69.0	20.3	48.7	38.1	49.1	0.081
	Current Mortality	56.5	16.6	39.8	31.2	40.2	0.062
	Current ICRP-60	47.5	14	33.5	26.2	33.9	0.047
	ICRP-60 actual	40.0	20	20.0	30.0	36.3	0.050
Ovary	Current Incidence	12.6	7.1	5.5	10.5	11.7	0.019
	Current Mortality	21.2	12.0	9.2	17.6	19.7	0.030
	Current ICRP-60	23.4	13	10.2	19.4	21.8	0.030
	ICRP-60 actual	14.3	10	4.3	13.0	14.6	0.020
Bladder	Current Incidence	42.7	12.2	30.5	23.0	16.4	0.027
	Current Mortality	71.7	20.4	51.3	38.7	27.5	0.042
	Current ICRP-60	100.4	29	71.8	54.2	38.5	0.053
	ICRP-60 actual	60.0	30	30.0	45.0	29.3	0.040
Thyroid	Current Incidence	23.5	1.6	22.0	7.1	9.2	0.015
	Current Mortality	23.3	1.6	21.8	7.1	9.1	0.014
	Current ICRP-60	120.3	8	112.3	36.4	47.0	0.065
	ICRP-60 actual	80.0	8	72.0	15.2	15.2	0.021

Tissue	Method of calculation	Nominal risk (cases per 10,000 persons per Sv)			Lethality adjusted nominal risk*	Detriment	Relative detriment+
		Total	Fatal	Non-fatal			
Bone Marrow	Current Incidence	41.9	28.0	13.9	37.7	61.5	0.101
	Current Mortality	53.9	36.0	17.9	48.9	79.1	0.123
	Current ICRP-60	42.1	28	13.9	37.9	61.8	0.096
	ICRP-60 actual	50.5	50	0.5	50.5	104.0	0.143
Other Solid	Current Incidence	188.6	92.5	96.1	144.6	148.9	0.244
	Current Mortality	226.3	111.0	115.3	173.4	178.6	0.275
	Current ICRP-60	216.9	106	110.5	166.2	171.2	0.215
	ICRP-60 actual	70.4	50	20.4	64.5	58.7	0.081
Gonads	Current Incidence	20.0	16.0	4.0	19.3	25.4	0.042
(hereditary)	Current Mortality	20.0	16.0	4.0	19.3	25.4	0.039
	Current ICRP-60	20.0	16	4.0	19.3	25.4	0.035
	ICRP-60 actual	100.0	100	0.0	100.0	133.3	0.183
Total	Current Incidence	1755	440	1315	605	609.5	1.0
	Current Mortality	1801	474	1327	645	649.2	1.0
	Current ICRP-60	1976	479	1497	709	719.9	1.0
	ICRP-60 actual	1836	600	1236	709	725.3	1.0

Footnote and numerical values as per Table 4.1.

4.4.1.4 The use of relative detriment from incidence data for a tissue weighting system

The Commission has made a policy decision that there should only be a single set of w_T values that are averaged over both genders and all ages.

A set of w_T values could be proposed that closely follows the respective values of relative detriment based on incidence data given in Table 4.1 together with the supporting comparative data of Table 4.2. However, the Task Group feels that additional judgements need to be exercised to include subjective factors, not reflected in the mathematical formulation of detriment. In particular, the following judgements were applied.

- The detriments for heritable effects and cancer following gonadal irradiation were aggregated to give a w_T of 0.08.
- The detriment of thyroid cancer was increased to 0.05 to take account of the concentration of cancer risk in childhood, i.e. young children are considered to be a particularly sensitive sub-group.
- Cancer risk in salivary glands and brain, whilst not specifically quantifiable, is judged to be greater than that of other tissues in the remainder fraction and for this reason each is ascribed a w_T of 0.01.

Re-ordering of w_T values using the above judgements was made ensuring that these values did not diverge from the relative detriments of Table 4.1 by more than around two-fold. This reassignment gives a w_T value for the remainder tissues of 0.12. The Task Group presents a new proposal on the way in which the weighting of remainder tissues is treated.

According to this proposal the w_T for remainder tissues (0.12) is divided equally between the 15 tissues given in the footnote to Table 4.3, 0.008 each, which is lower than the w_T for the lowest of the named tissues (0.01). The number of tissues included in remainder could be increased if necessary. The system preserves additivity in effective doses. This is judged to be an appropriate simplification on the scheme of *Publication 60* in which the w_T for the remainder is divided among the five remainder tissues which receive the highest does ie a non-additive system. Mass weighting of tissues in the remainder fraction was explored but rejected. The principal reason for this rejection was that the very large disparities in tissue masses caused unacceptable distortions of effective dose for certain radionuclides. A notable feature of detriment in Table 4.1 is that the heritable detriment from gonadal irradiation is distinguished from that of cancer risk (i.e. in ovary and testes). For the purposes of the new Recommendations, these w_T values need to be aggregated.

On the basis of the detriment data of Tables 4.1 and 4.2 plus the judgements summarised above, the Task Group proposes the tissue weighting scheme given in Table 4.3.

Table 4.3 Proposed tissue weighting factors

Tissue	w_T	Σw_T
Bone-marrow, Colon, Lung, Stomach, Remainder Tissues* (Nominal w_T applied to the average dose to 15 tissues)	**0.12**	0.60
Breast, Gonads	**0.08**	0.16
Bladder, Oesophagus, Liver, Thyroid	**0.05**	0.20
Bone surface, Brain, Salivary glands, Skin	**0.01**	0.04

*__Remainder Tissues (15 in total)__

Adipose tissue, Adrenals, Connective tissue, Extrathoracic (ET) region[a], Gall bladder, Heart wall, Kidneys, Lymphatic nodes, Muscle, Pancreas, Prostate, Small intestine (SI) Wall, Spleen, Thymus, Uterus/cervix.

[a] *As defined in ICRP Publication 66, includes anterior (ET1) and posterior nasal passages, larynx, pharynx and mouth (ET2). ICRP will be giving consideration to specifically including oral mucosa in remainder tissues.*

It should be noted that the w_T for gonads is applied to the mass-weighted mean of the doses to testes and ovaries (i.e. the average dose in gonadal tissue), and that the dose to the colon is taken to be the mass-weighted mean of ULI and LLI doses, as in the *Publication 60* formulation.

4.4.2 Nominal probability coefficients for cancer and hereditary effects

New data on the risks of radiation-induced cancer and hereditary effects have been used by the Task Group in risk modelling and disease detriment calculations in order to estimate nominal probability coefficients for consideration by the Commission.

On the basis of these calculations (Table 4.1) the Task Group proposes nominal probability coefficients for lethality adjusted cancer risk as 5.9 10^{-2} Sv^{-1} for the whole population and 4.6 10^{-2} Sv^{-1} for adult workers aged 18-64. For hereditary effects, the lethality adjusted nominal risk in the whole population is estimated as 0.2 10^{-2} Sv^{-1} and in adult workers as 0.1 10^{-2} Sv^{-1}. These estimates are shown in Table 4.4, where they are compared with the estimates of detriment used in the 1990 Recommendations.

Table 4.4: Detriment adjusted nominal probability coefficients for cancer and hereditary effects (10^{-2} Sv^{-1})[1]

Exposed population	Cancer		Heritable effects		Total	
	Present	ICRP60	Present	ICRP60	Present	ICRP 60
Whole	**5.9**	**6.0**	**0.2**	**1.3**	**6.1**	**7.3**
Adult	**4.6**	**4.8**	**0.1**	**0.8**	**4.7**	**5.6**

[1]Values from Tables 4.1a, 4.1b and ICRP *Publication 60*.

In respect of Table 4.4 it is important to note that the detriment adjusted nominal probability coefficient for cancer estimated here has been computed in a different manner from that of *Publication 60*. The present estimate is based upon lethality/life impairment weighted data on cancer incidence with adjustment for relative life lost whereas in *Publication 60* detriment was based upon fatal cancer risk weighted for non-fatal cancer, relative life lost for fatal cancers and life impairment for non-fatal cancer. In this respect it is also notable that the detriment unadjusted nominal probability coefficient for fatal cancer in the whole population that may be projected from the cancer incidence-based data of Table 4.2a is around 4% per Sv (computed value of 4.2%) as compared with the *Publication 60* value of 5% per Sv. The corresponding value using cancer mortality-based models is essentially unchanged at around 5% (computed value of 4.6% per Sv).

An additional point relating to the present detriment adjusted cancer coefficients of Table 4.4 is that during the period that new ICRP recommendations are likely to apply, the survival rates for many cancers are expected to rise. In this respect the nominal risk coefficient proposed here will tend to be an over-estimate of risks in the future.

The differences in the estimates of detriment adjusted heritable effects between the present report and *Publication 60* are explained and discussed under 6.5.

4.4.3 Cancer risk following prenatal (in-utero) irradiation

Studies on cancer risk following irradiation of the unborn child were reviewed in *Publication 90*.

The largest case-control study of cancer after *in-utero* irradiation, the Oxford Study of Childhood Cancers (OSCC), found that radiation increased all types of childhood cancer by approximately the same degree. The second largest study showed a larger relative risk of leukaemia than for solid tumours, while several cohorts studies of *in-utero* radiation found no clear evidence of radiation-induced childhood cancer. The data from the atomic bomb survivors suggest that the lifetime cancer risk from *in-utero* exposure may be similar to that from exposure in early childhood.

The OSCC data suggest that cancer induction is at least as likely following exposure in the first trimester as in later trimesters. From the data published to date, it is not possible to determine tissue-weighting factors in order to define cancer risk in different tissues and organs. Adequate human *in-utero* exposure data are not available to define the dose and dose-rate effectiveness factor (DDREF) for low-LET radiation or the RBE values for neutron or other high-LET radiations.

Given the limitations of the available data the Task Group have not attempted to derive a specific value for the nominal coefficient for life-time cancer risk after prenatal exposure and support the *Publication 92* judgement that it is reasonable to assume that this risk is, at most, a few times that of the population as a whole.

4.4.4 Genetic susceptibility to radiation-induced cancer

On the basis of the data analyses and judgements developed in *Publication 79* and further information reviewed in the UNSCEAR 2000 and 2001 reports, the Task Group believes that strongly expressing, high penetrance, cancer genes are too rare to cause significant distortion of the population-based estimates of low dose radiation cancer risk made in this Section of the report. However, as noted in *Publication 79*, there are likely to be implications for individual cancer risks, particularly for second cancers in gene carriers receiving radiotherapy for a first neoplasm. Although the Task Group recognises that weakly expressing variant cancer genes may, in principle, be sufficiently common to impact upon population based estimates of radiation cancer risk, the information available is not sufficient to provide a meaningful quantitative judgement on this issue.

4.4.5 Allowing for the possibility of a low dose threshold for cancer risk

In the preceding discussion and computations it has been assumed that, at low doses and at low dose rates, site-specific cancer risk from low-LET radiation is proportional to radiation dose, consistent with the so-called linear, no-threshold (LNT) hypothesis. Thus, the possibility that there might be a threshold dose, below which there would be no radiation-related cancer risk, has been ignored. The LNT hypothesis is not universally accepted as biological truth, but rather, because we do not actually know what level of risk is associated with very low-dose exposure, it is considered to be a prudent judgement for public policy aimed at avoiding unnecessary risk from exposure.

As discussed at length in *Publication* LDR-C-1, the LNT hypothesis receives considerable, although not decisive, support from epidemiological studies of radiation-related cancer risk, in the sense that the risk of mortality and morbidity from all solid cancers combined is proportional to radiation dose down to about 100 mGy, below which statistical variation in baseline risk, as well as small and uncontrollable biases, increasingly tend to obscure evidence concerning radiation-related risk. This uncertainty is the main reason why it is generally impossible to determine, on epidemiological grounds alone, that there is, or is not, an increased risk of cancer associated with radiation exposures of the order of 10 mGy and below. Risk estimates for such exposures are obtained through the use of mathematical models that assume a simple relationship eg, linear, linear-quadratic, or linear with a dose and dose rate effectiveness factor (DDREF)) between risk at higher doses, where epidemiological data tend

to be informative, and at doses so low that direct epidemiological observation is uninformative.

In spite of the biological evidence supporting the LNT hypothesis with respect to the induction by ionising radiation of complex DNA damage, for which repair mechanisms in mammalian species tend to be error-prone, the possibility of a threshold for cancer induction at some unknown low dose cannot be ruled out (see 4.1).

At the molecular level, the generation of multiple DNA lesions within close spatial proximity, creating complex damage for which mammalian repair mechanisms tend to be error-prone, is believed to be the primary mechanism by which ionising radiation contributes to the induction of mutations and chromosome aberrations and hence to the pathogenesis of cancer. Such clustered damage in DNA, in principle, can be induced even by a single radiation track through a cell. Also, while many of the cells containing such radiation-induced damage may be eliminated by damage response pathways involving cell cycle checkpoint control and apoptotic cell death, it is clear from analysis of cytogenetic and mutation data that damaged or altered cells are capable of evading these protective measures and propagating.

Considered as a whole, the emerging results from cellular studies with regard to radiation-related adaptive response, genomic instability, and bystander effects suggest that the risk of low level exposure to ionising radiation is uncertain, and a simple extrapolation from high dose effects may not be wholly justified in all instances. However, a better understanding of the mechanisms for these phenomena, the extent to which they are active *in vivo*, and how they are interrelated is needed before they can be evaluated as factors to be included in the estimation of potential risk to the human population of exposure to low levels of ionising radiation.

Recent studies using newly developed animal models, cellular, cytogenetic and molecular data for acute myelogenous leukaemia (AML), intestinal tumours, and mammary tumors, and cytogenetic and molecular studies on the induction of AML and mammary cancer support the view that the essential radiation-associated events in the tumorigenic process are predominantly early events involving DNA losses targeting specific genomic regions harbouring critical genes. As such, the response for early initiating events is likely to correspond to that for the induction of cytogenetic and mutagenic damage. On this basis, mechanistic arguments support a linear response in the low dose region, i.e., the process should be independent of dose rate because interactions between different electron tracks should be rare. Quantitative analyses of dose responses for tumorigenesis and for life shortening in laboratory animals also support this prediction.

As discussed in *Publication LDR-C-1*, the statistical uncertainty highlighted earlier in this section is accompanied by other uncertainties, on the model assumptions needed to estimate the risk of radiation-related cancer at low radiation doses. These latter uncertainties are usually subject to only subjective quantification. Such uncertain assumptions include, among others, the DDREF to be applied at low doses and low dose rates, the relationship between excess and baseline cancer rates when transferring estimates from one population to another, and the relationship between estimated and true radiation dose in the exposed population from which the risk estimate was derived (See 4.4.1.2). All of these assumptions can profoundly affect the estimated risk and its probabilistic uncertainty limits. If one also allows for the uncertain possibility of a universal threshold dose at some known level or a threshold the value of which is highly uncertain, or which varies widely among members of the exposed population, this also affects the risk estimate and its uncertainty limits. In an exercise described in *Publication LDR-C-1* it was found that, unless the existence of a threshold was assumed to be virtually certain, and its possible values restricted well beyond that which can be justified on current knowledge, the effect of introducing the uncertain possibility of a threshold was equivalent to that of an uncertain increase in the value of DDREF, i.e. merely a variation on the result obtained by ignoring the possibility of a threshold.

The existence of a low dose threshold for cancer induction in certain tissues is not implausible. Indeed, as noted in *Publication LDR-C-1* there is no clear evidence for a radiation-associated excess of cancers for a number of tissues eg chronic lymphocytic leukaemia, testicular cancer, melanoma skin cancer.

Although the available data do not exclude the existence of a universal low dose threshold, the evidence as a whole, as summarised in this report, does not favour this proposition. It may be that the long standing question on the true validity of the linear-no threshold (LNT) hypothesis will provide to be beyond definitive scientific resolution and that 'weight of evidence' arguments and practical judgements will continue to apply in the foreseeable future.

In summary the Task Group judges that there is at present no good reason to include the possibility of a low dose threshold in cancer risk calculations for the purposes of radiological protection. On this basis it is recommended that the LNT hypothesis, combined with an uncertain judged value of DDREF for extrapolation from high doses, remains a prudent basis for the practical purposes of radiological protection at low doses and low dose rates.

Appendix 1 to Section 4

Further details of the detriment calculations

Table A1: Values for lethality factors, non-fatal case weights, and relative life lost values used in the current computations, together with the corresponding values in ICRP Publication 60

Site	Current			ICRP 60	
	Lethality (k)	Non-fatal case weight (q)	Relative life lost	Lethality (k =q)	Relative life lost
Oesophagus	0.93	0.935	0.87	0.95	0.65
Stomach	0.83	0.846	0.88	0.90	0.83
Colon	0.48	0.530	0.97	0.55	0.83
Liver	0.95	0.959	0.88	0.95	1.00
Lung	0.89	0.901	0.80	0.87	0.90
Bone Surface	0.45	0.505	1.00	0.72	1.00
Skin	0.002	0.002	1.00	--	1.00
Breast	0.29	0.365	1.29	0.50	1.21
Ovary	0.57	0.609	1.12	0.70	1.12
Bladder	0.29	0.357	0.71	0.50	0.65
Thyroid	0.07	0.253	1.29	0.10	1.00
Bone Marrow	0.67	0.702	1.63	0.99	2.06
Other Solid	0.49	0.541	1.03	0.71	0.91
Gonads	0.80	0.820	1.32	--	1.33

k, q and the relative life lost are defined in section 4.4.1.2. In particular, q is taken as q_min + (1-q_min)*k in the current calculations, where q_min is 0 for skin, 0.2 for thyroid and 0.1 for all other sites.

Table A2: Coefficients in the current cancer incidence-based ERR models

Site	Gender	ERR per Gy at age 70 for exposure at age 30	Age at exposure: % change in ERR per decade increase	Power of Attained age by which the ERR varies	F:M ratio	$P_{Consistency}$
All solid	M	0.35	-18%	-1.74	1.66	
	F	0.58				
Oesophagus	M	0.52	-18%	-1.74	1.66	0.58
	F	0.87				
Stomach	M	0.23	-18%	-1.74	1.66	0.91
	F	0.38				
Colon	M	0.49	5%	-4.21	0.70	--
	F	0.34				
Liver	M	0.21	-18%	-1.74	1.66	0.91
	F	0.35				
Lung	M	0.60	12%	-1.74	1.66	0.09
	F	1.00				
Breast	F	0.99	-5%	-1.74	--	0.21
Ovary	F	0.44	-18%	-1.74	--	0.99
Bladder	M	0.66	-18%	-1.74	1.66	0.52
	F	1.10				
Thyroid	M	0.44	-63%	0.00	1.00	0.36
	F	0.44				
Other	M	0.26	-34%	-1.74	0.90	0.50
	F	0.23				

Table A3: Coefficients in the current cancer incidence-based EAR models

Site	Gender	Excess deaths per 10000 persons per year per Gy at age 70 for exposure at age 30	Age at exposure: % change in EAR per decade increase	Power of Attained age by which the EAR varies	F:M ratio	$P_{Consistency}$
All Solid	M	43.69	-27%	2.39	1.42	
	F	62.19				
Oesophagus	M	1.86	-27%	2.39	0.06	0.17
	F	0.12				
Stomach	M	10.92	0%	2.39	1.00	0.53
	F	10.92				
Colon	M	9.13	-51%	6.96	--	--
	F	3.84		2.19		
Liver	M	1.13	-27%	2.39	1.42	0.55
	F	1.60				
Lung	M	9.49	0%	4.33	1.00	0.89
	F	9.49				
Breast	F	9.04	-30%	3.27* -2.02		0.002§
Ovary	F	1.39	-27%	2.39	--	--
Bladder	M	2.57	0%	5.24	1.00	0.24
	F	2.57				
Thyroid	M	0.34	-43%	0.00	3.21	0.25
	F	1.09				
Other	M	10.16	-27%	1.40	1.42	0.12
	F	14.46				

§ Test of hypothesis that spline in attained age is unnecessary.
* Upper term is age effect before age 50 and lower term is effect for age greater than 50.

2301 **Table A4: Coefficients in the current mortality-based ERR models**
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Site	Gender	ERR per Gy at age 70 for exposure at age 30	Age at exposure: % change in ERR per decade increase	Power of Attained age by which the ERR varies	F:M ratio	$P_{Consistency}$
Solid	M	0.35	-31%	-0.74	1.68	
	F	0.58				
Oesophagus	M	0.76	-31%	-0.74	1.68	0.47
	F	1.27				
Stomach	M	0.26	-31%	-0.74	1.68	0.48
	F	0.43				
Colon	M	0.25	-31%	-4.46	1.00	0.43
	F	0.25				
Liver	M	0.21	-31%	-0.74	1.68	0.94
	F	0.34				
Lung	M	0.55	-4%	-0.74	1.68	0.76
	F	0.92				
Breast	F	0.96	-31%	-0.74		0.70
Ovary	F	0.67	-31%	-0.74		0.67
Bladder	M	0.74	12%	-0.74	1.68	0.75
	F	1.24				
Other	M	0.13	-56%	-0.74	1.68	0.40
	F	0.22				

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Table A5: Coefficients in the current mortality-based EAR models

Site	Gender	Excess deaths 10000 persons per year per Gy at age 70 for exposure at age 30	Age at exposure: % change in EAR per decade increase	Power of Attained age by which the EAR varies	F:M ratio	$P_{Consistency}$
All Solid	M	28.91	-24%	3.63	1.04	
	F	29.99				
Oesophagus	M	0.98	-24%	3.63	1.00	0.42
	F	0.98				
Stomach	M	5.79	-24%	3.63	1.00	0.45
	F	5.79				
Colon	M	2.24	-24%	3.63	1.00	0.66
	F	2.24				
Liver	M	6.46	-24%	5.56	0.37	0.42
	F	2.36				
Lung	M	6.72	-24%	6.56	1.00	0.70
	F	6.72				
Breast	F	15.73	-44%	5.78 -2.83		0.01*
Ovary	F	1.40	-24%	3.63		0.90
Bladder	M	0.83	0%	8.04	1.00	0.23
	F	0.83				
Other	M	3.68	-52%	3.63	1.00	0.29
	F	3.68				

* Test of hypothesis that a spline in attained age is unnecessary.

Table A6: Female Euro-American cancer incidence rates by age and site

Number of cases per 100,000 persons per year

Age	All Cancer	All Solid	Oesophagus	Stomach	Colon	Liver	Lung	Breast	Ovary	Bladder	Thyroid	Leukaemia	Non-CLL Leukaemia	CLL
0-4	18.37	10.95	0.00	0.01	0.01	0.32	0.01	0.02	0.05	0.06	0.01	6.95	6.92	0.03
5-9	9.03	5.28	0.00	0.01	0.03	0.03	0.04	0.00	0.23	0.00	0.08	3.07	3.05	0.02
10-14	10.20	6.57	0.00	0.04	0.11	0.04	0.02	0.01	0.69	0.00	0.54	2.15	2.15	0.00
15-19	17.49	11.03	0.01	0.08	0.25	0.07	0.04	0.12	1.77	0.07	1.80	2.20	2.19	0.00
20-24	29.46	21.96	0.02	0.09	0.36	0.09	0.19	1.19	2.89	0.19	3.87	1.63	1.59	0.04
25-29	51.15	43.58	0.04	0.27	0.83	0.17	0.39	7.17	4.03	0.31	5.60	1.66	1.61	0.04
30-34	83.77	76.06	0.10	0.75	1.27	0.24	1.04	23.53	5.82	0.50	6.38	1.90	1.86	0.04
35-39	137.56	129.33	0.13	1.17	3.27	0.39	3.20	54.12	9.00	0.98	7.00	2.41	2.27	0.14
40-44	227.67	215.47	0.50	2.28	6.00	0.64	8.29	107.57	13.73	1.85	7.20	3.72	3.41	0.31
45-49	372.68	355.20	1.07	3.31	11.90	1.42	20.20	183.33	24.54	4.05	8.48	4.52	3.72	0.80
50-54	540.14	512.41	2.42	5.02	21.92	2.43	40.44	243.57	34.33	7.90	8.07	7.61	5.28	2.34
55-59	703.34	663.31	5.27	8.76	41.98	4.07	67.32	263.17	41.39	13.25	7.97	9.99	6.59	3.40
60-64	907.16	851.75	7.92	14.26	63.80	6.73	106.00	298.07	49.35	22.38	7.16	15.15	9.82	5.33
65-69	1127.22	1048.58	11.24	21.99	94.46	9.82	154.72	305.57	55.60	33.45	7.79	21.91	12.96	8.94
70-74	1385.31	1279.59	16.96	33.48	138.10	14.11	190.74	328.61	62.04	47.83	8.53	30.29	17.72	12.57
75-79	1557.27	1427.72	21.52	47.53	177.76	17.32	191.05	339.09	61.42	56.59	8.13	37.99	21.96	16.03
80-84	1707.07	1565.32	26.77	65.22	234.14	22.02	166.82	365.99	56.31	68.67	8.73	43.94	26.88	17.05
85-89	1660.82	1667.88	34.82	76.14	241.25	21.66	127.96	335.97	49.39	83.68	8.73	43.98	26.91	17.07
90+	1720.81	1706.61	23.34	73.73	266.50	16.94	76.51	382.23	38.63	54.69	8.73	73.39	44.90	28.48

Table A7: Male Euro-American cancer incidence rates by age and site

Number of cases per 100,000 persons per year

Age	All Cancer	All Solid	Oesophagus	Stomach	Colon	Liver	Lung	Breast	Ovary	Bladder	Thyroid	Leukaemia	Non-CLL Leukaemia	CLL
0-4	21.64	12.70	0.00	0.01	0.00	0.62	0.01			0.12	0.00	7.78	7.77	0.01
5-9	11.66	6.18	0.00	0.00	0.00	0.10	0.00			0.01	0.05	3.80	3.80	0.00
10-14	12.26	6.18	0.00	0.00	0.06	0.05	0.03			0.02	0.13	3.07	3.07	0.00
15-19	18.72	11.10	0.00	0.06	0.13	0.10	0.11			0.10	0.43	2.73	2.73	0.00
20-24	29.00	20.81	0.02	0.10	0.33	0.15	0.19			0.39	0.77	1.98	1.98	0.00
25-29	43.12	32.54	0.09	0.27	0.92	0.22	0.36			0.60	1.54	2.36	2.33	0.03
30-34	58.48	45.37	0.21	0.82	1.75	0.32	0.99			1.27	1.47	2.87	2.80	0.07
35-39	77.82	61.65	0.64	1.45	3.15	0.72	3.19			2.52	1.78	3.61	3.20	0.41
40-44	115.96	95.95	1.94	3.27	6.71	2.06	9.41			5.70	2.15	4.65	3.81	0.84
45-49	198.61	170.47	4.26	6.02	12.42	3.12	23.28			12.63	2.83	6.67	4.85	1.82
50-54	380.05	337.58	9.47	11.72	25.26	5.53	56.22			25.29	3.34	11.59	7.20	4.38
55-59	676.04	617.96	15.68	21.64	47.90	9.60	108.53			46.07	3.81	16.47	9.56	6.91
60-64	1136.55	1053.31	24.79	36.02	84.67	15.00	189.00			79.67	4.16	25.34	14.06	11.28
65-69	1767.07	1651.87	33.72	58.28	129.65	22.80	304.06			132.28	5.24	37.75	20.92	16.83
70-74	2415.76	2255.06	46.59	87.72	185.35	30.88	400.78			184.53	5.69	56.29	30.97	25.33
75-79	2882.34	2680.83	49.57	114.49	248.89	36.70	456.24			229.94	5.98	68.43	39.48	28.95
80-84	3225.05	2983.09	55.88	145.00	310.36	36.96	459.96			275.56	6.26	86.36	50.15	36.21
85-89	3033.46	3166.00	59.36	165.76	316.71	37.73	404.07			266.44	6.26	91.89	38.53	53.36
90+	3676.73	3290.99	49.36	137.84	335.18	39.21	337.79			376.32	6.26	102.86	43.13	59.73

Table A8: Female Euro-American cancer mortality rates by age and site

Number of deaths per 100,000 persons per year

Age	All Cause	All Cancer	All Solid	Oesophagus	Stomach	Colon	Liver	Lung	Breast	Ovary	Bladder	Leukaemia	Non-CLL Leukaemia	CLL
0-4	114.61	2.22	1.46	0.00	0.00	0.00	0.06	0.02	0.00	0.01	0.00	0.76	0.76	0.00
5-9	11.35	2.01	1.42	0.00	0.00	0.00	0.02	0.01	0.00	0.01	0.01	0.59	0.59	0.00
10-14	13.28	2.05	1.34	0.00	0.02	0.01	0.02	0.01	0.00	0.03	0.00	0.71	0.71	0.00
15-19	28.51	2.76	1.74	0.00	0.03	0.04	0.05	0.02	0.00	0.10	0.00	1.02	1.02	0.00
20-24	33.03	3.40	2.46	0.01	0.05	0.06	0.10	0.04	0.09	0.21	0.00	0.94	0.94	0.00
25-29	40.17	5.97	5.10	0.02	0.14	0.21	0.11	0.10	0.96	0.31	0.01	0.87	0.87	0.00
30-34	55.43	12.77	11.86	0.04	0.41	0.35	0.15	0.53	3.85	0.74	0.06	0.91	0.91	0.00
35-39	81.36	26.07	24.79	0.10	0.69	1.11	0.28	1.90	9.49	1.41	0.09	1.27	1.27	0.00
40-44	122.96	48.98	47.14	0.30	1.23	2.02	0.58	5.45	18.24	3.34	0.19	1.84	1.84	0.00
45-49	193.21	88.79	86.48	0.87	1.76	4.59	1.07	13.34	31.03	7.13	0.49	2.31	2.31	0.00
50-54	309.20	150.52	147.17	1.87	2.98	8.82	1.82	28.25	45.67	13.39	1.00	3.34	3.34	0.00
55-59	489.59	232.48	227.46	3.93	5.16	16.19	3.28	48.94	57.28	21.10	1.82	5.15	5.02	0.13
60-64	801.25	343.06	335.47	6.24	8.47	25.88	5.31	81.35	68.26	27.83	3.70	7.59	7.59	0.00
65-69	1283.49	487.75	476.42	9.10	14.54	39.32	8.87	123.13	82.37	34.97	6.63	12.06	11.33	0.73
70-74	2098.33	654.11	636.96	13.79	21.54	58.94	12.40	158.51	97.91	42.39	11.95	17.97	17.15	0.83
75-79	3406.46	801.53	778.31	20.07	32.16	81.11	16.83	167.46	117.85	45.48	17.98	25.36	23.22	2.15
80-84	5934.90	988.90	956.69	26.37	47.48	118.84	21.81	159.62	146.37	47.35	29.09	35.14	32.21	2.94
85-89	9876.82	1178.13	1146.03	35.87	64.84	165.46	26.79	137.93	188.77	46.61	48.53	38.97	35.71	3.25
90+	19441.90	1220.69	1172.64	24.05	62.78	182.78	20.95	82.47	214.76	36.46	31.72	65.02	59.59	5.43

Table A9: Male Euro-American cancer mortality rates by age and site

Number of deaths per 100,000 persons per year

Age	All Cause	All Cancer	All Solid	Oesophagus	Stomach	Colon	Liver	Lung	Breast	Ovary	Bladder	Leukaemia	Non-CLL Leukaemia	CLL
0-4	143.02	2.75	1.97	0.00	0.00	0.00	0.11	0.00			0.00	0.78	0.78	0.00
5-9	15.39	2.74	1.70	0.00	0.00	0.00	0.05	0.01			0.01	1.04	1.04	0.00
10-14	19.43	2.52	1.39	0.00	0.00	0.01	0.02	0.01			0.01	1.12	1.12	0.00
15-19	66.78	3.50	2.10	0.00	0.01	0.04	0.05	0.02			0.00	1.41	1.41	0.00
20-24	94.71	4.50	3.27	0.02	0.06	0.13	0.09	0.12			0.01	1.23	1.23	0.00
25-29	99.79	5.87	4.56	0.05	0.14	0.28	0.12	0.20			0.01	1.31	1.31	0.00
30-34	124.33	9.09	7.75	0.18	0.36	0.55	0.21	0.64			0.05	1.34	1.34	0.00
35-39	160.80	16.28	14.65	0.48	0.83	1.12	0.50	2.23			0.14	1.63	1.63	0.00
40-44	224.83	34.98	32.89	1.66	1.78	2.46	1.33	7.19			0.46	2.08	2.08	0.00
45-49	321.50	69.83	67.16	3.62	3.33	5.22	2.38	18.84			1.00	3.09	2.67	0.42
50-54	505.70	143.81	139.31	7.94	6.11	10.74	3.90	45.14			2.87	4.79	4.50	0.30
55-59	821.44	262.09	254.99	13.88	11.61	20.26	7.03	89.61			6.09	7.64	7.11	0.54
60-64	1378.11	457.53	446.19	21.98	21.78	35.75	11.69	162.02			12.33	12.85	11.34	1.51
65-69	2241.12	734.15	714.15	30.93	34.77	56.32	17.62	260.63			23.18	20.56	20.00	0.56
70-74	3590.14	1065.72	1036.77	41.20	53.11	85.62	24.51	354.10			39.44	32.65	28.94	3.70
75-79	5634.15	1427.76	1387.32	49.19	75.51	116.26	31.46	421.65			61.53	45.15	40.44	4.71
80-84	9122.79	1880.96	1826.90	55.21	103.50	165.63	36.27	464.57			96.92	64.25	54.06	10.19
85-89	13879.10	2208.86	2287.11	63.41	132.47	221.43	37.50	445.09			135.96	82.03	69.02	13.01
90+	24029.19	2677.26	2377.40	52.73	110.15	234.35	38.98	372.08			192.04	91.82	77.26	14.57

Table A10: Female Asian cancer incidence rates by age and site

Number of cases per 100,000 persons per year

Age	All Cancer	All Solid	Oesophagus	Stomach	Colon	Liver	Lung	Breast	Ovary	Bladder	Thyroid	Leukaemia	Non-CLL Leukaemia	CLL
0-4	16.18	10.16	0.00	0.00	0.00	0.41	0.00	0.00	0.017	0.23	0.00	4.63	4.63	0.00
5-9	7.47	4.04	0.00	0.00	0.00	0.15	0.00	0.00	0.248	0.00	0.18	2.44	2.44	0.00
10-14	10.32	6.13	0.00	0.00	0.00	0.15	0.05	0.00	1.170	0.00	0.55	3.25	3.25	0.00
15-19	9.62	7.27	0.00	0.20	0.30	0.11	0.12	0.00	1.485	0.00	1.54	1.62	1.62	0.00
20-24	16.76	13.77	0.00	0.95	0.26	0.22	0.14	0.51	2.075	0.06	3.26	1.58	1.58	0.00
25-29	29.87	26.73	0.11	2.41	1.52	0.32	0.86	3.62	2.492	0.15	3.84	1.76	1.76	0.00
30-34	61.04	56.94	0.05	8.54	2.40	0.92	1.26	14.77	3.452	0.13	5.74	2.02	2.02	0.00
35-39	113.76	107.71	0.20	15.25	5.53	2.25	2.97	38.85	5.848	0.43	6.78	3.29	3.27	0.01
40-44	184.71	177.61	0.65	24.58	9.34	3.69	7.70	67.94	9.592	0.75	10.45	3.93	3.92	0.01
45-49	242.53	233.01	1.15	27.18	16.76	5.89	12.55	86.55	13.050	0.94	13.31	4.26	4.18	0.08
50-54	302.19	290.49	2.17	34.98	28.27	11.12	19.96	81.36	15.142	2.80	12.54	6.02	5.89	0.13
55-59	401.39	386.17	6.38	52.62	44.43	21.21	34.36	76.81	16.122	4.62	11.59	5.96	5.60	0.36
60-64	592.40	565.68	12.35	75.78	71.50	46.70	63.49	88.33	19.615	7.49	12.86	9.70	9.19	0.51
65-69	776.54	744.60	17.66	113.21	89.08	75.39	89.27	86.57	19.888	10.82	12.59	11.11	10.75	0.36
70-74	1017.79	974.89	28.42	159.53	126.39	84.23	145.22	84.42	20.507	18.15	13.96	15.34	14.84	0.49
75-79	1177.00	1127.05	34.69	195.44	138.59	96.89	171.64	82.73	20.268	25.43	13.00	14.35	13.56	0.79
80-84	1338.05	1279.76	38.69	260.54	152.09	111.69	176.17	82.34	15.482	35.23	11.16	19.49	18.58	0.92
85-89	1470.65	1400.73	28.65	284.69	174.60	114.47	184.59	52.17	21.20	50.41	11.16	21.61	19.69	1.91
90+	1733.18	1653.38	27.96	354.64	244.83	113.01	193.15	65.36	23.17	34.96	11.16	22.70	20.69	2.01

Table A11: Male Asian cancer incidence rates by age and site

Number of cases per 100,000 persons per year

Age	All Cancer	All Solid	Oesophagus	Stomach	Colon	Liver	Lung	Breast	Ovary	Bladder	Thyroid	Leukaemia	Non-CLL Leukaemia	CLL
0-4	16.69	10.30	0.00	0.08	0.00	0.74	0.03			0.03	0.00	5.17	5.09	0.08
5-9	10.73	4.54	0.00	0.05	0.00	0.24	0.05			0.00	0.02	4.73	4.73	0.00
10-14	10.72	5.48	0.00	0.06	0.06	0.33	0.07			0.00	0.23	3.31	3.31	0.00
15-19	12.15	7.20	0.00	0.33	0.10	0.13	0.14			0.06	0.59	3.51	3.51	0.00
20-24	13.97	9.68	0.00	0.81	0.50	0.70	0.41			0.31	0.74	2.30	2.30	0.00
25-29	21.59	16.88	0.10	2.29	0.91	1.67	0.51			0.59	0.99	2.94	2.89	0.05
30-34	37.04	31.17	0.13	5.05	3.54	3.60	2.30			0.81	1.16	3.55	3.49	0.06
35-39	72.78	65.58	0.80	14.96	5.45	11.41	5.09			2.20	1.67	3.03	2.93	0.10
40-44	140.70	131.55	2.94	29.51	12.43	21.68	14.83			3.59	2.15	3.90	3.71	0.19
45-49	227.28	213.75	7.05	47.43	24.55	36.58	23.27			5.14	3.17	5.45	5.30	0.15
50-54	357.46	339.23	14.35	76.73	39.96	54.82	44.64			10.69	2.82	7.01	6.67	0.34
55-59	588.80	564.44	25.49	127.25	72.34	95.29	80.55			17.08	2.86	9.51	9.07	0.43
60-64	1059.95	1019.71	44.55	217.15	119.83	170.87	176.67			33.03	3.84	13.36	12.55	0.81
65-69	1523.88	1468.59	58.10	316.67	162.08	195.63	317.21			55.42	5.13	20.21	18.61	1.60
70-74	1948.97	1878.15	82.63	412.58	186.30	192.09	439.32			73.66	5.16	27.13	25.46	1.67
75-79	2267.27	2180.80	92.66	488.08	214.56	183.31	509.83			108.13	4.68	30.62	28.83	1.79
80-84	2470.31	2375.91	94.17	520.98	222.27	187.30	540.57			120.05	4.35	31.68	28.87	2.81
85-89	3372.14	3223.64	69.75	716.89	326.54	232.57	682.18			158.97	4.35	49.11	44.17	4.94
90+	3907.81	3742.07	68.97	863.48	422.02	215.09	608.83			264.33	4.35	49.86	44.84	5.02

Table A12: Female Asian cancer mortality rates by age and site

Number of deaths per 100,000 persons per year

Age	All Cause	All Cancer	All Solid	Oesophagus	Stomach	Colon	Liver	Lung	Breast	Ovary	Bladder	Leukaemia	Non-CLL Leukaemia	CLL
0-4	127.18	3.38	1.70	0.00	0.01	0.00	0.10	0.02	0.00	0.01	0.01	1.34	1.34	0.00
5-9	16.67	3.08	1.33	0.00	0.00	0.00	0.03	0.00	0.00	0.01	0.00	1.33	1.33	0.00
10-14	15.15	3.52	1.42	0.01	0.00	0.01	0.05	0.00	0.01	0.04	0.00	1.66	1.66	0.00
15-19	18.31	3.39	1.46	0.02	0.07	0.04	0.08	0.04	0.01	0.13	0.01	1.24	1.24	0.00
20-24	27.75	3.97	2.31	0.01	0.28	0.17	0.20	0.16	0.08	0.19	0.00	1.16	1.16	0.00
25-29	33.29	6.37	4.66	0.04	0.89	0.39	0.40	0.38	0.36	0.20	0.01	1.15	1.15	0.00
30-34	44.91	13.20	11.14	0.06	2.28	1.02	0.98	1.06	1.67	0.52	0.04	1.43	1.43	0.00
35-39	62.83	23.88	21.06	0.15	4.13	1.95	1.79	2.27	4.58	1.24	0.06	1.79	1.79	0.00
40-44	107.45	45.04	41.40	0.46	7.14	3.39	3.74	5.45	8.89	2.26	0.09	2.32	2.32	0.00
45-49	162.17	66.72	62.51	1.26	9.31	5.26	6.20	9.08	12.01	4.36	0.16	2.65	2.65	0.00
50-54	237.87	94.83	90.12	2.16	12.01	7.43	9.43	15.19	14.91	6.52	0.38	2.71	2.57	0.14
55-59	399.63	151.41	144.12	4.31	19.77	12.43	15.91	29.64	17.01	6.21	0.81	3.65	3.57	0.08
60-64	740.16	245.00	234.08	8.43	30.60	20.91	28.82	54.90	17.67	9.05	1.45	5.44	5.26	0.18
65-69	1239.84	357.21	342.78	15.26	47.37	30.14	41.39	83.63	18.97	9.55	3.27	6.05	5.32	0.72
70-74	2184.11	508.02	488.66	25.09	73.47	46.13	57.19	115.76	20.60	10.22	6.20	8.56	7.23	1.33
75-79	3682.84	653.04	630.76	34.41	101.60	64.40	67.38	138.34	24.32	11.85	10.27	8.60	7.58	1.02
80-84	6509.31	780.83	755.96	37.66	134.47	82.36	73.27	148.97	31.19	9.55	15.88	9.19	8.56	0.63
85-89	8923.98	712.91	693.30	39.96	126.81	75.93	63.03	119.29	29.99	8.63	21.78	6.95	6.71	0.23
90+	17750.63	840.17	818.35	39.00	157.96	106.46	62.23	124.82	37.57	9.43	15.10	7.30	7.05	0.25

Table A13: Male Asian cancer mortality rates by age and site

Number of deaths per 100,000 persons per year

Age	All Cause	All Cancer	All Solid	Oesophagus	Stomach	Colon	Liver	Lung	Breast	Ovary	Bladder	Leukaemia	Non-CLL Leukaemia	CLL
0-4	149.24	3.79	1.75	0.00	0.00	0.01	0.15	0.02			0.02	1.60	1.60	0.00
5-9	24.88	3.96	1.62	0.00	0.00	0.01	0.08	0.01			0.00	1.77	1.77	0.00
10-14	23.65	4.78	2.00	0.00	0.01	0.01	0.10	0.01			0.00	1.98	1.98	0.00
15-19	35.16	4.81	2.20	0.00	0.09	0.05	0.18	0.09			0.01	1.66	1.66	0.00
20-24	50.43	5.06	2.87	0.02	0.25	0.19	0.47	0.22			0.02	1.44	1.44	0.00
25-29	59.21	7.79	5.40	0.06	0.62	0.37	1.36	0.59			0.03	1.46	1.46	0.00
30-34	80.39	14.60	11.97	0.17	1.67	0.91	3.75	1.70			0.04	1.74	1.74	0.00
35-39	114.64	29.41	25.77	0.48	3.83	1.99	8.34	4.17			0.14	2.13	2.12	0.00
40-44	188.22	58.32	53.62	2.13	8.05	3.58	17.40	9.85			0.25	2.61	2.55	0.06
45-49	276.69	95.90	90.33	5.09	14.22	5.43	26.64	18.17			0.57	3.03	2.59	0.44
50-54	399.85	149.26	141.77	9.83	23.38	8.45	36.85	31.35			1.04	3.48	2.97	0.51
55-59	646.43	252.16	242.34	17.39	42.54	14.49	55.24	58.84			2.09	4.85	4.73	0.12
60-64	1257.04	482.58	466.03	34.20	80.47	28.65	95.25	130.56			5.07	6.98	6.33	0.65
65-69	2107.53	755.18	732.35	54.58	130.26	43.47	118.07	230.26			11.07	10.31	9.74	0.57
70-74	3550.26	1065.73	1035.03	82.96	194.71	65.39	131.80	335.02			19.49	13.49	12.52	0.97
75-79	5749.87	1365.66	1325.91	102.71	259.01	90.86	142.09	409.23			37.80	16.55	15.52	1.02
80-84	9661.98	1661.07	1614.41	121.87	328.69	122.29	155.29	446.43			62.69	18.78	16.66	2.12
85-89	12799.94	1586.63	1542.42	121.60	307.77	128.12	137.19	397.35			73.45	19.76	18.03	1.74
90+	22367.18	1838.67	1790.47	120.24	370.70	165.59	126.88	354.63			122.13	20.06	18.30	1.76

Appendix 2 to Section 4

Estimates of Selected Gender-Specific Population Detriments
Estimates based on cancer-incidence data

Tissue	Relative Detriment	
	Male	Female
Breast	-	0.150
Ovary	-	0.036
Thyroid	0.008	0.021
Gonads (heritable effects)	0.045	0.039

5. Non-cancer Diseases after Radiation Exposure

Since 1990 evidence has accumulated that the frequency of non-cancer diseases is increased in irradiated populations. The strongest evidence for the induction of these non-cancer effects at doses of the order of 1 Sv derives from the A-bomb LSS and the most recent mortality analysis (Preston et al 2003) has strengthened the statistical evidence for an association with dose – particularly for heart disease, stroke, digestive disorders and respiratory disease. However, the Task Group notes current uncertainties on the shape of the dose-response at low doses and that the LSS data are consistent both with there being no dose threshold for risks of disease mortality and with a threshold of around 0.5 Sv. It is unclear what forms of cellular/tissue mechanisms might underlie such a diverse set of non-cancer disorders reported among the LSS data although some association with sub-clinical inflammation (e.g. Hayashi et al 2003) is possible.

Additional evidence of the non-cancer effects of radiation, albeit at high doses, comes from studies of cancer patients receiving radiotherapy. For example, Hancock et al (1993) studied 2232 patients treated for Hodgkin's disease with a median follow-up time of 9.5 years and reported a three-fold risk of death due to heart disease after 30 Gy based on 88 deaths. Similarly, a recent analysis of cause-specific mortality among 1261 Hodgkin's patients, with a median follow-up of 17.8 years, demonstrated a relative risk (RR) for cardiovascular mortality of 6.3 after mediastinal radiotherapy based on 45 deaths. For patients treated before age 21, the RR increased to 13.6 based on 6 deaths (Aleman et al 2003). Significant increases in risks for cardiovascular disease have also been demonstrated in some other groups of patients treated with radiotherapy for malignant disease, such as breast cancer (eg Early Breast Cancer Trialists Collaborative Group 2000).

Whilst recognising the potential importance of these observations on non-cancer diseases, the Task Group judges that the data available do not allow for their inclusion in the estimation of detriment following radiation doses in the range up to a few tens of mSv. The Task Group notes that UNSCEAR is currently developing a view on these non-cancer effects and ICRP will follow these developments closely.

6. Risks of Heritable Diseases

6.1 Introduction

The term 'genetic risks' as used in this document denotes the probability of harmful genetic effects manifest in the descendants of a population that has sustained radiation exposures. These effects are expressed as increases over the baseline frequencies of genetic diseases in the population per unit dose of low LET, low dose/chronic irradiation.

Since the publication of the 1990 recommendations of the ICRP (ICRP 1991), the 1990 BEIR report (NRC 1990) and the UNSCEAR (1993) report, several important advances have been made in the prediction of genetic risks of exposure of human populations to ionising radiation. On the basis of these, UNSCEAR (2001) revised its earlier risk estimates. The aim of this section of the report is to provide a brief background on the available information and the methods that are used for risk estimation, summarize the recent advances, present the revised risk estimates and indicate how the new estimates can be used to derive a risk coefficient for genetic effects.

6.2 Background information

6.2.1 Naturally-occurring genetic diseases

The genetic diseases of interest in the present context are those due to mutations in single genes (Mendelian diseases) and those which are due to multiple genetic and environmental factors (multifactorial diseases). Historically, UNSCEAR, the BEIR Committees and ICRP had also considered an additional class of genetic diseases, namely, chromosomal diseases which are due to gross structural and numerical abnormalities of chromosomes.

Mendelian diseases are further subdivided into autosomal dominant, autosomal recessive and X-linked recessive categories depending on the chromosomal location (autosomes or the X-chromosome) of the mutant genes and their transmission patterns. In the case of an autosomal dominant disease, a single mutant gene inherited from either parent (i.e., in a heterozygous state) is sufficient to cause disease (e.g., achondroplasia, neurofibromatosis, Marfan syndrome etc.). The somewhat unusual genetics of dominantly inherited cancer predisposition are discussed in *Publication 79*. Autosomal recessive diseases, however, require two mutant genes, one from each parent, at the same locus (i.e., homozygosity) for disease manifestation (e.g., cystic fibrosis, haemochromatosis, Bloom syndrome, ataxia telangiectasia etc.). In the case of X-linked recessive diseases, since males have only one X-chromosome, usually only males are affected (e.g., haemophilia,

Duchenne muscular dystrophy, Fabry disease etc.). However, some X-linked dominant diseases are also known (e.g., Rett syndrome), but for the purpose of the present document, they are included under X-linked recessive diseases. The important general point with respect to Mendelian diseases is that the relationship between mutation and disease is simple and predictable.

Multifactorial diseases are aetiologically complex and consequently the relationship between mutation and disease is also complex i.e., these do not show Mendelian patterns of inheritance. The two sub-groups that constitute multifactorial diseases are the common congenital abnormalities (e.g., neural tube defects, cleft lip with or without cleft palate, congenital heart defects etc.) and chronic diseases of adults (e.g., coronary heart disease, essential hypertension, diabetes mellitus etc.). Evidence for a genetic component in their aetiology comes from family and twin studies which show that the first-degree relatives of affected individuals have a higher risk of disease than matched controls. For most of them, knowledge of the genes involved, the types of mutational alterations and the nature of environmental factors still remain limited. Among the models used to explain the inheritance patterns of multifactorial diseases and estimate recurrence risks in relatives is the multifactorial threshold model (MTM) of disease liability. This is considered in a later section.

Chromosomal diseases arise as a result of gross numerical (e.g., Down syndrome due to trisomy for chromosome 21) or structural abnormalities of chromosomes (e.g., Cri du chat syndrome, due to deletion of part or whole short arm of chromosome 5) generally detectable in cytological preparations of cells. This is really not an aetiological category and further, deletions (microscopically detectable or not) are now known to contribute to a number of genetic diseases grouped under autosomal dominant, autosomal recessive and X-linked diseases.

6.2.2 The doubling dose method

In the absence of human data on radiation-induced genetic diseases, all the methods that have been developed and used since the mid-1950s up to the present are indirect; their aim is to make the best use of mutation data obtained in radiation studies with mice, data on baseline frequencies of genetic diseases in the population and population genetic theory, to predict the radiation risk of genetic diseases in humans. One such method that has been used from the early 1970s onwards until now (e.g., UNSCEAR 2001) is the doubling dose method. This method enables one to express the expected increase in the frequencies of genetic diseases in terms of their baseline frequencies using the following equation:

$$\text{Risk per unit dose} = P \times [1/DD] \times MC \qquad (1)$$

where P is the baseline frequency of the genetic disease class under study, DD is the doubling dose (and [1/DD] is the relative mutation risk per unit dose) and MC is the disease-class specific mutation component.

The genetic theory that underlies the use of the DD method for risk estimation is what is referred to as the equilibrium theory which population geneticists use to explain the dynamics of mutant genes in populations. The theory postulates that the stability of mutant gene frequencies (and thus of disease frequencies) in a population is the result of the existence of a balance between the rate at which spontaneous mutations enter the gene pool of the population in every generation and the rate at which they are eliminated by natural selection i.e., through failure of survival or reproduction. Under normal conditions (i.e., in the absence of radiation exposures), the population is assumed to be in equilibrium between mutation and selection.

When the mutation rate is increased as a result of radiation, say, in every generation, the balance between mutation and selection is disturbed by the influx of induced mutations, but the prediction is that the population will eventually attain a new equilibrium (over a number of generations) between mutation and selection. The amount of increase in mutation frequency, the time it takes for the population to reach the new equilibrium and the rate of approach to it are all dependent on induced mutation rates, the intensity of selection, the type of genetic disease and whether radiation exposure occurs in one generation only or generation after generation. Worth mentioning here is that, since the starting population (before radiation exposure) is assumed to be in equilibrium between mutation and selection, the quantity P in equation (1) represents the equilibrium incidence.

Doubling dose. The doubling dose (DD) is the amount of radiation that is required to produce as many mutations as those that arise spontaneously in a generation. Ideally, it is estimated as a ratio of the average rates of spontaneous and induced mutations in a given set of genes:

DD = Average spontaneous mutation rate/average induced mutation rate (2)

The reciprocal of the DD (i.e., [1/DD] is the relative mutation risk (RMR) per unit dose. Since RMR is a fraction, the smaller the DD, the higher is the RMR and vice versa.

Mutation component. Formally defined, mutation component (MC) is the relative increase in disease frequency per unit relative increase in mutation rate:

$$MC = [\Delta P/P]/ [\Delta m/m] \quad (3)$$

where P is the baseline disease frequency, ΔP its change due to Δm change in mutation rate and m, the spontaneous mutation rate. The procedures used for estimating MC are relatively straightforward for autosomal dominant and X-linked diseases, slightly complicated for autosomal recessives (since an induced recessive mutation does not precipitate a recessive disease in the immediate post-radiation generations) and more complex for multifactorial diseases and depends on the model that is used to explain their stable frequencies in the population.

6.3 Recent advances in understanding

The advances that have been made during the past few years include: (a) an upward revision of the estimates of the baseline frequencies of Mendelian diseases; (b) the introduction of a conceptual change in the calculation of the DD; (c) the elaboration of methods for estimating MC for Mendelian and chronic diseases; (d) the introduction of an additional factor called the 'potential recoverability correction factor' (PRCF) in the risk equation to bridge the gap between the rates of radiation-induced mutations in mice and the risk of radiation-inducible genetic disease in human live births and (e) the introduction of the concept that the adverse effects of radiation-induced genetic damage in humans are likely to be manifest predominantly as multi-system developmental abnormalities in the progeny. All these have been discussed in detail in a series of recent publications (Chakraborty et al., 1998; Denniston et al, 1998; Sankaranarayanan 1998, 1999; Sankaranarayanan and Chakraborty 2000a,b,c; Sankaranarayanan et al., 1994, 1999).

6.3.1. Baseline frequencies of genetic diseases

Until the 1993 UNSCEAR report, the baseline frequencies used in risk estimation were based on those compiled by Carter (1977) for Mendelian diseases, by UNSCEAR (1977) for chromosomal diseases, by Czeizel and Sankaranarayanan (1984) for congenital abnormalities and by Czeizel et al. (1988) for chronic diseases. While the estimates for the last three groups of diseases have remained unchanged, those for Mendelian diseases have now been revised upwards (Sankaranarayanan 1998). Both the earlier and the current estimates (the latter used in UNSCEAR 2001) are presented in Table 6.1.

Table 6.1: Baseline frequencies of genetic diseases in human populations

Disease class	Baseline frequencies (per cent of live births)	
	UNSCEAR (1993)	UNSCEAR (2001)
Mendelian		
Autosomal dominant	0.95	1.50
X-linked	0.05	0.15
Autosomal recessive	0.25	0.75
Chromosomal	0.40	0.40
Multifactorial		
Chronic diseases	65.00 [a]	65.00 [a]
Congenital abnormalities	6.00	6.00

[a] Population frequency

6.3.2 The doubling dose

A re-examination of the assumptions involved in using the DD based on mouse data for risk estimation. The DD used until the 1993 UNSCEAR report was 1 Gy (for chronic, low LET radiation conditions) and was based entirely mouse data on spontaneous and induced rates of recessive mutations in 7 genes. One of the assumptions underlying the use of mouse-data-based DD for risk estimation is that both the spontaneous and induced mutation rates in mice and humans are the same. The assumption regarding induced rates of mutations, while unavoidable, is defensible on the grounds of generally similar gene organization, 70 to 90% homology in DNA sequence of genes and substantial conservation of synteny for many (although not all) chromosomal regions in both the species. However, the situation is different with respect to spontaneous mutation rates.

Arguments supporting the view that the spontaneous mutation rates in mice and humans are unlikely to be similar have been discussed (Sankaranarayanan 1998; Sankaranarayanan and Chakraborty 2000a; UNSCEAR 2001). Briefly, unlike in the mouse, in humans, there are pronounced sex-differences in spontaneous mutation rates (being higher in males than in females), and the mutation rate increases with the age of the father (paternal age-effect). These when considered with the fact that the human life span is longer than that of the mouse, suggest that extrapolating from the short-lived mouse to humans is unlikely to provide a reliable average spontaneous rate in a heterogeneous human population of all ages. Additionally, recent analyses of mouse data on mutations that arise as germinal mosaics (which result in clusters of identical mutations in the following generation) have introduced considerable uncertainty about the spontaneous mutation rate in the mouse (Selby, 1998).

The use of human data on spontaneous mutation rates and mouse data for induced mutation rates for DD calculations. In view of the reasons stated in the preceding paragraphs, UNSCEAR (2001) considered it prudent to base DD calculations on human data on spontaneous mutation rates and mouse data on induced mutation rates, as was first done in the 1972 BEIR

report (NRC 1972). The advantages of using human data in DD calculations are: (a) they pertain to human disease-causing genes; (b) the mutation rate estimates in humans, because they are averaged over the sexes, automatically include paternal age effects and (c) in estimating mutation rates, human geneticists count all mutations irrespective of whether they are part of a cluster or not; consequently, had clusters occurred, they would have been included.

Average spontaneous mutation rate for human genes. For calculating an average spontaneous mutation rate for human genes, UNSCEAR (2001) focused on published data on those genes for which estimates of selection coefficients (*s*) were also available, the reason being that the latter are relevant for estimating MC (to be discussed in the next section). Further, only autosomal dominant diseases, but not X-linked ones, were included in the analysis the rationale being that (a) among Mendelian diseases, autosomal dominants constitute the most important group from the standpoint of genetic risks; (b) while X-linked diseases are also expected to respond directly to an increase in mutation rate, their incidence in the population is an order of magnitude lower than that of autosomal dominants (0.15% versus 1.50%) and, consequently (c) the assumption of similar average mutation rates for these two classes of disease in the context of risk estimation is unlikely to result in an underestimate of the risk.

The average (unweighted) spontaneous mutation rate based on a total of 26 autosomal dominant disease phenotypes (which on current knowledge relate to mutations in an estimated 135 genes) was $(2.95 \pm 0.64).10^{-6}$ gene^{-1} generation^{-1} (Sankaranarayanan and Chakraborty 2000). This estimate is well within the range of $0.5.10^{-5}$ to $0.5.10^{-6}$ per gene assumed in the 1972 BEIR report (NRC 1972). The data used for spontaneous mutation rate calculations also permit an estimate of 0.294 for average selection coefficient (s) associated with these diseases.

Average rate of induced mutations in mice. As mentioned earlier, until the 1993 UNSCEAR report, the average rate of induced mutations used in DD calculations, was based on data from studies of recessive specific locus mutations in 7 genes. In the 2001 report, however, UNSCEAR expanded the database to include not only the above, but also data from studies of enzyme activity mutations, as well as dominant mutations at four loci (*Sl*, *W*, *Sp* and *T*). All these data come from studies of males in which the irradiated germ cell stages were stem-cell spermatogonia (the relevant germ cell stages in males from the standpoint of risks). The data from studies with female mice were not used since, as discussed in the 1988 UNSCEAR report, there is uncertainty whether the mouse immature oocytes (with nearly zero sensitivity to mutation induction after acute as well as chronic irradiation) would provide a good model for assessing the mutational radiosensitivity of human immature oocytes that are the relevant germ cell stages in the females. For the purpose of risk

estimation, to err on the side of caution, it was assumed that the induced rates in females will be the same as those in males.

Details of the data used are discussed in the UNSCEAR 2001 report and by Sankaranarayanan and Chakraborty (2000a). The average induced mutation rate, based on mutations recovered at a total of 34 mouse genes is $(1.08 \pm 0.30).10^{-5}$ gene^{-1}Gy^{-1} for acute X-or γ-irradiation. With a dose-rate reduction factor of 3 traditionally used, the rate for chronic irradiation conditions becomes $(0.36 \pm 0.10).10^{-5}$ gene^{-1}Gy^{-1}.

The doubling dose. With the revised estimates for average spontaneous mutation rate $(2.95 \pm 0.64).10^{-6}$ gene^{-1} generation^{-1} for human genes and for average rate of induced mutations $(0.36 \pm 0.10).10^{-5}$ gene^{-1}Gy^{-1} for mouse genes, the new DD becomes (0.82 ± 0.29) Gy. This estimate, however, is not very different from 1 Gy that has been used thus far but which was based entirely on mouse data.

UNSCEAR (2001) has suggested the continued use of the 1 Gy estimate in order to avoid the impression of undue precision, but noting that a conceptual change has now been made (i.e., use of human data on spontaneous and mouse data on induced mutation rates) and that the present estimate is supported by more extensive data than had been the case thus far. The Task Group supports the UNSCEAR judgement and propose that ICRP retain a DD value of 1 Gy.

6.3.3 Mutation component

As noted in section 2.2, the quantity 'mutation component' (MC) used in equation (1) provides a measure of the relative change in disease frequency per unit relative change in mutation rate for the different classes of genetic diseases. The elements of the basic MC concept were introduced already in the 1972 BEIR report (NRC 1972) and was subsequently considered in the papers of Crow and Denniston (1981, 1985). Within the framework of an ICRP Task Group, set up in 1993, the problem was studied in detail and the concept, theory, methods for estimation and algebraic formulations were fully elaborated for both Mendelian and multifactorial diseases. The Task Group Report has since been published (ICRP 1999). The methods developed in the above ICRP document now enable the evaluation of the magnitude of MC for any post-radiation generation of interest, after either a one-time or a permanent increase in mutation rate (i.e., radiation exposure in every generation). In what follows, a brief summary of the main findings is presented.

Mutation component for autosomal dominant diseases. For autosomal dominant diseases (for which the relationship between mutation and disease is straightforward) the estimation procedure is relatively simple. For a one-time increase in mutation rate which produces a one time

increase in mutation rate ('burst', indicated by the subscript 'b' in MC_b below), the change with time 't' (in generations) is given by the equation:

$$MC_b(t) = s(1-s)^{t-1} \quad (4)$$

For radiation exposure to many successive generations producing a permanent increase in mutation rate (indicated by the subscript 'p'),

$$MC_p(t) = [1-(1-s)^t] \quad (5)$$

Equations (4) and (5) show that $MC_b = MC_p = s$ for the first post-radiation generation following either a one-time or a permanent increase in mutation rate. With no further irradiation in subsequent generations, the value of MC will decay back to zero at a rate of (1- s) per generation. With a permanent increase in mutation rate, however, the MC value will slowly increase to 1 at the new equilibrium. Consistent with these changes in MC, for a one-time irradiation scenario, the disease frequency will show a transitory increase in the first generation, but over time, reach the earlier or 'old' equilibrium value; for a permanent increase in mutation rate, the disease frequency will continue to increase until the new equilibrium value of MC = 1 is reached. At the new equilibrium, an *x*% increase in mutation rate will result in an *x*% increase in disease frequency.

Mutation component for X-linked and autosomal recessive diseases. For X-linked diseases, for a one-time increase in mutation rate, the first generation MC = s as in the case of autosomal dominants, but the s value needs to be adjusted to take into account the fact that only one-third of the total X-chromosome complement is in males. The dynamics of change in MC in subsequent generations is similar to that for autosomal dominants. For autosomal recessives, MC in the first generation is close to zero (consistent with the fact that an autosomal recessive mutation does not result in disease in the first generation)

With a permanent increase in mutation rate, for both kinds of diseases, MC progressively increases to reach a value of 1 at the new equilibrium, but the rates of approach to the new equilibrium are different and dictated by s values and time (in generations) following irradiation. In particular, for autosomal recessive diseases, the rate of approach to the new equilibrium is very slow and much slower than that for autosomal dominants and X-linked diseases.

The important point that emerges from the above discussion is that MC is related to s and therefore given s, one can estimate the dynamics of increase in MC and in disease frequencies for any post-radiation generation of interest. As mentioned in section 3.2, the average selection coefficient estimated from data on naturally-occurring autosomal dominant

diseases is 0.294. This value rounded to 0.30 is the one used as the best estimate for MC for autosomal dominant and X-linked diseases.

Mutation component for chronic diseases. As mentioned earlier, multifactorial diseases have a high population frequency, but, unlike in the case of Mendelian diseases, the lack of adequate models to explain their stable frequencies in the population precluded any meaningful assessment of the radiation risk of these diseases. *Descriptive* models such as the multifactorial threshold model (MTM) of disease liability to explain the observed transmission patterns of these diseases and to estimate risks to relatives of affected individuals from data on population frequencies have existed for a long time, but as such, they are not suitable for assessing the impact of an increase in mutation rate on disease frequency. Similarly, although there was a wealth of literature on mechanistic models (that invoke mutation and selection as opposing forces in the evolution and maintenance of variability of polygenic/quantitative traits in populations), none of these models was geared towards assessing the impact of an increase in mutation rate on the frequency of multifactorial diseases.

The ICRP Task Group (1999) took the first step in addressing the above issue by formulating a 'hybrid model' which included some elements of the MTM and some of the mechanistic models mentioned above. The hybrid model is henceforth referred to as the *f*inite *l*ocus *t*hreshold *m*odel (FLTM). Although the original intention was to use the model to estimate MC for both congenital abnormalities and chronic diseases, it soon became clear that its use for congenital abnormalities is not biologically meaningful and consequently, the Task Group decided to limit its use for chronic diseases only. As discussed later, this does not pose any problem for estimating the risk of congenital abnormalities since this can now be done without recourse to the DD method. To provide a background, the assumptions and use of the MTM are first discussed below.

Multifactorial threshold model (MTM) of disease liability. In the absence of information on the genetic or environmental factors that underlie multifactorial diseases, in the early 1960s, the MTM used in quantitative genetics for threshold characters was extended to these diseases to explain their transmission patterns and estimate risks to relatives. Since multifactorial diseases are 'all-or-none' traits (unlike quantitative traits (such as height or weight), in order to use the MTM for these diseases, it was necessary to postulate a hypothetical variable called 'liability' that underlies multifactorial diseases and a 'threshold' of liability which, when exceeded, would result in disease (Carter 1961; Falconer 1965). Worthy of note here is the fact that the MTM has been (and remains) useful for our understanding of familial aggregations and recurrence risks in families and makes good predictions even when there is uncertainty about the underlying mechanisms. Details of the MTM for disease liability have been discussed in a number of publications (see ICRP 1999 for a listing of the references).

Briefly, the assumptions of the standard version of MTM are the following:

(a) all environmental and genetic causes can be combined into a single continuous variable called 'liability' which, as such cannot be measured;

(b) liability is determined by a combination of numerous (essentially infinite number of) genetic and environmental factors, that act additively without dominance or epistasis, each contributing a small amount of liability and therefore show a Gaussian (normal) distribution; and,

(c) the affected individuals are those whose liability exceeds a certain threshold value.

The MTM enables the conversion of information on the incidence of a given multifactorial disease in the population (P) and in the relatives of those affected (q) into an estimate of correlation in liability between relatives from which a quantity called heritability (h^2) which provides a measure of the relative importance of genetic factors in disease causation, can be estimated.

Heritability. Heritability, a common statistic used in quantitative genetics, provides a measure of the relative importance of transmissible genetic variation to the overall phenotypic variation. Since the phenotype owes its origin to genetic and environmental factors, in the analysis of variance, the total phenotypic variance (V_P) is usually partitioned into two components, genetic (V_G) and environmental (V_E), assuming that these are independent of each other (i.e., they are not correlated). The ratio V_G/V_P is called the 'broad-sense heritability', or degree of genetic determination, symbolized by h^2. Estimates of the heritability of liability for many multifactorial diseases have been published in the literature and are in the range from about 0.30 to 0.80 although for most types of cancer the heritability coefficient is judged to be less than 0.30.

The genotypic variance, V_G, can be subdivided into an additive component (V_A) and a component due to deviations from additivity. Additive genetic variance is the component that is attributable to the average effects of genes considered singly, as transmitted in the gametes. The ratio, V_A/V_G, called 'narrow-sense heritability', determines the magnitude of correlation between relatives (Falconer, 1960).

The Finite-locus-threshold model used for estimating MC for chronic diseases. The FLTM incorporates the assumptions of liability threshold from the MTM (but suitably redefined to take into account mutations at a finite number of genes) and the concepts of mutation and selection from models on the maintenance and evolution of polygenic variability underlying quantitative traits. The choice of the FLTM was dictated by two main considerations: (a) current knowledge of the genetic basis of well-studied chronic diseases, such as coronary heart disease (CHD), supports the view that a large proportion the variability of intermediate quantitative

traits (such as serum cholesterol levels, a risk factor for CHD) in the population is due to mutations at a limited number of gene loci (ICRP 1999; Sankaranarayanan et al. 1999) and (b) in the absence of precise information on the genetic basis of most multifactorial diseases, the FLTM provides a useful starting point, because with such a model, the meaning of parameters reflecting mutation rates and selection can be quantitatively assessed in terms of those for single gene effects.

Briefly, the FLTM assumes that the liability to disease, made up of genetic and environmental factors, is a continuous variable. The genetic component of liability is discrete i.e., it is determined by the total number of mutant genes (defined as a random variable, *g*, the number of mutant genes in a genotype at *n* loci) and the environmental effect, *e* is a random variable which has a Gaussian (normal) distribution with mean = 0 and variance = V_e. The total liability, thus, has two components: (a) a function [*f(g)*] of the number of mutant genes in the *n*-locus genotype of an individual and (b) a normally distributed environmental effect, *e* . The threshold characteristic of the model is described by assuming that individuals with liability exceeding *T* are phenotypically affected and have a fitness of (1 – *s*) and those below it, are normal with fitness equal to 1. Although the mathematical formulations of the FLTM cannot be expressed in the form of a single equation, the predictions of the model can be iteratively evaluated from the computer programme that was developed for this purpose. The steps include the following: first, with a defined set of parameter values (mutation rate, selection coefficients, threshold etc), the programme is run until the population reaches equilibrium between mutation and selection. When once this is achieved, the mutation rate is increased once or permanently and the computer run is resumed with the new mutation rate (with the other parameters remaining the same). The changes in the magnitude of MC and its relationship to heritability of liability (h^2) are examined in desired generations and at the new equilibrium. The h^2 estimates are not inputs, but outputs of the programme, obtained with different combinations of parameter values (for the numbers of gene loci from 3 to 6, mutation rate, selection coefficients, environmental variance and threshold). The conclusions discussed below are for the 5-locus model, but they remain qualitatively unaltered for other values of the number of gene loci.

Main conclusions of the computer simulation studies. In these studies, a 5-locus model was used and the relationship between h^2 and changes in MC were assessed for two scenarios: (a) the population sustains an increase in mutation rate every generation and (b) the population sustains an increase in mutation rate in one generation only. The initial (spontaneous) mutation rate assumed in the calculations was 10^{-6} per gene and the effects were examined for a 15% increase in mutation rate (i.e., 10^{-6}/gene to $1.15.10^{-6}$/gene) with selection coefficients, *s* = 0.2 to 0.8. The conclusions are the following:

(a) Under conditions of a permanent increase in mutation rate, the MC at the new equilibrium is close to 1 over a wide range of h^2 values from about 0.3 to 0.8 that are of importance in the present context; stated differently, an *x*% increase in mutation rate will cause an *x*% increase in disease frequency at the new equilibrium.

(b) Again, under the same conditions and over the same range of h^2 values the MC in the first several generations is very small in the range from 0.01 to 0.02, often more close to 0.01 than to 0.02. In other words, the predicted relative increase in disease frequency is very small;

(c) If the population sustains radiation exposure in one generation only, the MC in the first generation is as indicated above under item (b) and its value gradually decays back to zero; and,

(d) Conclusions (a to c) are valid when there is no sporadic component of disease i.e., non-occurrence of individuals with disease that is unrelated to the genotype; when sporadics occur, the effect is to reduce the MC both in early generations and at the new equilibrium.

The conclusions discussed above hold for so many different combination of parameter values (i.e., threshold, selection coefficient, number of loci, environmental variance, spontaneous mutation rate, increases in mutation rate etc that they can be considered robust. Additionally, it was found that for mutation rates of the order known for Mendelian genes, the FLTM with a few loci and weak selection provides a good approximation to study the possible increases in the frequencies of chronic diseases in populations exposed to radiation.

In its 2001 report UNSCEAR used MC = 0.02 as the best estimate in the risk equation for estimating the risk of chronic diseases.

6.3.4 The concept of potential recoverability correction factor

The use of equation (1) (i.e., risk = P $\times$ [1/DD] $\times$ MC) for risk estimation implies that the genes at which spontaneous mutations are known to cause disease (included under P) will also respond to induced mutations, that such mutations will be compatible with viability and therefore recoverable in live born progeny of irradiated individuals. This assumption gained support from studies of induced mutations in specific genes in several model systems. However, no radiation-induced germ-cell gene mutations, let alone induced genetic diseases have thus far been identified in human studies.

Advances in human molecular biology and in radiobiology have now shown that: (a) spontaneous disease-causing mutations and radiation-induced mutations in experimental systems, differ in several respects, both in their nature and mechanisms by which they arise (or induced); (b) there are both structural and functional constraints that preclude the recoverability of induced mutations in all genomic regions i.e., only a

small proportion of human genes of relevance from the disease point of view is likely to be responsive to radiation-induced mutations that are recoverable in live born progeny and (c) genes that have hitherto been used in studies on induced mutations are those that are non-essential for viability and also happen to be located in genomic regions, also non-essential for viability (reviewed in Sankaranarayanan 1999). The crux of the argument then, is that the induced mutation rate from mouse studies that are used in risk estimation are likely to be over-estimates of the rate at which induced mutations in humans will precipitate disease.

Since there is no alternative to the use of mouse data on induced mutations for risk estimation, methods need to be devised to bridge the gap between empirically determined rates of induced mutations in mice and the rates at which disease-causing mutations may be recovered in human live births. One such method that has been developed, involves the incorporation of a correction factor termed *p*otential *r*ecoverability *c*orrection *f*actor (or PRCF) into risk equation (1) so that the risk now becomes a product of 4 quantities instead of the original three:

$$\text{Risk per unit dose} = P \times [1/DD] \times MC \times PRCF \qquad (6)$$

where the first three are as defined earlier and PRCF is the disease-class specific potential recoverability correction factor. Since PRCF is a fraction, the estimate of risk will now be lower.

In order to estimate *potential recoverability* of induced mutations, a set of criteria was first defined using molecular information on recovered mutations in experimental systems. The operative words are the italicized ones, since (a) knowledge of the structural and functional genomics of the human genome is not yet complete; (b) so far, no radiation-induced human germ cell mutations have been recovered to provide a frame of reference and (c) the criteria may change with advances in knowledge in the coming years. The criteria that could be developed were then applied to human genes of relevance from the disease point of view, taking into gene size, organisation, function, genomic context (i.e., whether the gene is located in a 'gene-rich' or 'gene-poor' region), spectra of spontaneous mutations in the gene, whether deletions, including contiguous genes are known in the region and the known mutational mechanisms. The question asked was: if a deletion (the predominant type of radiation-induced change) were to be induced in this gene/gene region, is it potentially recoverable in a live birth?

Details of the criteria used and the classification of the genes into three groups i.e., group 1, 'induced deletion is unlikely to be recovered', group 2, 'uncertain recoverability' and group 3, 'potentially recoverable' are discussed in detail by Sankaranarayanan and Chakraborty (2000) and in the UNSCEAR (2001) report. Since the assignment to group 1 is less subjective (and therefore relatively more reliable), to err on the side of

caution, potential recoverabililty was calculated as follows: if a total of *N* genes are analysed and if *n* among them could be excluded as 'unlikely to be recovered', the remainder (made up of groups 2 and 3) constitute (*N*–*n*) and the fraction (*N*–*n*)/N provides a crude measure of genes at which induced mutations may be recoverable. This fraction is called the 'unweighted' PRCF.

The PRCF as estimated above, however, does not take into account differences in incidence of the different diseases. For example, if a disease with high incidence belongs to group 1, societal concern will be far less than when it belongs to the other groups. Consequently, a weighted PRCF was also calculated. If *P* is the total incidence of diseases due to mutations in *N* genes, and *p* is the incidence of diseases due to mutations in (*N*–*n*) genes, then [p(*N*–*n*)/PN] represents the 'weighted PRCF'.

The results of analysis of a total of 67 autosomal and X-linked genes are summarized in Table 6.2.

Table 6.2: Summary of assessments of potential recoverability of radiation-induced mutations in autosomal and X-linked genes

Groups	No. of genes	Unweighted [a] PRCF	Incidence (x 10^4)[b]	Weighted[c] PRCF
Autosomal dominants				
1 (unlikely to be recovered)	42	-	46.45	-
2 & 3 (uncertain + potentially recoverable)	17	0.29	55.90	0.157
Sub-total	59		102.35	
Autosomal dominants + X-linked				
1 (unlikely to be recovered)	43	-	48.95	-
2 & 3 (uncertain + potentially recoverable)	24	0.36	60.90	0.199
Total	67		109.85	

[a]Unweighted PRCF: aut. dominants: 17/59 = 0.29; aut. dominants + X-linked = 24/67 = 0.36
[b]Estimates from Sankaranarayanan (1998) and Sankaranarayanan and Chakraborty (2000)
[c]Weighted PCRF: aut. dominants: (55.9 x 17)/(102.35 x 59) = 0.157; aut. dominants + X-linked: (60.9 x 24)/(109.85 x 67) = 0.199

PRCF for autsomal dominant and X-linked diseases. In view of the fact that autosomal dominants have an order-of-magnitude higher overall incidence than X-linked ones (1.5% versus 0.15%), the PRCFs for the former are more relevant. UNSCEAR, therefore suggested the use of the PRCF range of 0.15 to 0.30 in the risk equation for estimating the risk of both autosomal dominant and X-linked diseases.

PRCF for autosomal recessives. While the recoverability of induced recessive mutations is also subject to structural and functional constraints, in view of the fact that these mutations are first present in heterozygotes (and 50% of the gene products are generally sufficient for normal function), one can assume that even large deletions may be recoverable in

the heterozygotes. Additionally, as discussed earlier, induced recessive mutations do not, at least in the first several generations, result in recessive diseases. Consequently, no attempt was made to estimate PRCF for recessive diseases. It should be noted however that, ignoring PRCF in the risk equation is equivalent to assuming PRCF = 1, but in reality, this does not affect the estimate of risk (since MC is nearly zero in the first several generations, the product of P and MC is already zero).

PRCF for chronic diseases. As may be recalled, in the FLTM used to estimate MC for chronic diseases, one of the assumptions is that of simultaneous increase in mutation rate in all the underlying genes which, in turn, causes the liability to exceed the threshold. A crude approximation of the PRCF for each multifactorial phenotype is the x^{th} power of that for mutations at a single locus, where x is the number of gene loci, assumed to be independent of each other, that underlie the disease. Since the PRCF for single gene mutations is in the range from 0.15 to 0.30, for chronic diseases, the figures become 0.15^x to 0.30^x. With the assumption of just 2 loci, the estimates become 0.02 to 0.09 and with more loci, substantially smaller. Intuitively, these conclusions are not unexpected when one considers that here, one is estimating the probability of simultaneous recoverability of induced mutations at more than one independent gene.

UNSCEAR adopted the PRCF range of 0.02 to 0.09 with the view that the use of this range will not underestimate risk.

PRCF for congenital abnormalities. The available data do not permit PRCF estimation for congenital abnormalities. However, since risk estimation for this class of diseases is now done without using the DD method (see the next section), our inability to estimate PRCF is not a problem.

6.3.5 The concept that multi-system developmental abnormalities are likely to be the major manifestations of radiation-induced genetic damage in humans

As discussed in the preceding paragraphs, in genetic risk estimation, the emphasis has been on expressing risks in terms of inducible genetic diseases, the expectation being that their phenotypes will be similar to those known from studies of naturally-occurring genetic diseases. However, when one considers the following facts it is clear that the emphasis on genetic diseases gives only a partial answer to the question of genetic risks. The facts and observations are:

(i) radiation induces genetic damage through random deposition of energy;

(ii) the whole genome is the target;

(iii) most radiation-induced mutations studied in experimental systems are DNA deletions, often encompassing more than one gene;

(iv) the recoverability of induced deletions is subject to structural and functional constraints so that only a small proportion of them is compatible with live births, and,

(v) the phenotype of viability-compatible deletions will reflect the gene functions that are lost because of the deletion and we do not as yet have 'windows' for all genomic regions.

It follows therefore, that the problem in genetic risk estimation is one of delineating the phenotypes of viability-compatible deletions that may be induced in different genomic regions which may or may not have counterparts in naturally-occurring genetic diseases.

Microdeletion syndromes in humans. Some inferences are now possible on the potential phenotypes of radiation-induced deletions from studies of naturally-occurring microdeletion syndromes in humans. These result from deletions of multiple, physically contiguous often functionally unrelated genes that are compatible with viability in heterozygous condition and are identified clinically through a characteristic association of unusual appearance and defective organ development. Many examples of microdeletions have been (and continue to be) reported in the human genetics literature. They have been found in nearly all the chromosomes, but their occurrence in different chromosomal regions is non-random (e.g., Brewer et al. 1998). This is not unexpected in the light of differences in gene density in different chromosomes/chromosomal regions. The important point here is that despite their occurrence in different chromosomes, the common denominators of the phenotype of many of these deletions are: mental retardation, a specific pattern of dysmorphic features, serious malformations and growth retardation. These findings in humans are supported, among others, by studies of Cattanach et al. (1993, 1996) showing that, in the mouse, radiation-induced multi-locus deletions constitute the genetic basis for a significant proportion of growth retarded animals recovered in their work

It was therefore suggested that the predominant adverse effects of gonadal irradiation in humans are likely to be manifest as multi-system developmental abnormalities which are formally called 'congenital abnormalities' (Sankaranarayanan 1999). However, unlike naturally-occurring congenital abnormalities which are interpreted as being multifactorial, radiation-induced congenital abnormalities, because they are multi-locus deletions, are predicted to show, by and large, autosomal dominant patterns of inheritance. This prediction has been fulfilled in mouse radiation studies on skeletal abnormalities (Ehling 1965, 1966; Selby and Selby 1977), cataracts (Favor 1989), growth retardation (Searle and Beechey 1986) and congenital anomalies (Kirk and Lyon 1984; Lyon and Renshaw 1988; Nomura 1982, 1988, 1994). No transmission tests

could be carried out however, for congenital abnormalities because they were ascertained in utero.

Risk of developmental abnormalities. UNSCEAR (2001) used the mouse data on skeletal abnormalities, cataracts and congenital abnormalities (appropriately adjusting the rates for chronic low LET radiation conditions) to obtain an overall estimate of the risk of developmental abnormalities about $20.10^{-4}.Gy^{-1}$ (given in Table 6.3 in this document under the heading 'congenital abnormalities' as $2{,}000.10^{-6}$. Gy^{-1} for the first generation). All the data used in these calculations come from studies of irradiation of males and the rate so estimated was assumed to be applicable to both sexes.

6.4 The 2001 UNSCEAR Risk Estimates

6.4.1 Estimates of genetic risk for a population sustaining radiation exposure generation after generation

Table 6.3 summarizes the risk estimates presented in the 2001 UNSCEAR report. The risks are expressed as the predicted number of additional cases (i.e., over the baseline) of different classes of genetic disease per million progeny per Gy for a population exposed to low LET, low-dose or chronic irradiation generation after generation. For all classes except congenital abnormalities, the estimates are based on a DD of 1 Gy and the respective values of P, MC and PRCF for the different classes. For congenital abnormalities, the risk estimate comes from mouse data (discussed in the preceding paragraph) and is not based on the DD method.

As can be noted, the first generation risk (i.e., the risk to the children of an exposed population) is estimated to be of the order of 750 to 1,500 cases for autosomal dominant and X-linked diseases, zero for autosomal recessive diseases, 250 to 1,200 cases for chronic diseases and 2,000 cases of congenital abnormalities. The total risk is of the order of about 3,000 to 4,700 cases which represent about 0.4 to 0.6% of the baseline risk.

The risk to the second generation (i.e., to the grandchildren) becomes slightly higher for all classes except for chronic diseases in view of the fact that the mutation component for these diseases does not increase over the first several generations.

Table 6.3: Current estimates of genetic risks from continuing exposure to low LET, low-dose or chronic irradiation (UNSCEAR 2001) with assumed doubling dose of 1 Gy

Disease class	Baseline frequency (per million live births)	Risk per Gy per million progeny 1st generation up to 2nd generation	
Mendelian			
Autosomal dominant & X-linked	16,500	~750 to 1,500[a]	~1,300 to 2,500
Autosomal recessive	7,500	0	0
Chromosomal	4,000	[b]	[b]
Multifactorial			
Chronic	650,000[c]	~250 to 1,200	~250 to 1,200
Congenital abnormalities	60,000	~ 2,000[d]	~ 2,400 to 3,000[e]
Total	738,000	~3,000 to 4,700	~3,950 to 6,700
Total per Gy expressed as per cent of baseline		~0.41 to 0.64	~0.53 to 0.91

[a] The ranges reflect biological and not statistical uncertainties

[b] Assumed to be subsumed in part under autosomal dominant and X-linked diseases and in part under congenital abnormalities

[c] Frequency in the population

[d] Estimated from mouse data without using the DD method

[e] Newly-induced damage of pre-existing damage (it is assumed that between 20 and 50% of the progeny affected in the first generation will transmit the damage to the next generation resulting in 400 to 1,000 cases.)

6.4.2 Estimates of genetic risks for a population that sustains radiation exposure in one generation only

The estimates of genetic risk under conditions when the population sustains radiation exposure in one generation only (and no further radiation in subsequent generations) are presented in Table 6.4. Again, all estimates are expressed per Gy per million progeny. As expected, the first generation risks (i.e., risks to the children of those exposed) are the same as those given in Table 6.3. With no further radiation, the risk of autosomal dominant and X-linked diseases to the second generation (i.e., to the grandchildren) declines as a result of selection. For chronic multifactorial diseases, since the mutation component remains low for several generations, the risk to the second generation remains about the same as that in the first generation. The risk of congenital abnormalities is predicted to be of the order of 400 to 1,000 cases (under the assumption that about 20 to 50% of those affected in the first generation transmit the damage to the next generation).

Table 6.4: Current estimates of genetic risks from one-generation exposure to low LET, low-dose or chronic irradiation (UNSCEAR 2001) with assumed doubling dose of 1 Gy

Disease class	Baseline frequency (per million live births)	Risk per Gy per million progeny	
		1st generation up to 2nd generation	
Mendelian			
Autosomal dominant & X-linked	16,500	~750 to 1,500[a]	~500 to 1,000
Autosomal recessive	7,500	0	0
Chromosomal	4,000	[b]	[b]
Multifactorial			
Chronic	650,000[c]	~250 to 1,200	~250 to 1,200
Congenital abnormalities	60,000	~ 2,000[d]	~ 400 to 1,000[e]
Total	738,000	~3,000 to 4,700	~1,150 to 3,200
Total per Gy expressed as per cent of baseline		~0.41 to 0.64	~0.16 to 0.43

[a] Risk to second generation is lower than that in the first because of the assumption that the radiation exposure occurs in one generation only; the risk will progressively decrease with time (in generations)

[b] Assumed to be subsumed in part under the risk of autosomal dominant and X-linked diseases and in part under that of congenital abnormalities

[c] Frequency in the population

[d] Estimate obtained using mouse data on developmental abnormalities and not with the doubling dose method

[e] Under the assumption that about 20 to 50% of those affected in the first generation transmit the damage to the next generation

6.4.3 Strengths and limitations of the risk estimates

On the basis of UNSCEAR (2001) the Task Group have, for the first time, been able to provide ICRP estimates of risks for all classes of genetic diseases. While these estimates reflect our current knowledge in this area, the strengths and limitations of these estimates need to be borne in mind, in view of various assumptions that have been used.

Equal mutational sensitivity of human males and females. The prevalent view that the mouse immature oocytes may not be an adequate model for assessing the mutational radiosensitivity of human immature oocytes necessitated the assumption that human females and males have the same mutational radiosensitivity which in turn is equal to that of mouse males. If, however, human females have a lower sensitivity in this regard, the average rate of induced mutations would be expected to be lower than the one used. In turn, this implies that the DD will be higher (and 1/DD will be smaller than 0.01 that has been used). At present it is not possible to address this issue.

Average spontaneous and induced mutation rates used in DD calculations. As may be recalled, the average estimate of $2.95.10^{-6}$ per human gene was based on an estimated 135 genes underlying some 26 autosomal dominant disease phenotypes which constitute a subset of such diseases

included in the estimate of baseline frequencies. Bearing in mind the fact that the human genome contains about 30,000 genes, one can only speculate whether the above average spontaneous mutation rate estimate is an over- or underestimate of the true average rate.

Similarly, although the estimate of induced mutation rate for mouse genes is based on more data than was the case until now, the total number of genes included in the present analysis is still only 34 and in a sizeable proportion of them, induced mutations were rare. Therefore, while the possibility remains that the presently-estimated induced rate may be biased upwards, its extent is difficult to determine at present.

Mutation components. The estimate MC = 0.3 for autosomal dominant and X-linked diseases is based on the average s value for the autosomal dominant diseases (since MC = *s* in the first generation) the data of which provided the basis for spontaneous mutation rate calculations. It should be realized, however, that for a substantial proportion of diseases, onset is in middle and later ages (i.e., beyond the age of reproduction) which means that *s* is smaller and therefore, the MC value used may be an over-estimate.

Potential recoverability correction factors. For autosomal dominant and X-linked diseases, a range of PRCF from 0.15 to 0.30 was used, the lower limit being a weighted estimate and the upper limit, the unweighted one. However, the criteria developed for potential recoverability of induced deletions do not include breakpoint specificities which are undoubtedly important in the case of deletion-associated naturally-occurring Mendelian diseases. It seems unlikely that radiation-induced deletions would share these specificities, and certainly not in all genomic regions. If these specificities are indeed relevant for recovering induced deletions, even the weighted PRCF may be an over-estimate.

For chronic diseases, it has been assumed that the PRCF may simply be the x^{th} power of that for a single gene disease, with x = the number of genes which have to be simultaneously mutated to cause disease; the values of 0.02 to 0.09 have assumed $x = 2$ (the minimum number). Although, statistically, such a calculation can be defended, the implicit biological assumption that at low doses of radiation, two independent mutations underlying a chronic disease may be simultaneously induced and recovered seems unrealistic.

There is an additional issue here, namely that, the PRCF for chronic diseases is very sensitive to x (e.g., even if $x = 3$, the PRCF range becomes 0.003 to 0.03). The essence of the argument then is that the PRCFs used for chronic diseases may over-estimate the risk.

Overlap in estimates of risk. It should be recalled that: (a) the estimates for autosomal dominant and X-linked diseases have been obtained using

the DD method; (b) the risk of induced congenital abnormalities which are also adverse dominant effects have been estimated independently using mouse data without recourse to the DD method and (c) the risk of 'chromosomal diseases' has been assumed to be subsumed under the risk of autosomal dominant and X-linked diseases. The important point here is that, since all these represent dominant effects (and mutations in many developmental genes are known to cause Mendelian diseases), there must be overlap between the classes of risk grouped under the headings of 'autosomal dominant + X-linked' and 'congenital abnormalities' although it is difficult to assess its magnitude. The consequence is that the sum may over-estimate the actual risk of dominant effects.

6.5 ICRP'S earlier and present assessments of risk estimates for deriving risk coefficients for genetic effects

6.5.1 ICRP Publication 60

In *Publication 60* (ICRP 1991), ICRP used the genetic risk estimates then available (UNSCEAR 1988; NRC 1990) as a starting point for deriving risk coefficients for 'severe hereditary effects'. It is important to mention here that in ICRP's calculations then, while the DD assumed (1 Gy) was the same as that used now, the baseline frequency of Mendelian diseases was only about one-half of that currently used (1.25% then versus 2.4% now). Additionally, for multifactorial diseases as a whole (estimated baseline frequency of 71%; same as now), the ICRP assumed that MC = 0.05 for all post-radiation generations (this assumption is incorrect in the light of current calculations; see section 3.3) and besides, incorporated an additional arbitrary correction factor (called 'severity correction factor') of 1/3 to estimate the proportion of inducible multifactorial diseases that may be deemed 'severe' (no such correction is used in the present assessments).

For a population exposed to low dose rate, low LET irradiation, the risk coefficients estimated by ICRP (1991) are summarized in Table 6.5 (see also Table 3 of Sankaranarayanan 1991).

Table 6.5: Estimates of risk coefficients in ICRP Publication 60 (ICRP 1991; Sankaranarayanan 1991)

Time span	Disease category	Risk coefficient in % per Gy for	
		Reproductive Population	Total Population
Up to two generations	Mendelian & chromosomal	0.3	0.1
	Multifactorial	0.23	0.09
	Total	0.53	0.19
New equilibrium	Mendelian & chromosomal	1.2	0.5
	Multifactorial	1.2	0.5
	Total	2.4	1.0[a]

[a] The estimate used by ICRP (1991) in its summary of 'nominal probability coefficients for stochastic effects' (Table 6.3; ICRP 1991); the figure given in this Table of $1.3.10^{-2}.Gy^{-1}$ takes into account a weighting factor for years of life lost (ICRP 1991)

The estimates for the 'reproductive population' apply when the radiation doses received by all individuals in the population are genetically significant. However, when the total population of all ages is considered, the genetically significant dose will be markedly lower than the total dose received over a lifetime. Genetic damage sustained by germ cells of individuals who are beyond the reproductive period, or who are not procreating for any reason, poses no genetic risks. On the assumption that the average life expectancy at birth is of the order of 75 years, the dose received by 30 years of age (i.e., the mean reproductive age) is 40% (i.e., 30/75 = 0.4) of the total dose. The risk coefficients for the total population, therefore, are estimated to be 40% of the above values.

Although ICRP (1991) presented risk coefficients for the first two generations as well as for the new equilibrium, it used the equilibrium estimate of 1.0. $10^{-2}.Gy^{-1}$ for the total population (with an additional weighting factor for years of lost life to arrive at a figure of $1.3.10^{-2}.Gy^{-1}$ for 'severe hereditary effects' in its summary table of 'nominal probability coefficients' (Table 3; ICRP 1991).

6.5.2 Current assessments.

In its current assessments, the Task Group used the estimates of risk presented in Table 6.3 as starting points. The upper and lower limits of each of the estimated ranges were first used to obtain average estimates and the latter are then combined to generate a single estimate of risk coefficient for all genetic effects. Details of calculations are given in the next section.

Risk coefficients up to generation 2 for a population sustaining radiation exposure in every generation

(a) risk of Mendelian diseases = 1,300 to 2,500 cases per 10^6 progeny per Gy (= $0.13.10^{-2}$ to $0.25.10^{-2}.Gy^{-1}$; average: $0.19.10^{-2}.Gy^{-1}$);

(b) risk of chronic multifactorial diseases = 250 to 1,200 cases per 10^6 progeny per Gy (= $0.03.10^{-2}.Gy^{-1}$ to $0.12.\ 10^{-2}.Gy^{-1}$; average: $0.08.10^{-2}.Gy^{-1}$);

(c) risk of congenital abnormalities = 2,400 to 3,000 cases per 10^6 progeny per Gy ($0.24.10^{-2}$ to $0.30.10^{-2}.Gy^{-1}$; average: $0.27.10^{-2}.Gy^{-1}$) and,

(d) risk of all classes (i.e., [a] to [c], combined) = 3,950 to 6,700 cases per 10^6 progeny per Gy or $0.40.10^{-2}$ to $0.67.10^{-2}.Gy^{-1}$; average: $0.54.10^{-2}.Gy^{-1}$

The above estimates are for a reproductive population. For the total population, the estimates are multiplied by 0.4. All the estimates are summarized in Table 6.6.

Table 6.6: Risk coefficients for the reproductive and the total population obtained with method 1 (all values expressed in percent per Gy) and up to 2 generations when the population sustains radiation exposure generation after generation

Disease class	Reproductive population		Total population
	Range	Average[a]	Average[b]
(a) Mendelian diseases	0.13 to 0.25	0.19	0.08
(b) Chronic diseases	0.03 to 0.12	0.08	0.03
(c) Congenital abnormalities	0.24 to 0.30	0.27	0.11
Total for all classes		0.54	0.22

[a] Average of the limits of the indicated ranges

[b] 40% of that for the reproductive population

It is evident that, despite different baseline frequencies for Mendelian diseases, MCs and differences in risk estimates for comparable classes of diseases, the present estimates for the reproductive (0.54) as well as for the total population (0.22) are remarkably similar to those arrived at in ICRP Publication 60 (1991; respectively, 0.53 and 0.19; see Table 5.). It should be stressed that this similarity is a matter of pure coincidence!

As may be recalled, the ranges in the estimates of risk coefficients for Mendelian and chronic diseases are a reflection of the ranges of PRCFs (0.15 to 0.30 for autosomal dominant and X-linked diseases and 0.02 to 0.09 for chronic diseases). Arguments to suggest that the upper limits of these ranges may represent over-estimates and that the actual values may be closer to the lower limits were presented in Section 6.3. If this reasoning is accepted, then it is meaningful to use the lower limit of the ranges for the above two classes of diseases and the average of the range for congenital abnormalities. When this is done, the risk coefficients become smaller than those presented in Table 6.6 as noted below:

Reproductive population:

Mendelian diseases, 0.13; chronic diseases, 0.03, congenital abnormalities, 0.27, Total: $0.43.10^{-2}$. Gy^{-1}

Total population:

Mendelian diseases, 0.05; chronic diseases, 0.01; congenital abnormalities, 0.11, Total: $0.17.10^{-2}$. Gy^{-1}

Risk coefficients for the first post-radiation generation only

The risk coefficients for the first post-radiation generation are summarized in Table 6.7. Again as expected, the values are smaller than those up to the first two generations.

Table 6.7: Risk coefficients for the reproductive population and the total population for the first post-irradiation generation (all values are expressed as per cent per Gy)

Disease class	Reproductive population		Total population
	Range	Average[a]	Average[b]
(a) Mendelian diseases	0.075 to 0.150	0.11	0.05
(b) Chronic diseases	0.025 to 0.120	0.07	0.03
(c) Congenital abnormalities	-	0.20	0.08
Total for all classes		0.38	0.16

[a] Average of the limits of the indicated ranges

[b] 40% of that for the reproductive population

If, however, the lower limits of the ranges for Mendelian and chronic diseases are used, then the estimates are $0.30.10^{-2}$. Gy^{-1} for the reproductive population (i.e., 0.075 + 0.025 + 0.20 = 0.30) and $0.12.10^{-2}$. Gy^{-1} for the total population (i.e., [0.075 × 0.4] + [0.025 × 0.4] + [0.20 × 0.4] = 0.12).

6.5.3 Justifications for using risk estimates up to generation two versus the first post-radiation generation for calculating risk coefficients

In a strict sense, genetic risk coefficients cannot be compared or combined with those for cancers. This is because of the fact that cancer risk coefficients quantify the probability of harmful effects of radiation to the exposed individuals themselves, and genetic risk coefficients quantify the probability of harmful effects to the descendants of those exposed. In the case of genetic risk coefficients, the inclusion of risk up to two generations in the calculations can be justified on the basis that people are generally interested in the well-being of their children and grandchildren. The estimate restricted to the first post-radiation generation has the advantage that it is more comparable to those for cancers and therefore deserves serious consideration. For the purpose of tissue weighting, the use of the first post-radiation generation risk might be considered as preferable in

order to make comparisons with cancer risk more consistent. However, given the breadth of the judgements needed for the choice of tissue weighting factors and for the purposes of simplicity the Task Group recommend the use of the estimates of risks up to the second generation shown in Table 6.6.

The population genetic theory of equilibrium between mutation and selection that underlies the use of the doubling dose method and the available mathematical formulations permit, in principle, the prediction of genetic risks at the new equilibrium (under conditions of continuous radiation in every generation). As stated earlier, in order not to underestimate genetic risks, ICRP Publication 60 (ICRP 1991) used the equilibrium estimates as a basis for calculating risk coefficients for genetic effects. The arguments against such a procedure, apart from reasons stated in the preceding paragraph, entails the very unrealistic and untestable assumptions that (a) the estimates of selection coefficients, mutation components and the other quantities used in the risk equation, will remain valid for tens or hundreds of human generations; (b) the population structure, demography and health care facilities will remain constant over hundreds of years.

In the view of the Task Group these assumptions can no longer be sustained and the Task Group recommends that for the practical purposes of radiological protection ICRP adopts a genetic risk estimate based upon risks up to the second generation. UNSCEAR (2001) have made the same judgement on this matter.

The concepts that (a) radiation-induced genetic changes are predominantly deletions, often encompassing more than one gene and that only a small proportion of such induced deletions is compatible with live births, and (b) radiation-induced heritable effects in humans are more likely to be manifest as multi-system developmental abnormalities in the progeny rather than as diseases due to mutations in single genes, are particularly relevant to this issue. Because reproductive fitness of the affected progeny will be reduced, many radiation induced genetic changes affecting development are expected to be strongly selected against. It is judged therefore that expressing genetic risks up to the second generation will not lead to any substantial underestimate of the heritable effects of radiation.

In addition, the Task Group notes that because of the different ways used to calculate the risk of autosomal dominant plus x-linked disease (the DD method) and congenital abnormalities (directly from mouse data), there must be a considerable element of 'double counting' of risk. Therefore, the summing of these risk categories as used conventionally by UNSCEAR and ICRP must represent a significant overestimate of genetic risk overall.

7. Summary of Principal Conclusions and Proposals

Although additional work was required, many of the conclusions and proposals from the Task Group are based upon ICRP Committee 1 judgements developed over the last 8-10 years. Accordingly many sections of the report are themselves summaries of these pre-existing judgements. For this reason a simple tabular format (Table 7.1) has been used to provide an overall summary of the principal conclusions and proposals from the Task Group. The inclusion in Table 7.1 of identifiers for the relevant sections and tables for each topic serves to map the document and guide readers to the topic of interest. These sections often detail methodologies, uncertainties and caveats not fully reflected in Table 7.1. Accordingly Table 7.1 cannot be taken as being fully informative of Task Group views and judgements.

The Task Group also wish to emphasise an important issue discussed in ICRP Committee 2 Foundation Document (FD-C-2). The conclusions and proposals summarised in Table 7.1 are for the broad purposes of prospective planning in radiological protection. For other purposes many of the proposed judgements may well be insufficient and in these circumstances specific, well justified, judgements on radiation effects and their risks will need to be made.

Table 7.1: Summary of principal conclusions and proposals specifically intended for radiological protection purposes

	Topic	Data source / methodology	Conclusions / numerical judgements
1	Dose response at low doses/dose-rates for cancer and heritable effects *(Sections 2.1-2.5; 2.7-2.8; 4.1.1-4.1.2; 4.2.7)*	Judgements based on studies reviewed in *Publication LDR-C-1*; UNSCEAR 2000, 2001; NCRP 2001)	Uncertainties are considerable but the balance of evidence weighs in favour of the use of a simple proportionate relationship between increments of dose and risk
2	Role of induced genomic instability, bystander signalling and adaptive responses in the risk of induced health effects *(Sections 2.3; 2.5; 4.1.2-4.1.3)*	Judgements based on studies reviewed in *Publication LDR-C-1*; NCRP 2001; UNSCEAR 2000; UNSCEAR 1994	Knowledge of these biological effects is growing but is currently insufficient for radiological protection purposes
3	Relative biological effectiveness and radiation weighting factors (w_R). *(Section 4.3)*	Judgements based upon recommend-ations included in *Publication 92*	Judgements are fully developed in the Committee 2 Foundation Document *(FD-C-2)*
4	Dose and dose-rate effectiveness factor (DDREF) and the impact of a possible dose threshold. *(Sections 2.4; 4.2; 4.4.1.2; 4.4.5)*	Judgements largely based upon studies reviewed in *Publication LDR-C-1* and UNSCEAR 2000	A DDREF value of 2 should be retained for use by ICRP; the uncertain possibility of a low dose threshold for cancer risk is equivalent to an uncertain increase in the value of DDREF.
5	Radiation detriment and tissue weighting factors (w_T) *(Section 4.4.1)*	New judgements developed largely from cancer incidence in the A-bomb Life Span Study (LSS), international cancer mortality databases and new estimates of heritable effects (see 7 below); judgements supported by additional consideration of cancer mortality data.	Revised w_T scheme proposed; significant w_T changes for breast and gonads (see Table 4.3); revised method of treatment of remainder tissues (see Table 4.3).
6	Detriment adjusted nominal probability coefficients for cancer *(Section 4.4.1)*	New risk estimates developed are based upon lethality/life impairment weighted data on cancer incidence (see 5 above)	Detriment adjusted nominal probability coefficients of 5.9 10^{-2} Sv^{-1} for the whole population and 4.6 10^{-2} Sv^{-1} for adult workers are proposed (see Table 4.4.)

	Topic	Data source / methodology	Conclusions / numerical judgements
7	Detriment adjusted nominal probability coefficients for hereditary effects *(Section 6)*	New risks estimates are based upon UNSCEAR 2001 judgements using risks for all classes of hereditary effects up to the second post-irradiation generation (see Tables 6.4 and 6.6)	Second generation, detriment adjusted nominal risk coefficients of 0.2 10^{-2} Sv^{-1} for the whole population and 0.1 10^{-2} Sv^{-1} for adult workers are proposed (see Table 4.4). *Publication 60* used population genetic risks at a theoretical equilibrium so the present estimates are markedly lower.
8	Cancer risk following *in utero* exposures *(Section 4.4.3)*	Judgements based upon the studies reviewed in *Publication 90*	Life-time cancer risk judged to be no greater than that following exposure in early childhood
9	Genetic susceptibility to radiation-induced cancer *(Sections 2.7.3; 4.4.4)*	Judgements based upon studies reviewed and analyses made in *Publication 79* and UNSCEAR 2000, 2001	Strongly expressing cancer-predisposing disorders are too rare to appreciably distort risk estimates for the whole population; the impact of potentially common but weak genetic determinants remains uncertain
10	Radiation-induced tissue reactions in adults *(Sections 2.6; 3)*	Mechanisms have been re-evaluated and dose thresholds for morbidity/mortality revised on the basis of various data	Tables 3.1; 3.2 and 3.4 provide revised judgements but with few changes from other ICRP publications. The dose threshold for cataract is revised downwards. Dose limits for the lens of the eye remain unchanged but may require future attention.
11	*In utero* risks of tissue reactions, malformations and neurological effects *(Section 3.2)*	Judgements based upon studies reviewed in *Publication 90*	Strengthened judgement on the existence of a dose-threshold for tissue reactions, malformation and severe mental retardation - therefore, absence of risk at low doses. Greater uncertainty for IQ deficits but low dose risk judged to be insignificant
12	Risks of non-cancer diseases	Judgements based upon LSS data and studies on post-radiotherapy outcomes particularly for cardiovascular disease	Great uncertainty on the form of the dose-response below 1 Sv – no specific judgement on low dose risk is possible.

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