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Low-dose Extrapolation of Radiation-related Cancer Risk

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Aims and Scope

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Approved by the Commission in October 2004

Abstract–This report considers the evidence relating to cancer risk associated with exposure to low doses of low linear energy transfer radiation, and particularly doses below current recommended limits for protection of radiation workers and the general public. The focus is on evidence regarding linearity of the dose–response relationship for all cancers considered as a group, but not necessarily individually, at low doses [the so-called linear, non-threshold (LNT) hypothesis]. It looks at the possibility of establishing a universal threshold dose below which there is no risk of radiation-related cancer. The report is organised by scientific discipline, beginning with epidemiological studies of exposed human populations. Extrapolation of risk estimates based on observations at moderate to high doses continues to be the primary basis for estimation of radiation-related risk at low doses and dose rates. The fundamental role of radiation-induced DNA damage in the induction of mutations and chromosome aberrations provides a framework for the analysis of risks at low radiation doses and low-dose-rate exposures. Although cells have a vast array of damage response mechanisms, these mechanisms are not foolproof, and it is clear that damaged or altered cells are capable of escaping these pathways and propagating. Cellular consequences of radiation-induced damage include chromosome aberrations and somatic cell mutations. Current understanding of mechanisms and quantitative data on dose and time–dose relationships support the LNT hypothesis. Emerging results with regard to radiation-related adaptive responses, 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, although there are intrinsic uncertainties at low doses and low dose rates, direct epidemiological measures of radiation cancer risk necessarily reflect all mechanistic contributions including those from induced genomic instability, bystander effects, and, in some cases, adaptive responses, and therefore may provide insights about these contributions. Experimental approaches using animal models support the view that the response for early initiating events is likely to correspond to that for the induction of cytogenetic damage. On this basis, mechanistic arguments support a linear response in the low-dose region. Quantitative analyses of dose responses for tumourigenesis and for life shortening in laboratory animals also support this prediction. These studies also support a dose and dose rate effectiveness factor (DDREF) in the range of about 2 when data

are extrapolated to low doses from effects induced by doses in the range of 2–3 Gy. A formal quantitative uncertainty analysis combines the different uncertain components of estimated radiation-related cancer risk with and without allowing for the uncertain possibility of a universal low-dose threshold. Unless the existence of a threshold is assumed to be virtually certain, the effect of introducing the uncertain possibility of a threshold is 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 report concludes that while existence of a low-dose threshold does not seem to be unlikely for radiation-related cancers of certain tissues, the evidence does not favour the existence of a universal threshold. The LNT hypothesis, combined with an uncertain DDREF for extrapolation from high doses, remains a prudent basis for radiation protection at low doses and low dose rates.
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Keywords: LNT; DDREF; Radiation protection; Uncertainty; Dose response

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Guest Editorial

THE RISK TO HEALTH FROM EXPOSURE TO LOW LEVELS OF IONISING RADIATION

The shape of the dose–response relationship describing the excess risk of stochastic health effects (cancer and hereditary anomalies) following low levels of exposure to ionising radiation has been the subject of heated debate. The standard approach for the purposes of radiological protection is that the radiation-induced risk is directly proportional to the dose received [the linear, non-threshold (LNT) model], but some have argued that this approach underestimates the actual risk (i.e. the relationship is properly described by a supralinear curve), or that, in reality, there is a threshold dose below which either no effect, or even a beneficial (hormetic) effect, exists. Certain groups hold strong and entrenched views on this issue, and are vociferous in their criticism of the LNT model. This dispute between the 'radiological protection establishment' and its critics tends to leave those without particular expertise in the subject, including policy makers, bemused and perplexed, and it is difficult to avoid the thought that obfuscation might be an objective of some of the more campaigning of the dissenting groups. The present report of an ICRP Task Group is a timely review of the available evidence on the carcinogenic effect of low-level exposure to low linear energy transfer radiation, and collates and examines the findings from a range of relevant scientific studies.

Of course, the ideal solution to the problem of the nature of the dose–response relationship at low doses would be to derive the curve from fundamental biological principles, and basic radiobiological mechanisms do provide a rationale for the LNT model: at low doses and (for sparsely ionising radiations) low dose rates, the pertinent damage to DNA is caused (either directly or through free radical production) by independent particle tracks, so that the probability of non-lethal cellular modification is directly proportional to the number of tracks traversing cell nuclei (i.e. the dose). At higher doses and dose rates, the likelihood of track interactions increases to produce an upward turn in the dose response (although this does not occur for densely ionising radiations, a single track of which generates sufficient damage to DNA by itself). However, this simple and reassuring radiobiological picture is challenged by novel mechanisms: the bystander effect and genomic instability imply that damage occurs in cells that have not directly experienced a particle traversal, and the adaptive response suggests that cellular defence processes may modify the effects of protracted, relative to acute, irradiation. Just how these mechanisms, which undoubtedly exist under particular experimental conditions, might affect the risk

of radiation-induced cancer and hereditary disease in humans is, of course, the primary question, but it is not a question that may be answered with conviction on present radiobiological evidence. Hence, there is a need to revert to epidemiological studies, with all their complications, in an attempt to derive an appropriate dose–response relationship; epidemiological data will incorporate all the relevant radiobiological mechanisms that have led to the specific health outcomes under study.

Unfortunately, epidemiological studies bring their own interpretational problems. Epidemiology is principally an observational (i.e. non-experimental) science that is based upon data generated by the uncontrolled conditions of everyday life, since randomised controlled trials are unacceptable for the study of (actual or potential) hazardous exposures. Further, the excess risk predicted by the LNT model to be produced by low doses of radiation is small. Consequently, any signal of an effect of low-level irradiation will be easily hidden by the background noise of statistical and systematic deviations from expectation, and epidemiological data for low doses will inevitably be consistent with a number of curves describing possible dose–response relationships. All is not completely lost, however, since the broad range of epidemiological evidence may be capable of constraining the dose–response relationship to lie within an envelope of curves. Ultimately, scientific judgement is also required in deriving the most plausible dose–response relationship. For example, it is inevitable that at some dose, the overall risk of a certain health effect will be compatible (at some conventional level of statistical significance) with the absence of a radiation-induced excess risk. What is to be made of this? Can we reasonably conclude that no excess risk exists below this dose? My view coincides with that of the late Sir Richard Doll, who dryly observed in 1997 in an opening conference address that he believed that 'a linear dose–response relationship will not suddenly dive to zero immediately below the lowest level at which a statistically significant excess is observed'.

There is epidemiological evidence, mainly from studies of those medically exposed to x rays for diagnostic purposes, that the risk of cancer is raised following the receipt of doses of around 10 mGy, and that this increase is broadly consistent with the predictions of the LNT model. This evidence points away from a threshold dose, in particular because a cancer induced by a dose as low as $\sim$10 mGy of x rays is very likely to have been caused by the passage of a single electron through a cell nucleus. Further, if the risk from low-level exposure has been seriously underestimated by the LNT model, this should be apparent from the overall results of low-dose studies that are presently available; however, no such consistent pattern emerges. Of course, the evidence allows room for manoeuvre away from the LNT model at low doses, although only to an extent, and one might expect that different types of cancer have somewhat different dose–response curves; leukaemia is an obvious example. Nonetheless, the parsimonious choice of relationship for low-level exposures on the basis of the current evidence covering the generality of cancer induction, and one that has the decided advantage of practicality, is an excess risk that is directly proportional to the dose; the LNT model.

The evidence reviewed in the present report – the sophisticated treatment of uncertainties is especially impressive – and the inferences drawn from it should be paid

serious attention by those arguing against the LNT model. Clearly, the future accumulation of additional information is highly likely to lead to further debate, but this must be evidence based rather than mired in dogma. One can only hope that this report will help to provide a firm foundation from which constructive discussion can progress.

Richard Wakeford

CONTENTS

PREFACE

Following its meeting in Oxford, UK in 1997, Committee 1 of the International Commission on Radiological Protection proposed a Task Group to prepare a report on low-dose extrapolation of radiation-related cancer risk estimates based largely on higher-dose epidemiological data, and the possible implications for radiological protection. The Commission accepted this recommendation and established a Task Group, which began its work in April 1998.

The membership of the Task Group was as follows:

C.E. Land (Chair)	P.A. Jeggo	A.M. Kellerer
J.B. Little	D.A. Pierce	R.L. Ullrich

Corresponding members were:

V. Beral	E.S. Gilbert	K. Mabuchi
W.K. Sinclair	Z. Tao	

R. Cox, J.H. Hendry, C.R. Muirhead, and R. J. Preston of Committee 1 contributed additional text to the report.

The membership of Committee 1 during the period of preparation of this report was:

(1997–2001)

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J.H. Hendry	A.M. Kellerer	C.E. Land
J.B. Little	K. Mabuchi	R. Masse
C.R. Muirhead (Secretary)	R.J. Preston	K. Sankaranarayanan
R.E. Shore	C. Streffer	R. Ullrich (from 1999)
K. Wei	H.R. Withers	

(2001–2005)

R. Cox (Chair)	A.V. Akleyev	M. Blettner
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D.L. Preston	R.J. Preston	E. Ron
K. Sankaranarayanan	R.E. Shore	F.A. Stewart
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EXECUTIVE SUMMARY

(a) The present report considers the evidence relating to cancer risk associated with exposure to low doses of low linear energy transfer (LET) radiation, and particularly doses below current recommended limits for protection of radiation workers and the general public. The focus is on evidence regarding linearity of the dose–response relationship for all cancers considered as a group, but not necessarily individually, at low doses [the so-called linear, non-threshold (LNT) theory], and the possibility of a universal threshold dose below which there is no risk of radiation-related cancer. According to the LNT theory, the same number of radiation-related cancers would be predicted in a population of a given size exposed to a certain small average radiation dose and in an otherwise similar population many times times larger and exposed to a proportionally smaller average dose. According to the threshold theory, the radiation-related risk in the larger population would be zero if its average dose was sufficiently small.

(b) The present document has been preceded by other recent reports, notably those of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR, 1993; 2000) and the US National Council of Radiation Protection and Measurements (NCRP, 2001). These reports recommended that radiation protection should continue to be guided by the LNT theory. The Task Group concurs with those recommendations.

(c) This report is organised by scientific discipline, beginning with epidemiological studies of exposed human populations (Chapter 2). Epidemiological studies offer the most directly relevant information for risk-based radiation protection. The major scientific issues, as illustrated by the example of cancer incidence from all solid tumours combined in the Life Span Study population of atomic bomb survivors, are: (1) establishment of the existence of a dose-related risk in this population; (2) modelling radiation-related risk as a statistically uncertain parametric function of dose, modified by other factors such as sex, exposure age, attained age, and time following exposure; (3) extrapolation of estimated risk to other potentially exposed populations, with possible different baseline cancer rates; (4) projection of the risk in the population to the end of its natural life; and (5) extrapolation of risk estimates from moderate-to-high dose levels of acute exposure, characteristic of the most informative atomic bomb survivor data, to the far more common low-dose and/or protracted exposures that occur in occupational and general settings. Consideration of each of these issues leads to more refined risk estimates; however, because information about each is uncertain, the overall uncertainty of the improved estimates is increased. There is limited evidence of increased cancer risk associated with acute exposures of the order of a few tens of mGy, and this will be discussed in the report. However, firm epidemiological evidence of radiation cancer risk comes from studies that involve exposures of >100 mGy. Other evidence may be used to place an upper limit on the value of any universal threshold that may exist. Also, the risk of mortality and morbidity from all solid cancers combined is proportional to radiation doses down to approximately 100–150 mGy, below which statistical variation in baseline risk, and small and uncontrollable biases, tend to obscure evidence concerning

radiation-related risk. Extrapolation of risk estimates based on observations at moderate-to-high doses continues to be the primary basis for estimation of radiation-related risk at low doses and dose rates.

(d) The fundamental role of radiation-induced DNA damage in the induction of mutations and chromosome aberrations, and the apparent critical involvement of aberrations and mutations in the pathogenesis of cancer provides a framework for the analysis of risks at low-dose and low-dose-rate exposures (Chapter 3). A characteristic type of damage produced by ionising radiation (IR) involves multiple lesions within close spatial proximity. Such clustered damage can be induced even by a single radiation track through a cell. Although cells have a vast array of damage response mechanisms that facilitate the repair of DNA damage and the removal of damaged cells, these mechanisms are not foolproof, and emerging evidence suggests that closely spaced lesions can compromise the repair machinery. 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 pathways, it is clear from analysis of cytogenetics and mutagenesis that damaged or altered cells are capable of escaping these pathways and propagating.

(e) Cellular consequences of radiation-induced damage (Chapter 4) include chromosome aberrations and somatic cell mutations. The processing and misrepair of radiation-induced double-strand breaks, particularly complex forms, are responsible for chromosome/gene alterations that manifest as chromosome aberrations and mutations. Current understanding of mechanisms and quantitative data on dose and time–dose relationships support a linear dose–response relationship at low doses (i.e. LNT). Considered as a whole, the emerging results with regard to radiation-related adaptive responses, genomic instability, and bystander effects suggest that the risk of low-level exposure to IR 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 inter-related 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 IR. In addition, although there are intrinsic uncertainties at low doses and low dose rates, direct epidemiological measures of radiation cancer risk necessarily reflect all mechanistic contributions, including those from induced genomic instability, bystander effects, and, in some cases, adaptive responses, and therefore may provide insights about these contributions.

(f) Experimental approaches using animal models (Chapter 5) are well suited to precise control of radiation dose and dose rate, as well as genetic background and other possible modifiers of the dose–response relationship, and can facilitate precise determination of biological outcomes. Recent studies using newly developed animal models; cellular, cytogenetic and molecular data for acute myelogenous leukaemia (AML), intestinal tumours, and mammary tumours; and cytogenetic and molecular studies on the induction of AML and mammary cancer support the view that the essential radiation-associated events in the tumourigenic 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 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–response relationships for tumourigenesis and for life shortening in laboratory animals also support this prediction. These studies also support a dose and dose-rate effectiveness factor (DDREF) for reduction of estimated risk per unit dose based on acute, high-dose data in the range of about 2 when data are extrapolated to low doses from effects induced by doses in the range of 2–3 Gy. Extrapolation of results from less than 1 Gy would result in lower DDREF values.

(g) Chapter 6 presents a formal exercise in quantitative uncertainty analysis, in which the different uncertain components (as identified in Chapter 2) of estimated cancer risk associated with low-dose, low-LET radiation exposure to a non-Japanese population, in this case that represented by the US National Cancer Institute's SEER (Surveillance Epidemology and End Results) registry, are combined. Attention is paid to the resulting uncertainty distribution for excess relative risk (ERR) per Gy, with and without allowing for the uncertain possibility of a universal low-dose threshold below which there would be no radiation-related risk. In the example that involves risk from all cancers combined including leukaemia, except for non-melanoma skin cancer, the major sources of uncertainty are statistical variation in the estimated ERR at 1 Gy for the atomic bomb survivors, subjective uncertainty (informed by experimental and epidemiological data) about the DDREF to be applied at low doses and dose rates, and the postulated uncertainty concerning the existence of a universal threshold at some dose above that for which the calculation was being made. Unless the existence of a threshold was assumed to be virtually certain, 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.

(h) The conclusions of this report are given in Chapter 7. While existence of a low-dose threshold does not seem unlikely for radiation-related cancers of certain tissues, and cannot be ruled out for all cancers as a group, the evidence as a whole does not favour the existence of a universal threshold, and there seems to be no particular reason to factor the possibility of a threshold into risk calculations for purposes of radiation protection. The LNT theory, combined with an uncertain DDREF for extrapolation of risk from high doses, remains a prudent basis for radiation protection at low doses and low dose rates.

1. INTRODUCTION

(1) The purpose of the present report is to summarise scientific evidence relevant to the quantification of cancer risk associated with radiation exposure at (effective) doses of interest for radiation protection, particularly doses below current recommended limits for protection of radiation workers (e.g. 20 mSv/year) and the general public (e.g. 1 mSv/year). As a rough rule of thumb, effective doses of the order of 1 Sv, 100 mSv, 10 mSv, 1 mSv, and 0.1 mSv may be called 'moderately high', 'moderate', 'low', 'very low', and 'extremely low', respectively. However, in common usage, and in this report in particular, 'low' and 'high' are usually relative terms, i.e. shorthand for 'relatively low' and 'relatively high', which may refer to ranges of different numerical values depending on the context.

(2) Ionising radiation (IR) exposure is an established cancer risk factor. Compared with other common environmental carcinogens, it is relatively easy to determine organ-specific radiation dose and, as a result, radiation dose–response relationships tend to be highly quantified. Nevertheless, there can be considerable uncertainty about questions of radiation-related cancer risk as they apply to risk protection and public policy, and the interpretations of interested parties can differ radically. A major reason for disagreement is that public and regulatory concern is often focused on exposures at radiation doses far lower than those at which useful information about cancer risk can be obtained directly, i.e. than can be obtained by studying populations with such exposures. Thus, risk estimates promulgated by expert committees, for example, are usually based upon epidemiological dose–response data obtained at doses ranging up to 0.2 Gy, 0.5 Gy, 1 Gy, or higher, and the resulting estimates are then extrapolated, with appropriate caveats, to lower doses. The extrapolation rules are based, in part, upon epidemiological observations, such as the degree of curvature of fitted linear-quadratic dose–response models for leukaemia and solid cancer morbidity among atomic bomb survivors, and on models derived from experimental systems.

(3) The discussion in the present report is concerned ultimately with the biological effects of IRs of low linear energy transfer (low LET), such as photons (gamma rays and x rays) and electrons (beta particles) of various energies, as contrasted with high-LET radiations such as neutrons and alpha particles. However, some biological effects that have been observed mainly in connection with high-LET exposure are clearly relevant to questions of cancer risk at low levels of low-LET radiation.

(4) Currently, the ICRP radiation protection philosophy is based on the so-called linear, non-threshold (LNT) theory. According to this theory, total radiation-related cancer risk is proportional to dose at low and moderately low doses (of the order of 200 mGy or less) and dose rates (less than 6 mGy/h averaged over the first few hours) (EPA, 1999; UNSCEAR, 1993). The theory is not universally accepted as biological truth. However, because it is not actually known what level of risk is associated with very-low-dose exposure, this theory is considered by many to be a prudent rule of thumb for public policy aimed at avoiding risk from unnecessary exposure.

(5) A logical conclusion from the LNT theory is that at a sufficiently low dose D and sufficiently large population size N, exposure of N people to average dose D

would result in the same number of radiation-related cancers as exposure of $k \times N$ people to average dose D/k, for arbitrary $k > 1$. This logical consequence has been used to justify the concept of 'collective dose', that the product of average dose and the number of people exposed is proportional to the number of radiation-related cancers. The concept of collective dose is sometimes used to support a moral argument against widespread use of technologies or practices that would, according to the LNT theory, involve individual exposures at doses so low that any associated risk, from the standpoint of the individual, would be far smaller than other risks that are casually taken in everyday life. A so-called threshold theory, according to which there is no radiation-related risk associated with exposures at doses below some universal threshold dose, would obviate concern about exposures at doses below the threshold and, specifically, arguments based on the concept of collective dose. Aside from collective dose, however, it is worth emphasising that the practical importance of the LNT vs threshold question is associated with doses at which the associated risks, if they exist, are high enough to be of 'legitimate' concern, as determined by the usual social and political processes.

(6) Historically, the LNT vs threshold controversy has been associated with public policy issues related to exposures that are widespread but (typically) low for individuals, such as local and worldwide exposure to radioactive fallout from aboveground nuclear test explosions carried out by different governments, mainly during the 1950s (Caron, 2004; Lewis, 1957, 1963). The threshold theory, as applied to IR and to fallout exposure in particular, drew some of its legitimacy from the field of chemical toxicology, where thresholds are the rule (Brues, 1958, 1960), whereas the LNT theory is more consistent with findings from experimental radiation mutagenesis. As described by Caron (2004), the intellectual positions taken by proponents of the opposing sides during the fallout controversy of the 1950s (no compelling evidence of increased cancer risk at low radiation doses vs no compelling evidence against a radiation-related increase in cancer risk) are very similar to the situation at the present time. Some differences discussed in this report include the present general acceptance of a mutational basis for carcinogenesis, and evidence that radiation-related mutations tend to be more complex than more common mutations associated with endogenous and other causes.

(7) The present report has been preceded by other surveys of the biological and epidemiological information that underlies our understanding of low-dose risk and its estimation by extrapolation from data obtained at higher doses, notably and recently the comprehensive reports of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR, 2000, Annexes G and I) and the US National Council of Radiation Protection and Measurements (NCRP, 2001). The existence of these reports has allowed the present ICRP Task Group to be somewhat less comprehensive in its coverage of the field than may otherwise have been necessary, and to concentrate on updated coverage of developments in areas of epidemiology, fundamental biology, experimental radiation mutagenesis and carcinogenesis, and uncertainty analysis.

(8) Studies of cancer risk following exposure of human populations are the most obvious sources of information applicable to radiation protection policy. However,

as discussed in Chapter 2, generalisation of risk information obtained from one exposed population to other populations with different characteristics and potentially exposed to radiation from different sources, at different doses and dose rates, requires the use of dose–response models to describe the behaviour of risk as a function of radiation dose, as well as possible modification of the dose–response relationship by individual and environmental factors. It also requires making assumptions that are often based on uncertain information.

(9) Chapter 3 deals with events believed to be fundamental to radiation carcinogenesis: radiation-induced DNA damage and its repair. In particular, Chapter 3 discusses the nature of radiation-induced damage and damage response pathways including repair of DNA double-strand breaks (DSBs), cell-cycle checkpoint control, early sensors of DNA damage, and signal transduction after irradiation. Questions of particular relevance for the current investigation are comparability of molecular damage from radiation exposure and endogenous causes, and comparability between radiation-related damage from IR at high vs low doses and dose rates with respect to mechanisms, pathways, and fidelity of repair.

(10) Cellular consequences of radiation-induced damage are discussed in Chapter 4. Rates of radiation-induced chromosome aberrations and somatic cell mutations were among the earliest quantitative measures of the cellular effects of IR, and studies of these outcomes have been highly informative about the dose–response relationship over a wide range of doses, and about effects of dose rate and fractionation. Induction of bystander effects in cells not directly irradiated, genomic instability in the progeny of irradiated cells, and adaptive responses are radiation-related phenomena that evoke questions about the generality of inferences based on cellular studies.

(11) Considerations of statistical power, and possible bias due to unobservable and uncontrollable confounders, govern the extent to which useful epidemiological information can be obtained at exposure levels of regulatory interest, and some degree of extrapolation is unavoidable. Experimental approaches using animal models, discussed in Chapter 5, offer considerably more control of radiation exposure and dose, genetic background, and modifying factors including other exposures, and can facilitate very precise determination of biological outcomes. On the other hand, analogies between radiation-related risks in human beings and inbred strains of experimental animals are necessarily limited. Low statistical power for low-dose studies is problematic for experimental and epidemiological studies alike, but indirect approaches, based on protraction and fractionation of exposure resulting in moderate to high cumulative doses, offer insights into low-dose effects. Experimental studies can, of course, be replicated to provide a firmer basis for insights into mechanisms, tissue-modifying factors, and quantitative dose–response relationships.

(12) Chapters 2–5 highlight statistical variations inherent in estimates obtained by fitting parametric models to epidemiological and experimental data, but also more fundamental uncertainties about important factors that cannot be ignored, but about which there may only be limited information. The implications of these uncertainties for conventional estimates of radiation-related cancer risk, especially at low doses and/or low dose rates characteristic of exposures most commonly encountered by radiation workers and the general public, are investigated in Chapter 6. The

approach taken is an exercise in quantitative uncertainty analysis similar to approaches used in a number of recent exercises by expert committees concerned with such risks. Central to the approach is recognition of the fact that radiation protection is a political process, responsive to the interests and perceptions of stakeholders with differing points of view, and relying upon a knowledge base that is extensive but also uncertain. Acceptance of this fact implies that it is important, for the benefit and information of participants and stakeholders in the radiation protection process, to identify sources of uncertainty and to quantify the implications of such uncertainty for estimated risk. Among the questions addressed is the impact on radiation protection policy of treating the existence of a universal low-dose threshold for radiation-related cancer risk as an uncertain possibility.

2. EPIDEMIOLOGICAL CONSIDERATIONS

2.1. Introduction

(13) As for other areas of epidemiological research, the study of radiation-related cancer risk began with clinical observations, the earliest of which may have been the 16th century identification by the physician Georg Bauer (more often known by his Latinised name, 'Agricola') of a specific condition, which he called 'Joachimsthal Mountain Disease', among miners in the Joachimsthal region of the present-day Czech Republic. The disease, the description of which now appears consistent with radon-related lung cancer but which could also include other lung diseases such as silicosis (NAS/NRC, 1999), was thought by Agricola to be caused by 'metallic vapours' in mine atmospheres. Roentgen's discovery of x rays in 1895, Becquerel's discovery of natural radioactivity the following year, and the subsequent use of both in science, medicine, and industry led to the recognition, documented by case reports early in its history, that radiation exposure may be harmful (Doll, 1995). The Court Brown and Doll study (1958) of mortality among British radiologists (Berrington et al., 2001; Smith and Doll, 1981), which demonstrated a significantly increased risk of cancer mortality among radiologists who had registered with a radiological society before 1921 and who were therefore likely to have received higher doses than radiologists who began their practice later, is an example of an influential study in which the fact of exposure was related to risk but individual dose estimates were not available. However, experimental studies of radiation effects such as cell inactivation, mutation, and carcinogenesis have taken advantage of the experimenters' ability to regulate, with precision, radiation dose to target cells or tissues. Similarly, epidemiological investigations of exposed populations have benefited enormously from information enabling scientists to reconstruct individual, and even organ-specific, radiation doses. Benefits include the estimation of dose–response relationships and of the modification of such relationships by individual properties such as sex, age, lifestyle, and genetic inheritance. Thus, dose reconstruction is a fundamental component of the epidemiology of radiation carcinogenesis, and tends to be well worth the often considerable effort and expense required.

(14) 'Risk' is a concept in common use that is often applied to the past and future experiences of individuals, but a numerical risk value can be estimated and verified only on the basis of population rates, e.g. by comparing cancer rates in a population exposed to a given radiation dose with rates in an otherwise comparable population that is either not exposed or exposed to a much lower radiation dose. Thus, when we speak of an individual's risk, we are really referring to a property of a population similar to that to which the individual is assumed to belong.

(15) The implications of risk for public policy, and for radiation protection in particular, are controversial, largely because risk estimates are uncertain and because there are legitimate interests in avoiding radiation-related risks and in maintaining radiation-related benefits and/or avoiding costs associated with unnecessary exposure reduction. A person who may be at risk of radiation-related cancer will naturally insist on proof that the risk either does not exist or is small enough to be

tolerated in view of the presumed benefit. A person whose interest is in maintaining the benefit, or avoiding costs associated with reduction of exposure, will demand proof that there is a risk that is high enough to be of concern. The problem is inherently political, and its fair resolution requires information about risk, including its uncertainty, framed so as to address the concerns of both viewpoints.

(16) As epidemiological investigations of radiation-related cancer risk have evolved over time, emphasis has shifted from the discovery that radiation is indeed a cancer risk factor, to demonstration of a radiation dose–response relationship, to identification of factors that modify the dose–response relationship, to examination of assumptions inherent in the risk estimation process. IR exposure is a known, and well-quantified, human cancer risk factor. Nevertheless, estimation of cancer risk following radiation exposure is a very uncertain process for most cases of regulatory and/or popular concern. One reason is that risk estimates are usually applied to exposed populations different from those on which the estimates are based. Another is that public and regulatory interest is usually with exposures at radiation doses far lower than those at which useful information about risk can be obtained by studying populations with such exposures.

2.1.1. Evidence regarding radiation-related transgenerational cancer risk

(17) The current report is mainly concerned with the possibility that cancer risk may be increased following exposure to IR. There is a great deal of information about this question. A second possibility, which is also a matter of concern, is that exposure may be associated with increased transgenerational cancer risk. Various epidemiological and laboratory studies have examined whether risks of cancer are raised in offspring following parental radiation exposure. These studies have been reviewed in detail elsewhere (Boice et al., 2003; COMARE, 2002, 2004). Cellular and animal studies indicate that the induction of cancer in the offspring of irradiated parents is possible in principle. However, the findings in mice have not been consistent. No effect has been seen in some strains (Cattanach et al., 1995), whereas a raised risk has been observed that is greater than that predicted by the conventional induction rate for gene mutations in other strains (Nomura, 1982).

(18) Epidemiological studies conducted in several countries do not provide convincing evidence to suggest that occupational radiation exposure alone results in an increased incidence of childhood cancer in the offspring of male workers; data for the offspring of female radiation workers are too sparse to draw conclusions (COMARE, 2002). In the case of a cluster of childhood leukaemia cases among children in the village of Sellafield, UK, possibly associated with paternal employment at the nearby Sellafield nuclear reprocessing plant (Gardner et al., 1990), such an association received little or no support from other data (Wakeford, 2002). A better case can perhaps be made in the context of the well-documented phenomenon of increased levels of childhood leukaemia in so-called new towns, in which there has been an influx of residents from different areas; the postulated mechanism is an unknown viral aetiology affecting previously unexposed residents (Doll, 1999; Doll et al., 1994). In addition, follow-up of about 40,000 offspring of the Japanese atomic

bomb survivors has not shown any association between the incidence of cancer in children and young adults and parental dose (Izumi et al., 2003). Thus, the subject of transgenerational risk, while a legitimate subject of scientific investigation, is insufficiently developed to provide much information on risks associated with low-dose radiation. It is briefly discussed in Chapter 5 in connection with radiation-induced genomic instability, but is not pursued further in this report.

2.2. Dependence of cancer risk on radiation dose

(19) There is reasonably good epidemiological information on cancer risk following acute exposures in the range 0.2–5 Gy and (for partial-body exposures) above. There are numerous epidemiological studies of populations containing 'high-dose' subsets with radiation doses in this range. These populations include patients treated with radiation for benign and malignant disease; patients who received extensive diagnostic radiography over a lengthy illness, such as tuberculosis patients treated with lung collapse therapy monitored by frequent fluoroscopy examinations; people who received substantial exposures because of their occupations, such as uranium miners exposed to radon decay products in mine atmospheres, and instrument dial painters who ingested radium contained in luminescent paint; and survivors of the atomic bombings of Hiroshima and Nagasaki, Japan. These studies, and, in particular, inferences based on the moderate-to-high-dose component of the populations under study, form the primary epidemiological basis for estimation of radiation-related risk. Comprehensive reviews of epidemiological information on radiation-related cancer risk have been published recently (NCRP, 2001; UNSCEAR, 2000).

(20) Some benchmarks of radiation exposure levels are given in Table 2.1. Yearly natural background effective doses in normal background areas are 0.4 mSv from cosmic radiation, depending upon altitude (the dose from a typical round trip between New York and Paris by commercial airline would be 0.03 mSv); 0.5–4 mSv from radioactivity in rocks and soil, depending on local geology; 0.25 mSv from naturally occurring radionuclides in the human body; and of the order of 1.2 mSv effective dose ($\sim$10 mSv equivalent dose) to the lung from inhaled radionuclides (radon, thoron, and their decay products) (UNSCEAR, 2000). Common diagnostic examinations produce effective doses ranging from 0.01 mSv for x rays of a foot or hand, to 4 mSv for a barium enema (Mettler and Upton, 1995), to 25 mSv for a paediatric computer tomography scan of the abdomen if adult settings are used (Brenner et al., 2003). An astronaut may get $\sim$2–3 mSv tissue-weighted effective dose on a typical 3-day space shuttle mission, and about 50 mSv on a 60-day tour in the international space station (NCRP, 2000). Estimated acute, neutron-weighted doses to the colon (weighted dose = gamma dose plus 10 times neutron dose) from the atomic bombings of Hiroshima and Nagasaki ranged from less than 1 mGy to nearly 6 Gy for survivors who were exposed within 3 km of the explosions and who were still alive in October 1950. Among survivors with estimated doses between 5 mGy and 4 Gy, the average was 200 mGy (RERF, 2003). An acute, uniform whole-body dose of 5 Gy is very likely to be fatal without prompt medical attention, but partial-body radiation therapy for cancer often requires

Table 2.1. Some sources and amounts of ionising radiation exposure [unless noted, from Mettler and Upton (1995)]

Exposure	Effective dose (mSv)	
Natural background (world population)	Normal background areas	High background areas
Cosmic rays	0.38/year	2.0/year
Terrestrial γ rays	0.46/year	4.3/year
Radionuclides in tissue	0.25/year	0.6/year
Inhaled ^{222}Ra	1.2/year	10/year
Medical diagnostic (US population)	*Per examination*	
Skull	0.22	
Cervical spine	0.20	
Chest	0.08	
Cholioangiogram	1.89	
Lumbar spine	1.27	
Upper gastrointestinal series	2.44	
Abdomen (KUB)[+]	0.56	
Barium enema	4.06	
Intravenous pyelogram	1.58	
Pelvis	0.44	
Hip	0.83	
Extremities	0.01	
CT scan, head or body	1.11	
Paediatric CT scan, abdomen[*]	25 (stomach dose)	
Single screening mammogram[*]	3 (breast dose)	
Astronaut, 3-day space shuttle mission[†]	2–3	
Astronaut, 60-day space station mission[†]	50	
Average cumulative occupational dose in monitored radiation workers[‡]	Cumulative reported badge dose 20	
Average neutron-weighted colon dose for LSS population with doses between 0.005 and 4 Gy[§]	Colon dose 200	

CT, computer tomography; LSS, Life Span Study.

Computed using data set downloaded from Radiation Effects Research Foundation website (RERF, 2003).

[*] Brenner, D.J., et al., 2003. Proc. Nat. Acad. Sci. US 100, 13761–13766.

[‡] Gilbert, E.S., 2002. Radiat. Res. 158, 783–784.

[†] NCRP, 2001. Evaluation of the Linear-nonthreshold Dose–response Model for Ionizing Radiation. NCRP Report No. 136. NCRP, Bethesda, MD.

[§] Preston, D.L., et al., 2003. Radiat Res 160, 381–407.

[+] Kidney, ureter, bladder.

organ doses an order of magnitude higher. Fractionation or protraction of exposure can allow higher doses to be tolerated in terms of acute effects. Cumulative occupational exposures among monitored radiation workers were about 20 mSv in several major studies (Gilbert, 2002), and the recommended upper limit for radiation workers is 20 mSv/year averaged over 5 years, and no greater than 50 mSv in any one year (ICRP, 1991). However, yearly effective doses at the Mayak plutonium facility approached 1 Sv for some workers during the earlier years of production (Akleyev and Lyubchansky, 1994; Khokhrykov et al., 2000).

2.2.1. Existence of a dose–response relationship

(21) Dose–response data (e.g. pertaining to cancer morbidity) can be described in a number of ways, such as by arranging observations in order of dose, grouping them into consecutive dose intervals, and plotting cancer rates by dose interval (Fig. 2.1). Sophisticated modelling is not strictly necessary to establish the existence of a dose-response relationship; that can be done by a test of increasing trend, usually obtained by fitting the data to a simple model, e.g.:

$$\mathrm{ERR}(D) = \alpha D \tag{2.1}$$

$$\mathrm{ERR}(D) = \exp\{\beta D\} - 1 \tag{2.2}$$

(22) Here, ERR(D) is excess relative risk at radiation dose D, and α and β are unknown parameters. In testing for an increasing trend using model (2.1), the dose–response is 'statistically significant' when the evidence is statistically inconsistent with parameter values α less than or equal to zero or, for an analysis according to (2.2), with parameter value β less than or equal to zero. These simple models can be used in tests of overall tendency, or trend, and do not suffice to establish the shape of the dose–response curve. In Fig. 2.1, in fact, neither of the fitted functions agrees particularly well with the plotted, dose-specific data points, especially at high doses, but both simple models serve to establish the existence of a dose–response relationship.

(23) If statistical significance is not achieved by a trend test, it can be inferred that the evidence in favour of the existence of a dose–response relationship is not strong,

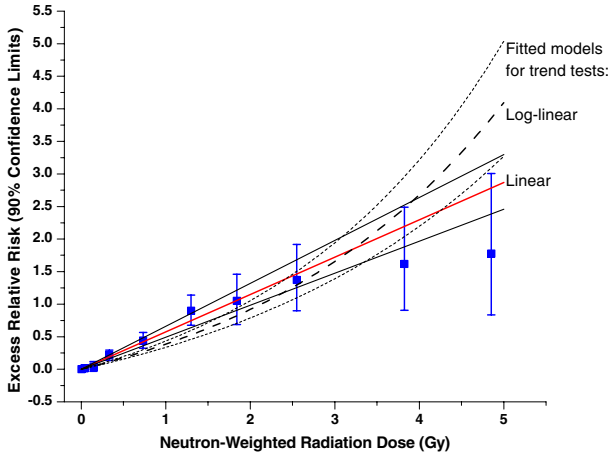


Fig. 2.1. Dose-specific excess relative risk of solid cancer among atomic bomb survivors, 1958–1987, by interval of neutron-weighted, estimated radiation dose to the colon. Fitted dose–response functions correspond to statistical tests of increasing trend according to the linear (relative risk = 1 + αD) and log-linear [relative risk = exp(βD)] dose–response models. The baseline risk is adjusted for city of exposure (Hiroshima or Nagasaki), sex, and 5-year intervals of exposure age and age at observation for risk, using a saturated model.

or that any relationship is too complex to be represented by such a simple parametric function. It cannot be inferred that there is no positive dose–response relationship, unless the trend is statistically significant in the negative direction; inadequate statistical power, because of an inadequate sample size for the range of doses covered, can result in failure to achieve statistical significance in the presence of a positive dose–response relationship (see Section 2.4.2).

2.2.2. Estimating the dose–response relationship

(24) The information that can be derived from a dose–response analysis is always conditional upon assumptions about the functional relationship between radiation dose and exposure-related excess risk. In Fig. 2.1, the interval-based estimates are based on virtually no such assumptions; the different estimates are minimally correlated with each other because they share a common reference (i.e. the value for the zero dose interval is constrained to be zero); thus, observations at any given non-zero dose interval contribute information towards the estimated ERR at that interval. However, for each of the two fitted models used for trend tests (the plots of which differ because their assumed functional forms are different), the corresponding dose-specific estimates are all determined by the same estimated parameter, α in Eq. (2.1) or β in Eq. (2.2), and are therefore perfectly dependent on each other, conditionally on the estimated dose values. The confidence intervals (CIs) on the fitted curves are accordingly much narrower than those on estimates computed separately for individual dose intervals along the abscissa.

(25) Once existence of a dose–response relationship has been established, it makes sense to find a parametric dose–response model that is consistent with the epidemiological data and plausible in terms of radiobiology. Such a model provides a way to use all dose–response data to estimate radiation-related risk at various dose levels, and at low dose levels in particular.

(26) Of the two models used here to test for trend, the linear model [Eq. (2.1)] is biologically plausible in the sense that the primary mechanism by which IR exposure is thought to influence subsequent cancer risk is damage to cellular DNA from ionising events, and the frequency of such ionising events in a defined volume of tissue is proportional to the absorbed radiation dose. The log-linear model [Eq. (2.2)] is less plausible but is often mathematically convenient (e.g. in logistic model analyses).

(27) An experimentally and theoretically derived general radiation dose–response model, often cited in connection with cancer risk related to low-LET radiation (NAS/NRC, 1980; Upton, 1961) is:

$$\mathrm{ERR}(D) = \alpha D \times (1 + \beta D) \times \exp(-\gamma D - \delta D^2) \qquad (2.3)$$

(28) Here α , β, γ , and δ are unknown, positive parameters. The linear term, αD, dominates at low doses (where D^2 is small), and the term $\alpha\beta\ D^2$ dominates at doses somewhat greater than the so-called 'crossover dose' ($D = 1/\beta$) at which the terms proportional to dose and dose-squared contribute equally to estimated risk. The exponential term, $\exp(-\gamma D - \delta D^2)$, represents the competing effect of 'cell killing' or cell reproductive death, observed experimentally, that would prevent a radiation-

damaged cell from becoming cancerous; this term dominates at high doses, leading to a reduction in slope and eventually to a turnover and gradual decline in risk. For the present purposes, the contribution of the parameter δ is of minor importance and we will assume δ = 0 in the following text. Like the other components of Eq. (2.3), the exponential cell-killing term is modelled as a continuous function of dose without threshold. Thus, cell killing is considered to be a stochastic effect, the probability of which increases with increasing dose, and not a deterministic effect, such as tissue injury, which becomes noticeable when the proportion of damaged cells exceeds a threshold level.

(29) The general dose–response function [Eq. (2.3)] is not often used in epidemiological research, mainly because the constrained parameters β and γ produce effects opposite in curvature that may, to some extent, cancel each other out. While the model is used successfully with very precise and numerous experimental data, most epidemiological dose–response data lack the statistical power needed to support estimates for a model of such complexity. Accordingly, the cancer risk estimates reported here are generally based on an assumed linear dose–response relationship. The exception to this is the leukaemia dose–response relationship from the Life Span Study (LSS), which is based on a linear-quadratic relationship. The problem of statistical power is illustrated here using the atomic bomb survivor data of Fig. 2.1 for total solid cancers following a whole-body exposure, among the most statistically powerful epidemiological radiation dose–response data in existence at the time they were published (Thompson et al., 1994). The general model fits these data reasonably well [Fig. 2.2 (dashed line) and Table 2.2], but is not significantly better than the linear model of Fig. 2.1 ($P = 0.11$). The estimated ERR per Gy at low doses (i.e. the estimated value of α), 0.52 (90% CI 0.16–0.83), does not differ markedly from that

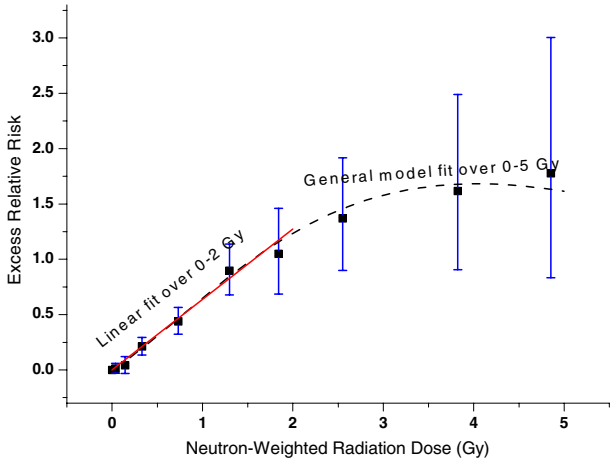


Fig. 2.2. General dose–response model, excess relative risk (ERR)(D) = $\alpha D \times (1 + \beta D) \times \exp(-\gamma D - \delta D^2)$, fit to the dose–response data of Fig. 2.1, and linear dose–response model, ERR(D) = αD, fit to the data subset restricted to radiation doses between 0 and 2 Sv. Details of the parameter estimates are given in Table 2.2. ERR, excess relative risk.

Table 2.2. Parameter estimates corresponding to the general dose–response model, $ERR(D) = \alpha D \times (1 + \beta D) \times \exp(-\gamma D - \delta D^2)$, where D is neutron-weighted (weight=10), reconstructed radiation dose to the colon from the atomic bombings, and $ERR(D)$ is the dose-related excess relative risk of solid cancer morbidity, 1958–1987, among members of the Radiation Effects Research Foundation's Life Span Study cohort of survivors of the bombings (available at www.rerf.or.jp)

Parameter	Estimate	90% CI	*P* value
α	0.52	0.16, 0.83	0.02
β	0.94	0*, 6.8	0.28
γ	0.84	0*, 0.68	0.07
α	0.71	0.56, 0.87	<0.001
β	0†	–	–
γ	0.11	0*, 0.24	0.07
α	0.57	0.48, 0.68	<0.001
β	0*	–	–
γ	0†	–	–
Analysis restricted to survivors with estimated doses of 2 Sv and less			
α	0.40	0*, 0.85	0.24
β	0.92	0*, 3.0	>0.5
γ	0.53	0*, 1.3	>0.5
α	0.61	0.35, 0.76	<0.001
β	0.045	0*, 0.68	>0.5
γ	0†	–	
α	0.64	0.54, 0.74	<0.001
β	0†	–	
γ	0*, 0†	–	

CI, confidence interval.

* Estimate constrained to be β0.

† Estimate set = 0.

according to the linear model, 0.57 (90% CI 0.49–0.66); however, the CIs are substantially wider for the more complex model, reflecting the wide range of combinations of positive values of the parameters α, β, and γ consistent with the data. The analysis offers little evidence in support of a positive value of the (dose-squared) parameter β ($P = 0.28$), but suggestive evidence in support of a non-zero value of the cell-killing parameter γ ($P = 0.07$).

(30) Less than 1% of the members of the LSS cohort for whom dose estimates have been calculated have estimates greater than 2 Gy, and there are reasons to believe that the dose estimates above 2 Gy may be biased upwards (Pierce and Preston, 2000). Restriction of the dose–response analysis to subjects with doses under 2 Gy yielded the linear-model parameter estimate $\alpha = 0.64$ (90% CI 0.54–0.74). Adding either the quadratic or the cell-killing terms to the model produced zero or minimal change, whereas adding both of them yielded parameter estimates so uncertain as to be of no predictive value (Table 2.2).

(31) In the remainder of this report, epidemiological risk estimates are based on linear dose–response analyses.

2.3. Inferences based on acute exposures in the moderate-to-high dose range

2.3.1. Modification of dose–response relationship by sex and age

(32) The information obtained from studies of the atomic bomb survivors and other populations mentioned above is rich in detail. For many cancer sites and groups of sites, we can estimate with some precision not only the dose-specific risk of radiation-related cancer, but also its variation by cancer site and by sex, age at exposure, attained age, and/or time following exposure. In general (but not always), radiation-related relative risk is higher among women and following exposure at young ages. The relationship to age at exposure is marked for thyroid cancer, acute leukaemia, and female breast cancer (Land et al., 2003; Preston et al., 1994, 2003; Ron et al., 1995). Risk decreases somewhat, in relative terms, with advancing age at observation, but increases in absolute terms because baseline cancer risk tends to increase as a power of age, and faster than dose-specific decreases in ERR (Pierce, 2002; Pierce and Vaeth, 2003; Thompson et al., 1994; UNSCEAR, 2000).

(33) The relative importance of exposure age and attained age as modifiers of the radiation dose–response relationship is uncertain because, in any epidemiological follow-up study, the two quantities are highly correlated and their effects are difficult to separate. With additional follow-up, as the major exposed populations are followed to the end of their life spans, the importance of this question for lifetime risk will become moot because projection to the end of life will no longer be required for subgroups exposed at young ages. However, the dependence of radiation-related risk on exposure age and attained age are likely to remain complicated. One consideration is the presence of secular trends in baseline risk in Japan during the period of follow-up for the atomic bomb survivors over the past half century, the reasons for which are not entirely clear (Parkin et al., 2002; Preston et al., 2003).

(34) Statistically stable descriptions can be obtained of the dependence of dose-specific risk on sex, age, and time for aggregations of cancer sites such as all cancers combined, all solid cancers, all leukaemia types, and other groupings. This is useful because radiation protection is concerned with the totality of possible adverse consequences of exposure, but also because overall patterns of dependence may emerge from such analyses that can be incorporated into site-specific estimates, resulting in greater statistical precision (NAS/NRC, 2000; NCI/CDC, 2003; Pierce and Preston, 1993).

2.3.2. Modification by lifestyle and other individual factors

(35) There is a relatively small but growing amount of epidemiological information (Table 2.3) on modification of radiation-related risk by history of lifestyle factors, such as tobacco smoking in the case of lung cancer (Kopecky et al., 1986; Lubin and Steindorf, 1995; NAS/NRC, 1999; Pierce et al., 2003; Prentice et al., 1983), childbearing and breastfeeding in the case of breast cancer (Boice and Stone, 1978; Land et al., 1994; Shore et al., 1980), ultraviolet light in the case of basal cell and squamous cell skin cancer (Ron et al., 1998; Shore, 2001; Shore et al., 2002),

Table 2.3. Modification of radiation-related risk by individual and lifestyle factors, and by other exposures

Organ site/cancer	Population	Factor	Main factor effect on risk	Interaction with radiation exposure	References
Female breast	LSS cohort	Young age at first full-term pregnancy	Decreased	Multiplicative*	Land et al. (1994)
	LSS cohort	Multiple births	Decreased	Multiplicative*	Land et al. (1994)
	LSS cohort	Lengthy lactation history	Decreased	Multiplicative*	Land et al. (1994)
	New York mastitis series	Associated with first delivery	Increased	Not tested	Shore et al. (1980)
	Massachusetts tuberculosis fluoroscopy series	Exposed year of first delivery	Increased (NS)	Not tested	Boice and Stone (1978)
Lung and bronchus	LSS cohort	Smoking history	Increased	Additive†	Pierce et al. (2003)
	US uranium miners	Smoking history	Increased	NS, closer to multiplicative than to additive	Lubin and Steindorf (1995)
Basal cell skin	LSS cohort	Sun-exposed vs covered areas of skin		Additive†	Ron et al. (1998)
	New York *Tinea capitis* series	White vs black patients	Higher in white patients	Multiplicative*	Shore et al. (2002)
Liver	LSS cohort	Hepatitis C infection	Increased	Strongly synergistic	Sharp (2003)
Female breast	LSS vs European/ American populations	Population rates	Japanese rate four-fold <US rate	Additive†	Preston et al. (2002)
Stomach	LSS vs US peptic ulcer patients	Population rates	Japanese rate 12-fold > US rate	NS, closer to multiplicative than to additive	Carr et al. (2002)

LSS, Life Span Study; NS, not significant.

* Additive interaction model rejected (statistically inconsistent with data).

† Multiplicative interaction model rejected.

and disease history in the case of type C hepatitis infection and liver cancer (Sharp et al. 2003). Much more needs to be learned about interactions of IR exposure with lifestyle factors and with exposures to other agents. It is not unlikely that some of our current inferences about the dependence of radiation-related risk on exposure age, attained age, and sex may reflect secular changes in lifestyle, and in exposure to environmental agents, that have been associated with changes over time (and with successive birth cohorts) in both baseline and radiation-related risk. Preston et al. (2000) noted concerns about the difficulties in interpreting radiation age at exposure effects in the LSS cohort.

2.3.3. Variation by population

(36) There does not appear to be an obvious, consistent relationship between baseline and radiation-related cancer risk, either across cancer sites within a single population or across populations for a single cancer site. In the female Japanese population, age-standardised (world) rates per 100,000 per year are generally similar, at about 31 for gastric cancer and 34 for breast cancer (Parkin et al., 2002), whereas in the USA, they are about 3 and 90, respectively. Among atomic bomb survivors, the radiation-related ERR at 1 Gy is 0.32 for gastric cancer and 1.6 for breast cancer (Thompson et al., 1994). Gastric cancer contributes a substantial proportion of total radiation-related risk, but that proportion is considerably less than the proportion of risk of baseline gastric cancer to total baseline cancer risk (about 22%) among atomic bomb survivors (Thompson et al., 1994) and among Japanese people generally (Parkin et al., 2002). In the USA, the ratio is 2% for males and 1% for females. For female breast cancer, the opposite is true; the baseline rate in Japan is among the lowest in the world for developed countries, whereas the total cancer rate is not much different from that in most other countries (Parkin et al., 2002). Among the atomic bomb survivors, breast cancer contributes a disproportionately large fraction of the total radiation-related cancer burden (Thompson et al., 1994). In the USA, by contrast, baseline breast cancer rates are high but the radiation-related excess risk (in absolute terms) per unit dose among medically exposed women is similar to that among the atomic bomb survivors (Preston et al., 2002). That is, the dose-specific, radiation-related component of total breast cancer risk is likely to be similar in absolute magnitude for exposed Japanese and Western populations, but is likely to be smaller in Western populations as a proportion of total breast cancer risk. For gastric cancer, on the other hand, the US baseline rate is an order of magnitude lower than that in Japan, whereas the limited information on dose-specific, radiation-related excess risk suggests that, as a multiple of baseline risk, it may be comparable to that in the atomic bomb survivors (Carr et al., 2002; Griem et al., 1994).

(37) The above information suggests that, for breast cancer, radiation-related ERR per Gy (excess risk per Gy expressed as a multiple of the Japanese baseline risk) based on atomic bomb survivor data would overestimate the risk for an exposed US population while, for gastric cancer, radiation-related excess absolute risk (EAR; the difference between risk following exposure and the Japanese baseline risk) would result in an overestimate of risk for the US population. In addition, data are available

for leukaemia and thyroid cancer from the atomic bomb survivors and medically and environmentally irradiated cohorts (Ron et al., 1995; UNSCEAR, 2000, Annex I, Table 21). For most other cancers, information of a similar nature is limited or non-existent (Table 2.3). This is not a trivial matter because any transfer of a risk estimate from one population to another requires making an assumption, explicit or implicit, about the relationship between excess and baseline risk. Moreover, for some sites (e.g. stomach, liver, and oesophagus), baseline rates can differ markedly between populations (Parkin et al., 2002).

(38) It should not be surprising that the relationship between radiation-related and baseline risk in different populations is not consistent for different cancer sites. There are reasons, as yet poorly understood, why baseline breast cancer rates are high in the USA, and why baseline gastric cancer rates are high in Japan. These reasons are almost surely related to differences in lifestyle, since the descendants of immigrants to the USA, for example, have tended to develop cancer rates that are typical of the general US population (Haenszel and Kurihara, 1968; Ziegler et al., 1993) and different from those of their countries of ancestral origin. The lifestyle factors affecting the rates for breast and stomach cancer are probably different, at least in part, and probably interact differently with radiation dose.

(39) Much of environmental, nutritional, and occupational cancer epidemiology is concerned with identifying cancer risk factors that may account for some part of the variation of site-specific baseline rates among populations. While there has been much progress, the problem is vast and, as discussed in Section 2.3.2, there is only limited information on interaction between radiation dose and lifestyle factors in terms of cancer risk. Thus, it is likely that, for the foreseeable future, the most useful information relevant to the transfer of radiation-related risk coefficients from one population to another will come from multinational comparisons of site-specific radiation-related risk, rather than from investigations of underlying cancer risk factors and their interactions with radiation dose.

2.3.4. Radiation quality

(40) Risk estimates for low-LET radiation protection purposes are based mainly on epidemiological studies of populations exposed to substantial doses of medical x rays, or to mixed gamma and neutron radiation from the Hiroshima and Nagasaki atomic bombs. According to the DS86 dose reconstruction algorithm (Roesch, 1987) as represented by public-use RERF data sets (RERF, 2003), the correlation between neutron and gamma doses within each city is greater than 95%, and the proportion of total absorbed bone marrow dose contributed by neutrons is only 0.7–2.7% in Hiroshima and 0.3–0.7% in Nagasaki, depending upon shielding and exposure distance. According to the as yet unpublished DS02 dose reconstruction system, the neutron component is reduced slightly, compared with DS86, in both Hiroshima and Nagasaki. In particular, an anticipated large increase of the neutron component for low-dose survivors in Hiroshima did not materialise (Preston et al., 2004). Due to the relatively small contribution from neutrons, there is minimal statistical power for estimating the relative biological effectiveness of the two radiation types based on the

atomic bomb survivor data. Moreover, there are essentially no useful data on cancer risks in populations exposed mainly to neutron radiation (IARC, 2001). Therefore, the relative biological effectiveness of neutron vs gamma-ray doses can only be estimated from experimental data. Risk coefficients for gamma-ray doses are obtained from the atomic bomb survivor data through the use of a nominal weighting factor of 10 for the neutron component of dose (Thompson et al., 1994). However, Preston et al. (2004) noted that with the advent of the DS02 atomic bomb survivor dosimetry system, the estimated neutron doses are so small that the question of variation in the estimated gamma-ray dose–response relationship due to uncertainty in the choice of the neutron-weighting factor is essentially moot.

(41) Cancer risks associated with alpha-radiation exposure have been studied for lung cancer among uranium miners exposed to inhaled radon decay products (NAS/NRC, 1999) and in populations exposed to lower radon levels in residential settings, for bone cancer associated with ingested ^{226}Ra and ^{228}Ra among former radium dial painters (Carnes et al., 1997; Fry, 1998; Stebbings et al., 1984) and with injected ^{224}Ra in patients treated for benign disease (Nekolla et al., 1999, 2000; Spiess and Mays, 1970), and for cancers of the liver and other organs in patients injected with x-ray contrast media containing thorium (Travis et al., 2003). Thus, estimates of cancer risk associated with exposure to alpha-particle radiation have a basis in direct observations, while estimation of risk associated with neutron exposure is indirect, relying on scaled estimates of risk from low-LET radiation using experimentally derived estimates of the effectiveness of neutrons compared with low-LET radiation.

(42) Epidemiological risk estimates based on exposure to gamma rays (photons with energies of >250 keV) and most medical x radiation (photons with energies in the 30–250 keV range) are often treated as interchangeable quantities (ICRP, 1991). However, it has long been considered, based on biophysical considerations, that medical x rays are more effective biologically than higher-energy gamma rays. This consideration has been cited as a factor that may complicate inferences based on comparisons of cancer risk associated with fractionated x-ray exposures and acute gamma-ray exposures (Brenner, 1999). Kocher et al. (2002; NCI/CDC, 2003) estimated uncertain radiation effectiveness factors (REF), compared with gamma radiation, for 30–250 keV and soft (<30 keV) x rays, assigning subjective uncertainty distributions with mean REF values of 2 and 2.7, respectively, and 95% uncertainty limits of 1–4.7 and 1.1–6.4, respectively, for the two x-ray energy ranges. Electrons at energies like those of secondary electron tracks induced by gamma-ray photons, i.e. above 30 keV, were assigned an REF value of 1, while lower-energy electrons were assigned an uncertain REF with a mean of 2.6 and 95% uncertainty limits of 1.2–5.0.

2.4. Estimation of risk at low doses and low dose rates

(43) Except for radiation therapy, where there is a recognised benefit from the radiation dose itself, very few people are exposed to radiation effective doses of 0.2 Sv and above. Most public concern is with exposures to less than 50 mSv, the historical annual limit for radiation workers before a reduced level (20 mSv) was

recommended in ICRP *Publication 60* (1991); that concern extends to effective doses well below 1 mSv, the annual population limit recommended by both the ICRP (1991) and the NCRP (1993), as well as the annual dose from natural background radiation for most tissues other than the lung. As mentioned previously, a chest x ray delivers about 0.1 mGy to lung tissue, the dose to breast tissue from a two-view mammography examination is about 3 mGy, and an astronaut may get about 2.4 mSv tissue-weighted effective dose on a typical 3-day space shuttle mission (NCRP, 2000).

2.4.1. Difficulties of direct estimation of low-dose risk

(44) Although such low-dose exposures (except, of course, the astronaut's) are very common, it is extremely difficult to estimate the associated excess cancer risks by studying populations with exposures limited to the low-dose range. This is because, at low doses, the radiation-related excess risk, which is thought to be proportional to dose or perhaps somewhat less when compared with risks at higher doses, tends to be dwarfed by statistical and other variation in the background risk level in the absence of exposure. As a result, truly enormous sample sizes (e.g. millions) would theoretically be required to obtain a statistically stable estimate of radiation-related risk, and even then the estimate would be untrustworthy because we do not understand, and therefore cannot control or adjust for, all of the sources of variation in baseline levels of risk (Land, 1980). At higher dose levels, there are fewer problems because the excess risk tends to be large relative to statistical variation in baseline risk, and we are more likely to understand the causes of any substantial variation in baseline risk that may be confounded with radiation dose.

2.4.2. Illustrative example

(45) Suppose that: (1) baseline cancer risk in a given population, for a certain (unspecified) subset of cancer sites, was known to be 10%; (2) exposure to a whole-body effective dose of 1 Sv would double the risk (i.e. add another 10%) of that same subset of cancers; and (3) excess risk was strictly proportional to radiation dose over the interval 0–1 Gy. Suppose also that it was possible to find large study populations with baseline risks known to be 10% and with uniform exposures to 1 Gy, 100 mGy, 10 mGy, or 1 mGy. (This is a simplified, and unrealistic, version of a study in which observed cancer frequencies in an exposed population are compared with expected frequencies calculated on the basis of published population rates. Note also that the assumed baseline rate, doubling dose, etc. were chosen to simplify the arithmetic and not to describe any actual population or subset of cancers.) The estimated excess cancer rate in such a population would be the number of cancers divided by the population size, less the known baseline rate of 10%. The estimated excess would be distributed approximately as a normal random variable with the mean equal to the baseline rate, 10%, times the dose D, in Gy, and variance equal to 10% times $(1 + D)$ divided by the population size, N. The population size needed to be able to detect the

Table 2.4. Statistical power calculations for a hypothetical study in which baseline cancer risk, for an (unspecified) subset of cancer sites, is known to be 10%, and the unknown radiation-related excess risk is 10% at 1 Gy and proportional to dose between 0 and 1 Gy

Radiation dose	Excess risk	Total risk	Standard deviation of the estimated excess risk under the null and alternative hypotheses		Population size N needed for 80% power to detect the excess risk at the 5% significance level
1 Gy	10%	20%	$0.316/N^{1/2}$	$0.447/N^{1/2}$	80
100 mGy	1%	11%	$0.316/N^{1/2}$	$0.332/N^{1/2}$	6390
10 mGy	0.1%	10.1%	$0.316/N^{1/2}$	$0.318/N^{1/2}$	620,000
1 mGy	0.01%	10.01%	$0.316/N^{1/2}$	$0.316/N^{1/2}$	61.8 million

excess risk associated with dose D with a probability of 80% using a one-sided test at the 5% significance level is shown in Table 2.4. The calculation is, in fact, unrealistically optimistic since, as illustrated in a later example, one can never be that sure of the baseline rate in any exposed population. If, as is almost always the case, we had to estimate the baseline rate by including an equal number of non-exposed subjects, more than twice as many total (exposed plus non-exposed) subjects would be required to have equal power for detecting the difference. Moreover, one could still not be sure, particularly at the lower dose levels, that the exposed and unexposed populations were truly comparable in terms of baseline rates at the level of resolution required.

(46) If an enormous study population is required to detect any excess risk associated with exposure to a small radiation dose, it follows that the implications are unexciting if we use a much smaller population and fail to detect any excess risk. A result predictable under both of two opposing hypotheses supports neither of them against the other. Thus, for example, failure of epidemiological studies to demonstrate a statistically significant excess cancer risk associated with exposures of the order of 1 mGy does not imply that there is no risk, although it does suggest that any such risk is small relative to baseline cancer rates.

(47) At low and very low radiation doses, statistical and other variations in baseline risk tend to be the dominant sources of error in both epidemiological and experimental carcinogenesis studies, and estimates of radiation-related risk tend to be highly uncertain because of a weak signal-to-noise ratio and because it is difficult to recognise or to control for subtle confounding factors. At such dose levels, and with the absence of bias from uncontrolled variation in baseline rates, positive and negative estimates of radiation-related risk tend to be almost equally likely on statistical grounds, even under the LNT theory. Also, by definition, statistically significant positive or negative findings can be expected in about one in 20 independent studies when the underlying true excess risk is close to zero. Thus, even under the LNT theory, the smaller the dose, the more likely it is that any statistically significant finding will be a purely chance occurrence, and that it will be consistent with either beneficial effects of radiation (hormesis) or a grossly exaggerated risk (Land, 1980). Such estimates tend to be only a small fraction of the total, but when selectively presented, they can give the appearance of a substantial and even overwhelming body of evidence in one direction or the other.

2.4.3. Studies of low-dose exposures

Medical studies

(48) There is, in fact, some direct epidemiological evidence of excess cancer risk associated with radiation exposures of the order of a few tens of mGy. One example is a relative risk of approximately 1.4 for mortality from leukaemia and solid cancer by 15 years of age, which has been observed in several case–control studies (Bithell and Stiller, 1988; Harvey et al., 1985; ICRP, 2003, Table 8.5; MacMahon, 1962; Monson and MacMahon, 1984; Stewart et al., 1956) among children exposed in utero to radiation from x-ray pelvimetry. There has been considerable debate on the interpretation of these in-utero studies. Difficulties cited have included the absence of an association in any cohort study, including the atomic bomb LSS, discrepancies between radiation-related failure to find increased childhood cancer rates among twins compared with singletons despite presumably higher exposure frequency among twins, and possible biases in the case–control approach based on the argument that similar estimated relative risks for leukaemia and solid cancers is an implausible finding (Boice and Miller, 1999; Doll and Wakeford, 1997; ICRP, 2003, Table 8.5).

(49) In a comprehensive review paper, Doll and Wakeford (1997) concluded that, on the balance of evidence, 'irradiation of the fetus in utero increases the risk of childhood cancer, that an increase in risk is produced by doses of the order of 10 mGy, and that in these circumstances the excess risk is approximately 6%/Gy'. They discussed four different grounds for controversy which have been raised to suggest that the estimates derived from the case–control studies may be unreliable. Three of these grounds [including the evidence for bias in the case–control studies emphasised by Boice and Miller (1999)] were considered by Doll and Wakeford (1997) to be probably or possibly invalid, and they judged that only the remaining one would appear to be serious, 'namely, the lack of any comparable excess in cohorts known to have been irradiated in utero, most notably in those exposed to radiation from the explosion of the atomic bombs in Japan'.

(50) The atomic bomb survivor study is discussed below. Regarding the possibility of a cohort study of childhood cancer following pelvimetry, however, childhood leukaemia and solid cancer are very rare, and the sample size requirement for a cohort study of adequate statistical power would be unmanageably large. For example, according to current SEER statistics, in the USA, the likelihood of dying from any cancer between birth and 10 years of age is 0.026%, and the likelihood of being diagnosed with any cancer is 0.164% (use 'FastStats' under http://seer.cancer.gov/statistics). If it were possible to select a cohort with equal numbers of exposed and non-exposed children, it would require a total sample size of over 630,000 children in order to detect, with 80% statistical power at the 5% level of significance, a 1.4 relative risk for cancer mortality among the exposed, and a total sample size of about 100,000 to detect a similar increase in cancer morbidity risk. If we could not easily select exposed and non-exposed children in advance, and if there were 10 times as many non-exposed as exposed children in the population [approximately the ratio observed by Stewart et al. (1956)], the required numbers to detect a relative risk of

1.4 would be about 2 million for mortality and 320,000 for morbidity. Thus, the absence of a positive cohort study based on pelvimetry exposure would not appear to be a strong reason to question the findings of the case–control studies of childhood cancer risk following in-utero exposure to x-ray pelvimetry.

(51) The atomic bomb survivor studies are a different matter. The total number of 3018 in-utero exposed subjects who survived until 1 October 1950 includes 313 with estimated doses between 0.1 and 0.5 Gy (mean 0.23 Gy), 88 with estimated doses between 0.5 and 1 Gy (mean 0.72 Gy), and 54 with estimated doses of 1 Gy or more (mean 2.4 Gy) (Delongchamp et al., 1997), and there would appear to be sufficient power to detect a linear dose–response relationship at an ERR per Gy consistent with the results of the case–control studies of children exposed through x-ray pelvimetry, given efficient detection of cancer cases at under 15 years of age. An examination of published studies (Delongchamp et al., 1997; Yoshimoto et al., 1988, 1994) of morbidity and mortality following in-utero exposure from the Hiroshima and Nagasaki bombs indicates that ascertainment of cancer among exposed and non-exposed children during the period 1945–1955 and, especially, 1945–1950 may have been incomplete. The most recent reports (Delongchamp et al., 1997; Yoshimoto et al., 1988, 1994) are confined to cancer mortality or morbidity among people alive as of 1 October 1950, excluding 198 deaths occurring before that date. Most of the early deaths were infant deaths that occurred shortly after the bombings, with little documentation of cause (Delongchamp et al., 1997). According to current SEER rates (http://canques.seer.cancer.gov), 5.0 incident baseline cancer diagnoses would be anticipated to occur before 10 years of age in a population of 3018; of these, nearly two-thirds would be expected to occur before 5 years of age. Thus, there is a definite possibility that, among members of the in-utero cohort and/or people who would have been included in the cohort if they had survived until 1 October 1950, radiation-related and/or baseline cases of childhood leukaemia occurred but were not detected for various reasons during the first 5 or more years following the bombings. However, an increase is observed when the lifetime risk is studied in this cohort (Delongchamp et al., 1997).

(52) A less direct example is increased breast cancer risk among young women exposed to high cumulative doses from multiple thoracic x-ray exposures, delivered in fractions that were, on average, of the order of 10 mGy (Boice et al., 1991; Davis et al., 1987; Doody et al., 2000; Howe and McLaughlin, 1996). In the case of fluoroscopy examinations during lung collapse therapy for tuberculosis where anterior–posterior exposure occurred, individual fractions could sometimes exceed 100 mGy and, in one such study, it was assumed, for dose reconstruction purposes, that 25% of the fluoroscopic examinations involved direct, frontal exposures for which the breast dose per examination was 54 mGy, and 75% were directed from the back, for which the average breast dose was 1.8 mGy (Boice et al., 1978). Successive exposures were separated by a week or more, but were repeated often enough to yield cumulative doses of hundreds or even thousands of mGy. Excess (absolute) risks per unit of total dose [about 10 excess cases/10,000 women/year/Gy at 50 years of age, following exposure at 25 years of age (Preston et al., 2002)] were comparable with those associated with acute doses among atomic bomb survivors (Boice et al., 1979; Land et al., 1980; Little and

Boice, 1999; Preston et al., 2002). A similar relationship for excess risk of lung cancer, compared with estimates based on high-dose, acute exposures, was not observed among fluoroscopy patients, even though lung doses were comparable with breast doses (Davis et al., 1987; Howe, 1995). Although excess lung cancer risk per unit dose of acute radiation is, in general, less than for breast cancer (Thompson et al., 1994), the difference between the breast and lung cancer findings among fluoroscopy patients suggests that there may be variation among cancer sites in terms of fractionation effects. It should be kept in mind, however, that exposure to tobacco smoke is by far the dominant risk factor for lung cancer. Among, for example, tuberculosis patients who underwent lengthy courses of lung collapse therapy associated with high cumulative radiation doses from fluoroscopic examinations, below-average exposure to tobacco smoke may mask a radiation-related increase in lung cancer risk, although attempts were made to control for smoking in the analyses.

(53) It is difficult to make inferences about protraction and fractionation effects from studies of thyroid cancer among irradiated populations, largely because risk estimates vary among populations for reasons that are poorly understood. A highly significant, dose-related excess risk of thyroid cancer was observed among 10,834 Israeli patients treated as children by x-ray depilation for ringworm of the scalp (*Tinea capitis*), with estimated (fractionated) dose to the thyroid gland averaging 90 mGy (range 40–500 mGy), compared with 16,226 non-exposed comparison subjects (Ron et al., 1995). The estimated linear model ERR per Gy was 32.5 (95% CI 14–57), based on 44 cases among the exposed and 16 cases among the non-exposed. On the other hand, no significant excess was observed among 2224 patients given similar treatment (average thyroid dose 60 mGy) in the USA compared with 1380 patients given topical ointment treatment alone; two thyroid cancers were found in the x-ray group, consistent with general population rates, and none were found in the non-irradiated group. However, the between-study difference in risk estimates was not statistically significant (Shore et al., 2003). More generally, a pooled analysis of data from five studies of thyroid cancer following irradiation during childhood (Ron et al., 1995), including the Israeli *T. capitis* patients, the youngest atomic bomb survivors, two populations treated by x ray for enlarged tonsils or lymphoid hyperplasia, and a population treated for supposedly enlarged thymus, obtained an overall ERR per Gy of 7.7 (95% CI 2.1–28.7). Two Swedish studies of skin haemangioma patients with low-dose-rate exposures from ^{226}Ra obtained similar estimates: ERR/Gy = 7.5 (95% CI 0.4–18.1) based on an estimated mean thyroid dose of 120 mGy (Lindberg et al., 1995), and ERR/Gy = 4.9 (95% CI 1.3–10.2) based on a mean dose of 260 mGy (Lundell et al., 1994).

Occupational studies

(54) Except for (mainly historical) worker populations with fairly high levels of exposure, such as uranium miners (NAS/NRC, 1999), radium dial painters (Stebbings et al., 1984), Russian plutonium workers (Gilbert, 2002), and early radiologists (Matanoski et al., 1975; Smith and Doll, 1981), most occupational studies can be classified as low dose and, therefore, of low statistical power. Their main utility is to validate generally accepted estimates in the sense that they are consistent with

estimated radiation-related risks among regulated radiation workers. For example, a large, combined analysis of cancer mortality among nuclear workers in the USA, the UK, and Canada found a statistically significant dose–response relationship for leukaemia and a non-significant dose–response relationship for all solid cancers (Cardis et al., 1995). Occupational radiation exposure and cancer mortality in the UK National Registry for Radiation Workers were similarly associated, and consistent with estimates based on the atomic bomb survivor studies (see below) (Muirhead et al., 1999). Patterns of cancer mortality were inversely related to year of first employment among US radiological technicians, consistent with a radiation aetiology given higher occupational exposures to radiation in earlier compared with more recent times (Mohan et al., 2002, 2003).

Atomic bomb survivor studies

(55) It is sometimes forgotten that the vast majority of the exposed (as distinguished from people not present at the time of the bombings) LSS cohort of atomic bomb survivors received radiation doses under 100 mGy (Table 2.5). For solid cancer mortality between 1950 and 1997 (Preston et al., 2003), direct assessment of risks at low doses obtained a statistically significant dose–response relationship when the analysis was restricted to survivors with dose estimates less than approximately 120 mGy. The estimated ERR per Gy over this range was 0.74 (90% CI 0.1–1.5). There was no indication that the slope of the fitted dose–response curve differed significantly ($P > 0.5$) from the estimate over the full dose range (ERR/Gy = 0.47), and no evidence of a threshold. As discussed below, a similar result was obtained from analyses of the same epidemiological data using the DS02 dose estimates (Preston et al., 2004).

(56) An earlier analysis of solid cancer incidence data from the LSS Tumor Registry for 1958–1994 (Pierce and Preston, 2000) focused on people exposed at distances under 3000 m, of whom approximately 10,000 had estimated neutron-weighted doses under 5 mGy and 41,000 had doses between 5 and 500 mGy. An analysis restricted to people exposed at distances less than 3000 m found a statistically significant linear

Table 2.5. Distribution of subjects, solid cancers, and estimated radiation-associated, excess solid cancers among 79,901 exposed members of the Life Span Study cohort of Hiroshima and Nagasaki atomic bomb survivors (Pierce and Preston, 2000)

Estimated colon dose	Number of subjects	Number of solid cancers	Estimated number of radiation-associated excess cancers*
Exposed beyond 3000 m	23,493	3230	0
<5 mGy, exposed within 3000 m	10,159	1301	1
5–100 mGy	30,524	4119	77
100–200 mGy	4775	739	60
200–500 mGy	5862	982	164
0.5—1 Gy	3048	582	177
1–2 Gy	1570	376	165
>2 Gy	470	126	80

* Fitted values, linear dose–response relationship.

dose–response relationship that was not overestimated by linear-model risk estimates computed over the wider dose ranges 0–2 Gy or 0–4 Gy (Fig. 2.3). A statistically significant estimate was obtained from an analysis restricted to the 0–120 mGy dose range; another finding was that any threshold over 60 mGy would be statistically inconsistent with the data.

(57) When cohort members exposed beyond 3000 m were included in the analysis, the estimated slope of the fitted dose–response relationship was reduced slightly (by 3%), and the statistical significance of the fitted linear dose–response relationship in the range 0–120 mGy was reduced. Fig. 2.3 shows a moving-average plot of dose-specific cancer rates over the 0–500-mGy range, with uncertainty bounds corresponding to ±1 standard deviation (SD). At 100 mGy, the moving-average estimate of relative risk is about 3.7 SD units above 1 for an analysis restricted to survivors exposed at distances under 3000 m, and about 2 SD units above the redefined baseline (represented by the dotted horizontal line at a relative risk of approximately 1.04) using the less restricted data set.

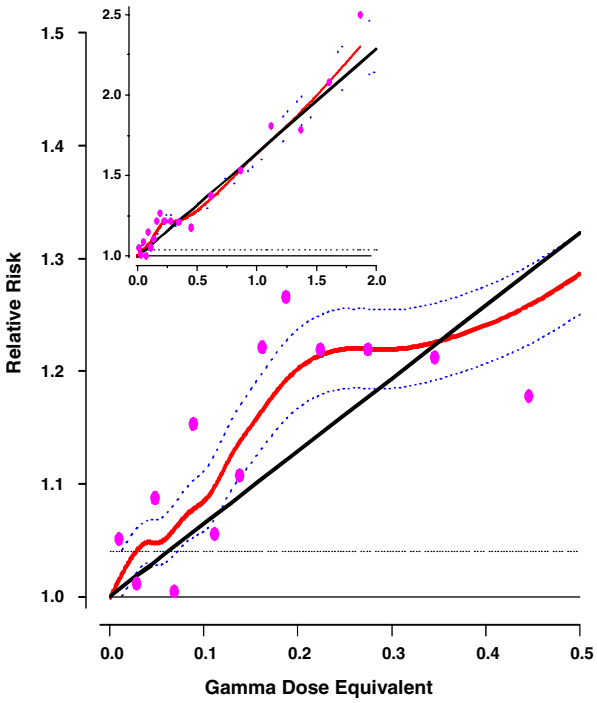


Fig. 2.3. Estimated low-dose relative risks. Dose-specific cancer rates over the 1958—1994 follow-up period relative to those for an otherwise similar exposed person, averaged over the follow-up, for sex, and for 30 years of age at exposure. The dotted lines represent 1 standard error limits for the smoothed curve. The straight line is the estimated linear dose–response relationship for 0–2 Sv (see inset). The unity baseline corresponds to zero-dose survivors exposed within 3 km of the bombs. The horizontal dotted line represents the alternative baseline if survivors exposed beyond 3 km had been included. Source: Pierce, D.A., Preston, D.L., 2000. Radiat. Res. 154, 178–186.

(58) Fig. 2.4 is based on the same data as Fig. 2.3 but shows linear regression estimates of the ERR per Gy over dose intervals that are progressively trimmed of high-dose data. Moving from right to left, the rightmost estimate and its standard error (SE) are based on observations over the dose range 0–2 Gy, the next on 0–1.5 Gy, and so on, while the leftmost estimate is based on data at 0–0.05 Gy. There is more variation between consecutive estimates on the left-hand side of each graph than there is on the right-hand side, and the ±SE limits become progressively wider towards the left-hand side of each panel as the dose range is further restricted at the high end (Donald Pierce, personal communication).

(59) The reference population used in the analyses of Figs. 2.3 and 2.4 is the group of 'proximal' survivors (exposed within 3 km) in Hiroshima and Nagasaki with neutron-weighted dose estimates less than 5 mGy. This choice was justified on the basis that the 'distal' population exposed beyond 3 km was more rural and may have experienced different cancer risk factors other than radiation compared with the more urban proximal survivors. The horizontal line in Fig. 2.3, corresponding to a relative risk of 1.04, represents the baseline if the distal survivors had been included in the analysis. Fig. 2.5 repeats the analysis of Fig. 2.4 with the distal survivors included. While estimates on the ERR per Gy based on higher-dose data are little affected by the change, the estimates at the left-hand side of Fig. 2.5 are substantially lower than those on the left-hand side of Fig. 2.4, with similarly wide error bounds. Comparison of Figs. 2.4 and 2.5 demonstrates the sensitivity of estimates, if based on low-dose data alone, to the influence of minor, and largely unknown or poorly understood, confounding factors.

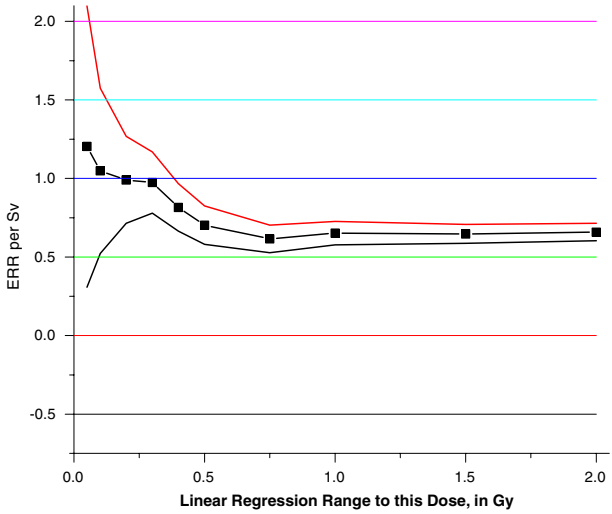


Fig. 2.4. Linear regression estimates of the excess relative risk (ERR) per Gy (points and connecting line, with error bounds of ± one standard error) for solid cancer incidence, based on Poisson regression over dose intervals of differing ranges from zero to the horizontal co-ordinate of the plotted point. The analysis is limited to proximal survivors exposed at distances under 3 km.

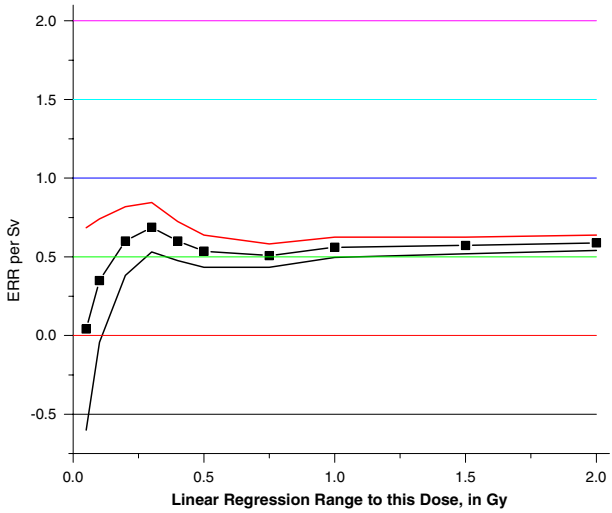


Fig. 2.5. Linear regression estimates of the excess relative risk (ERR) per Gy (points and connecting line, with error bounds of ± one standard error) for solid cancer incidence, based on Poisson regression over dose intervals of differing ranges from zero to the horizontal co-ordinate of the plotted point. The analysis is based on all exposed survivors with estimated radiation doses less than 2 Gy.

(60) The same overall patterns are seen in Fig. 2.6, an analysis similar to Fig. 2.5 (in that data for distal survivors contribute to the estimates) for LSS breast cancer incidence, 1950–1990 (Land et al., 2003). Together, Figs. 2.4–2.6 demonstrate that

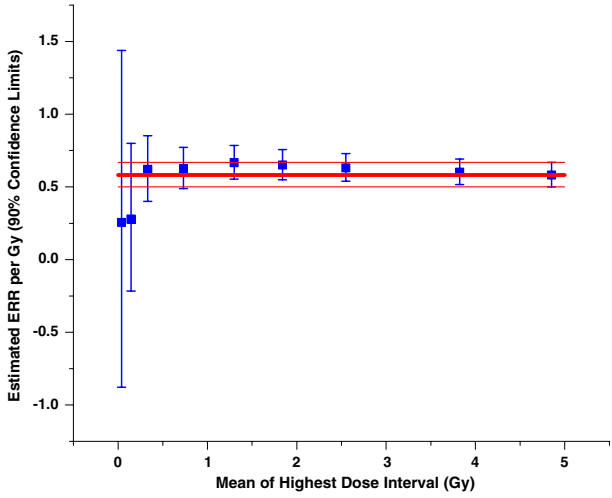


Fig. 2.6. All-age linear regression estimates of excess relative risk (ERR) per Gy for female breast cancer assuming a 12-year minimum latent period, with dose-specific data trimmed from the right. Horizontal placement corresponds to the mean breast tissue dose for the highest neutron-weighted kerma interval included in the regression. Thus, the rightmost point corresponds to the full dose range, the next point to the left to doses under 4 Gy, the next to doses under 3 Gy, and so on.

regression estimates of dose-specific cancer risk for combined sites and for some single sites are highly consistent with linearity, depend substantially on excess risk observed among survivors with estimated doses under 200 mGy, and are statistically unstable when based solely on data pertaining to doses under approximately 100 mGy. These analyses provide no strong evidence that excess risks per unit dose are substantially different at very low doses than at doses up to 4 Gy.

High background area studies

(61) There are a number of published epidemiological studies of cancer rates in populations living in areas where natural background levels are several times greater than those experienced by the vast majority of the world's population, e.g. the high background area in Yagjiang, China, where the estimated annual effective dose from natural background is about 6.4 mSv (three-fold higher than in most areas of the world). Studies of such populations generally find relative risks for cancer mortality or nodular thyroid disease (considered to be a biomarker for thyroid cancer risk) that are not significantly different from 1 (Tao et al., 1999, 2000; Wang et al., 1990). It is, of course, possible that no significant increase in risk is observed because there is none, but for reasons discussed in Sections 2.4.1 and 2.4.2, problems of a low signal-to-noise ratio in the epidemiological data, insufficient sample size, and difficulties recognising and controlling for possible confounding factors that may have effects of similar magnitude on risk, pose problems of interpretation of findings that are difficult or impossible to overcome.

2.4.4. Extrapolation to low doses and dose rates

(62) Epidemiological data are informative about radiation-related risks at acute doses, on a logarithmic scale, in the moderately high (~1 Gy), moderate (~100 mGy), and, to some extent, low (~10 mGy) dose ranges, but not in the very low (~1 mGy) and extremely low (~0.1 mGy) ranges. Arguably the most important single problem in radiation risk protection is how to extrapolate from statistically stable, and relatively unbiased, risk estimates that pertain to higher dose exposures down to the lower dose levels that are of greater concern in everyday life. The analyses of Figs. 2.3–2.6 suggest that for the 1958–1987 LSS solid cancer incidence data at least, linear extrapolation over one order of magnitude, e.g. from 2 Gy to 200 mGy, is justified. Dose–response analyses for leukaemia risk, on the other hand, support a linear-quadratic dose–response relationship with approximate equivalence of the linear and dose-squared components of risk at bone marrow doses of approximately 1 Gy (Preston et al., 1994). Solid cancer mortality data (all sites combined) for 1950–1997 (Preston et al., 2003) suggest linearity even for doses in the 0–150-mGy range. A later analysis, using the DS02 dosimetry, found statistically significant upward curvature over the restricted dose range 0–2 Gy, but the authors noted that linear model dose–response analyses restricted to 0–1 Gy, 0–0.5 Gy, and 0–0.25 Gy, considered to be more relevant to risk at low and very low doses, gave substantially higher estimates of low-dose risk and they therefore did not recommend using the linear-quadratic model to estimate low-dose risk (Preston et al., 2004).

Dose and dose-rate effectiveness factor

(63) The combined-site LSS solid cancer incidence data support linearity of the dose–response relationship down to low-LET radiation doses of the order of 200 and even 100 mGy. They provide no evidence that linearity does not continue down to zero dose, nor do they rule out the possibility of non-linearity at 10 mGy and lower. The in-utero pelvimetry studies and the fractionated fluoroscopy study breast cancer data suggest that radiation doses of the order of 10 mGy/fraction are associated with excess cancer risk. However, the same fluoroscopy cohort shows no evidence of increased lung cancer risk. The heterogeneity of dose distribution between patients has, however, been reported to be considerable (Boice et al., 1978), and these fluoroscopy data do not necessarily imply proportionality between radiation dose and excess cancer risk down to a few tens of mGy. The curvilinearity of the LSS leukaemia dose–response relationship is the main epidemiological evidence in support of a reduced risk per unit dose at low and very low doses [otherwise suggested by experimental observations (NCRP, 1980)]. Such curvilinearity is consistent with ICRP and UNSCEAR recommendations that extrapolated dose-specific risk estimates should be divided by a dose and dose-rate effectiveness factor (DDREF) of 2 for chronic exposures and for acute doses less than 200 mGy (ICRP, 1991; NCRP, 1993; UNSCEAR, 1993). A DDREF greater than 2 would, in the context of a linear-quadratic dose–response model, be statistically inconsistent with the 1958–1987 LSS solid cancer incidence data (Pierce and Preston, 2000), although not necessarily with the 1950–2000 LSS solid cancer mortality data (Preston et al., 2004).

(64) An independent analysis of the 1958–1987 tumour registry data by Little and Muirhead (2000) used a linear-quadratic model to assess possible overestimation of low-dose risk based on use of a linear dose–response model with these data, taking into account random errors in DS86 neutron and gamma dose estimates, and systematic errors in Hiroshima neutron dose estimates. They concluded that for all solid tumours combined, there was some indication of upward curvature over the 0–2-Gy dose range, but they expressed some caution about the interpretation of the data. As mentioned at the beginning of Section 2.4.4, the more recent analysis by Preston et al. (2004) of LSS solid cancer mortality data using the DS02 dosimetry found a statistically significant quadratic component of the dose–response relationship over the dose range 0–2 Gy, but the authors did not recommend using the linear-quadratic model for estimating risk at low doses. In particular, they noted that ongoing analyses of LSS incidence data did not indicate significant upward curvature, and that progressive trimming of the solid cancer mortality dose–response data from the right did not lead to decreased linear model estimates, as it did in the case of leukaemia.

(65) A DDREF would not be applied to the estimated linear-quadratic dose–response relationship for leukaemia, as it is already included in the model.

Site-specific differences

(66) The analyses of Figs. 2.3–2.5 are based on the numerous data for all solid cancers combined, and that of Fig. 2.6 is based on female breast cancer for which the radiation-related signal-to-noise ratio is high in the sense that dose-specific, radiation-

related risk tends to be high compared with the level of, and unexplained variation in, age-specific baseline breast cancer rates. Risk estimates for thyroid cancer and leukaemia are based on far fewer cases, but signal-to-noise ratios tend to be high on a dose-specific basis, especially for exposures at young ages. For these three cancer types, there is evidence of radiation-related excess risk at doses below 200 mGy, and for all except leukaemia, there is little evidence for departure of the dose–response relationship from linearity. For most other cancer sites, however, numbers of cases and/or radiation-related signal-to-noise ratios are too low to support strong statements about low-dose risk, although there is little or no evidence of departure from linearity (Thompson et al., 1994).

(67) The latter category of cancers includes some sites for which there is little or no epidemiological evidence that radiation exposure either is or is not associated with increased risk; examples include small intestine, prostate gland, testes, female genital organs other than ovary, malignant melanoma and squamous cell skin cancer, and chronic lymphocytic leukaemia (NCI/CDC, 2003; UNSCEAR, 2000). In the most recent analysis of cancer mortality among the atomic bomb survivors (Preston et al., 2003), rectal cancer mortality was not associated with radiation dose among men, based on 172 deaths during 1950–1997 and linear model estimates of ERR/Gy = −0.25 (90% CI <-0.3–0.15) for exposure at 30 years of age in a model with no dependence upon attained age, but was positively and significantly associated with dose among women, based on 198 deaths [ERR/Gy = 0.75 (CI 0.16–1.6), exposure at 30 years of age]. In addition, rectal cancer, bone cancer, and soft tissue sarcoma have been shown to be significantly associated with high-dose, partial-body exposure among patients given radiation therapy (Boice et al., 1988; UNSCEAR, 2000). Cancer of the small intestine, which is very rare in most populations (Parkin et al., 2002), can be induced in experimental animals by high-dose irradiation of exteriorised intestinal loops (Osborne et al., 1963; Watanabe et al., 1986), and the small intestine is therefore a susceptible organ. However, the small intestine appears to have characteristics that render it highly resistant to carcinogenesis at low-to-moderate levels of exposure to radiation and other environmental carcinogens (Cairns, 2002; Potten et al., 2002; see Section 5.2.1). Thus, inferences based on all cancers as a group, or on certain cancer sites for which there is substantial information about the dose-response relationship and its modification by other factors, need not necessarily apply to all site-specific cancers, or even to all histological subtypes of cancers of any given site. Nevertheless, for those cancers clearly inducible by radiation exposures under 5 Gy, there is evidence of some degree of commonality with respect to dose effects and their modification by sex and age (Pierce and Preston, 1993), and it is therefore useful and informative to examine radiation-related risk for certain groups of cancer sites.

2.5. Thresholds vs the linear, non-threshold theory

(68) The LNT theory (Brenner and Raabe, 2001) is part of the current basis for risk-based radiation protection. The theory assumes proportionality between radiation dose and subsequent cancer risk, usually with allowance for a DDREF to

reduce risk per unit dose of low-LET radiation at dose levels below 200 mGy (ICRP, 1991). However, at doses at which the DDREF applies fully, excess risk is assumed to be proportional to dose. A consequence of the LNT theory is that exposures resulting in very small average doses to very large populations are assumed to be associated with excess numbers of cancers that, although undetectable by epidemiological study, may be numerous.

(69) The threshold theory is a competing theory that, if generally accepted, may make it easier to ignore possible consequences of very-low-dose exposures. According to the theory, there is some 'threshold' dose below which there is either no radiation-related health detriment or a radiation-related health benefit that outweighs any detriment. If the threshold was a universal value for all individuals and all tissues, a consequence of the theory is that, at some point, a very low dose to any number of people would have no associated risk and could be ignored. Much, of course, depends upon the value of the assumed threshold dose, since even under the LNT theory, there must be a level of estimated risk so low that it is not worth the trouble to avoid. If, however, thresholds existed but were known or believed to differ widely among individuals and/or tissues, the effect of this knowledge on radiation practice and philosophy may be much less, and radiation protection may be even more complex than it is under the LNT theory.

(70) One argument made against the LNT theory is that there is little or no direct epidemiological evidence of excess cancer risk in populations exposed to less than 50 mGy or so. That is not quite true, as discussed above, but it is true that there is no direct, credible epidemiological evidence of a radiation-related risk associated with exposures of the order of 1 mGy, for example. Nevertheless, as also discussed above, the argument is specious; failure to detect a risk that (if it exists) is very small is not evidence that the risk is zero.

(71) A more subtle, and statistically more sophisticated, argument is to demonstrate that a dose–response model with a threshold, such as a linear model for dose-specific ERR with a fitted negative intercept at zero dose, can fit a data set as well as a linear or linear-quadratic model constrained to have a zero intercept (Hoel and Li, 1998; Little and Boice, 1999). The approach has the potential for showing disproportionality between excess risk and dose, consistent with a threshold (and usually, but not necessarily, also consistent with a linear-quadratic dose–response relationship), and could conceivably provide more substantial evidence of a threshold. That strong support for a threshold is hardly ever found in this way is more a reflection of low statistical power in the low-dose region than of statistical evidence against the existence of a threshold. In a more recent paper, Baker and Hoel (2003) modified the then-current DS86 atomic bomb doses for presumed systematic error in estimates of the neutron component of dose from the Hiroshima bomb, and a dose-dependent relative biological effectiveness for neutrons compared with gamma rays, finding that an improved fit to morbidity data for solid cancers and leukaemia was obtained by introducing a threshold. However, their assumptions about underestimation of the neutron dose for low-dose survivors of the Hiroshima bombing, on which their conclusions depended, have not been borne out by subsequent measurement data (Preston et al., 2004; Straume et al., 2003).

(72) It is clear that epidemiological studies are very unlikely to establish the presence or absence of a threshold at some low-dose level, although they can place limits on the likely value of any possible threshold (Pierce and Preston, 2000). Radiobiological evidence presented elsewhere in this report identifies the induction of DNA DSBs and more complex clustered DNA damage as (probably) the most important mechanism by which IR exposure contributes to radiation carcinogenesis. Such events have been demonstrated by calculation (Brenner and Ward, 1992; Goodhead, 1994) and by experiment (Boudaiffa et al., 2000a,b) to result from a single low-energy electron track produced by an x-ray or photon interaction. At low doses and low dose rates, the occurrence of such events is proportional to radiation dose and to the number of cells irradiated (Kellerer, 1985). Current research on development of timely assays for the presence and repair of DSBs may lead to findings that resolve the question of low-dose thresholds vs the LNT theory. As discussed in Section 4.5, the answer is still very much in doubt.

2.6. Conclusions: implications for low-dose cancer risk

(73) Epidemiological data from studies of human populations exposed to IR provide direct evidence that such exposure is associated with increased risk of cancer, and reason to believe that excess risk is not confined to people exposed to very high radiation doses. Our knowledge of radiation-related risk is highly quantified, more so than for any other common environmental carcinogen, and we have learned much about factors that modify that risk. Our understanding of risks associated with doses commonly encountered in daily life is not insignificant; we know, for example, that such risks are far lower than those observed in populations exposed to hundreds or thousands of mGy. However, the problem of quantifying risks that are so low as to be practically unobservable, and then recommending policies based on that quantification, is very difficult.

(74) It is highly likely that there will always be uncertainty about the risk of low doses, and that we will have to come to terms with that uncertainty. One way to do that is to quantify the uncertainty in a manner consistent with mainstream scientific information, and to evaluate actions and policies in terms of plausible probability distributions of risks associated with these actions and policies. An example of this type of approach is given in Chapter 6.

3. LOW-DOSE RISK – BIOLOGY

3.1. Introduction

(75) The fundamental role of radiation-induced DNA damage in the induction of mutations and chromosome aberrations, and the apparent critical involvement of aberrations and mutations in the pathogenesis of cancer provides a framework for the analysis of risks at low-dose and low-dose-rate exposures. Several key questions are important in considering the impact of exposure to low-dose and low-dose-rate radiation at the cell and molecular level with respect to subsequent development of chromosome aberrations, mutations, and cancer. These questions relate to the nature of radiation-induced damage, the nature of repair and damage response pathways, and their role and impact on induction of chromosome aberrations, mutations, and cancer. In this regard, the fundamental questions at the cell and molecular level to be considered for understanding risks at low doses are: (1) whether the damage caused by radiation is similar or distinct from endogenous damage; (2) does damage occur at low doses/dose rates by IR that cannot be repaired accurately; (3) is damage induced under low-dose and/or low-dose-rate conditions repaired by distinct mechanisms from damage induced at higher doses; and (4) are the signal transduction pathways activated by low-dose and/or low-dose-rate conditions and what impact do these pathways have in determining the propagation or elimination of radiation damage in cells and tissues. Early studies in biology related to radiation-induced cancer were largely descriptive in nature. This was mainly related to technical limitations in biological research. As such, the ability to study low-dose effects directly was limited. However, recent advances in techniques in cell and molecular biology are increasing our ability to approach these important questions directly.

3.2. Damage caused by radiation

(76) It has long been known that radiation produces a broad spectrum of DNA lesions including damage to nucleotide bases (base damage), single-strand breaks (SSBs), and DSBs. Certain types of DNA base damage, such as 8-hydroxydeoxyguanosine and thymine glycols, have significant biological importance, but the available data suggest that such isolated base damage by itself probably plays a minor role in radiation mutagenesis (Ward, 1995). It is generally accepted that unrepaired or misrepaired DSBs are the principal lesions of importance in the induction of chromosomal abnormalities and gene mutations (Goodhead, 1994; Ward, 1995). However, it has recently been recognised that an important feature of radiation damage is not the presence of any of these damages individually, but rather their close association, creating 'clustered damage'. Such clustered damage can arise from a combination of direct damage induced by the original radiation track plus damage generated from secondary reactive species arising from subsequent ionisation events (indirect damage) (Nikjoo et al., 1999). Recent evidence has, in fact, shown that substantial yields of DSBs may result from secondary electrons, with energies below the

ionisation threshold, generated from the ionised nucleotides (Boudaiffa et al., 2000a). Clustered damage may involve an SSB or DSB associated with base damage, but can involve far more complex associations including multiple closely spaced DSBs. Both the frequency and complexity of clustered damage depend upon the LET of the radiation. Using sophisticated modelling and track structure methods, it has recently been shown that nearly 30% of DSBs induced by low-LET radiation are of a complex form involving two or more DSBs. This value is 70% for high-LET radiation. When breaks associated with base damage are included, the complex proportion becomes 60% and 90% for low- and high-LET radiation, respectively (Nikjoo et al., 1999, 2000, 2001, 2002). It is likely that as the complexity of the damage increases, the damage will become less reparable and more likely to lead to biological consequences (see below for further discussion). An important aspect in considering the impact of exposure to low doses of IR is whether such damage is similar to that encountered endogenously. It is clear that a significant level of oxidative damage can arise in cells from the generation of reactive oxygen species (ROS) during normal cellular metabolism. In comparing ROS-induced damage with that induced by IR, there appear to be similarities but also important differences. One aspect of ROS- and IR-induced DSBs that can impact upon repair is the nature of their termini. Breaks induced by restriction enzymes have 3′-hydroxyl and 5′-phosphate moieties at their termini, a prerequisite for enzymatic ligation, while the majority of breaks generated by ROS and IR have 'damaged' termini, most frequently 3′phosphate or 3′phosphoglycolate end groups (Ward, 1998). Some 5′ termini with hydroxyl end groups are also generated. Such termini require processing prior to ligation. Excision of a damaged nucleotide will also frequently result in base loss at the break. Recent evidence concerning the repair of such lesions will be considered below. These aspects of the breaks are similar between ROS- and IR-induced damage, although they differ from DSBs induced during such metabolic processes as the rejoining of the variable, diversity, and joining segments during immune development (V(D)J recombination) and meiosis.

(77) The predominant forms of ROS-induced damage are base damages and SSBs. The frequency of DSBs generated by ROS depends upon the particular reactive species, but is typically less than 0.5% of the damage induced. More importantly, these DSBs are distributed relatively uniformly throughout the DNA. In contrast, due to non-homogeneous energy deposition, the damage from even low doses of IR occurs in clusters producing complex lesions. It is unlikely that such damage will arise endogenously at any appreciable frequency. The impact of this difference on repair will be discussed below.

(78) UNSCEAR have explored the proposition that data on the high abundance of spontaneously arising DNA damage could be used to argue that 'a further small increment of DNA damage from low doses of radiation will not impose significant risk; that risk only becomes significant at relatively high doses when at a given level of genomic damage, DNA repair capacity is exceeded' (UNSCEAR, 2000). The principal conclusion from UNSCEAR, which generally accords with that of the Task Group, is that differences in the complexity (as discussed above) and repair characteristics (see later in this chapter) of spontaneously arising and radiation-induced DNA lesions argue against this proposition.

3.3. Damage response pathways

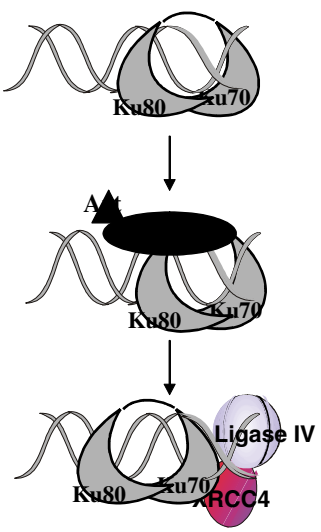
(79) The cellular responses to DNA damage include pathways of DNA repair, the operation of cell-cycle checkpoints, and the onset of apoptosis. The latter two responses overlap significantly and utilise, at least to some extent, the same sensor molecules or complexes involved in damage recognition and signal transduction. There is mounting evidence that the damage recognition complexes that control cell-cycle checkpoint arrest also influence or interact with the DNA repair machinery, although the interplay between the DNA repair pathways and between DNA repair and checkpoint control/apoptosis is currently unclear. The operation of these responses serves two functions: to enhance survival and to maintain genomic stability. These are not necessarily compatible outcomes. The principal evolutionary pressure for a lower organism such as yeast is the survival of individual cells, whereas in multicellular organisms, a strong selective pressure is the survival of the organism. Since the propagation of genetically altered cells has the potential to kill higher organisms by tumour formation, mechanisms have developed to prevent the growth of damaged cells. However, to achieve this, the survival of individual cells may be compromised. The role of apoptosis for this purpose has been evident for some time, but the function of checkpoint control in this context is just beginning to emerge. Thus, for radiation protection, it is necessary to evaluate not only the mechanisms that repair DNA damage and enhance survival but also the mechanisms that serve to limit the propagation of damaged cells. The processes that repair damage induced by IR, and the steps involved in the responses leading to checkpoint arrest and apoptosis will be considered below. Since DNA DSBs represent the major biologically significant lesion following radiation exposure, the focus of the discussion will be on damage response mechanisms triggered by DNA DSBs.

3.3.1. DNA DSB repair

(80) Two mechanistically distinct pathways for DNA DSB repair have been described: non-homologous end-joining (NHEJ), that requires little or no homology at the junctions; and homologous recombination (HR), that utilises extensive homology. A third process, single-strand annealing (SSA), that utilises short direct repeat sequences, has facets of both processes.

Non-homologous end-joining

(81) Five core proteins that function in NHEJ have been identified in mammalian cells (Fig. 3.1). These include the three components of the DNA-PK complex [Ku70, Ku80, and the DNA-PK catalytic subunit (DNA-PKcs)], together with XRCC4 and DNA ligase IV (Jeggo, 1998; Kanaar et al., 1998; Lees-Miller and Meek, 2003; Lieber et al., 2003). Mutations in any of these core components confer dramatic radiosensitivity and an impaired ability to rejoin DNA DSBs as monitored by pulsed-field gel electrophoresis (PFGE). Cells lacking these NHEJ components are also impaired in their ability to carry out V(D)J recombination, a process that involves the rejoining of site-specific DSBs (see below). Patients with hypomorphic mutations in DNA



1) Binding of Ku to the double-stranded DNA end. The crystal structure of Ku shows that the DNA passes through a cavity in the structure with Ku encircling the DNA (a single DNA end is shown for simplicity).

2) DNA -PKcs is recruited and the kinase activity activated. Autophosphorylation and phosphorylation of artemis likely ensues, potentially leading to release of DNA -PKcs Artemis nuclease activity may enhance processing of ends.

3) Ku enhances the recruitment of DNA ligase IV/XRCC4 complex and Ku translocates inwards to allow ligase IV/XRCC4 access to the DNA ends.

Note that only a single DNA end is shown for simplicity - one function of DNA -PKcs may be to enhance synapsis of the DNA ends.

Fig. 3.1. Model for DNA non-homologous end-joining. Proposed steps involved in the process.

ligase IV display immunodeficiency, and defective mice, when viable, display severe combined immunodeficiency phenotypes (SCID) (Jeggo, 1998; Jeggo and Concannon, 2001; O'Driscoll et al., 2001; Schwarz et al., 2003). Recently, a further component, Artemis, has also been shown to function in NHEJ and V(D)J recombination (Moshous et al., 2001). Artemis was identified as the defective protein in a class of SCID patients. Cell lines derived from these patients are sensitive to IR but, in contrast to lines defective in the other NHEJ components, Artemis-defective cell lines are proficient in DSB rejoining (Nicolas et al., 1998). Artemis is able to function as a single-strand-specific nuclease and its function in V(D)J recombination depends upon its ability to cleave a hairpin intermediate generated during this process (Ma et al., 2002). The role of Artemis in rejoining IR-induced breaks is less clear, but it has been speculated that it may function in modifying double-stranded ends with additional DNA damage (Jeggo and O'Neill, 2002). Finally, analysis of cell lines from human SCID patients has provided evidence that a further factor is required for NHEJ (Dai et al., 2003).

(82) In yeast, a range of additional proteins appears to be required for NHEJ. Mre11, Rad50, and Xrs2p are required for NHEJ in *Saccharomyces cerevisiae* but are dispensable in *Schizosaccharomyces pombe* (Jeggo, 1998). In higher organisms, cell lines derived from Nijmegen breakage syndrome (NBS) carry mutations in Nbs1, a functional homologue of Xrs2p (Carney et al., 1998; Varon et al., 1998). NBS cell lines are proficient in their ability to carry out V(D)J recombination, and

do not show the characteristic DSB-rejoining deficiency of NHEJ-defective cell lines, although they do show radiosensitivity (Yeo et al., 2000). Sir2p, Sir3p, and Sir4p are also required for NHEJ in *S. cerevisiae* (Tsukamoto et al., 1996). Current evidence suggests that their role may be regulatory. Recently, it has been established that NHEJ is regulated in a cell-type-specific manner by Nej1p/Lif2p in *S. cerevisiae* (Frank-Vaillant and Marcand, 2001; Kegel et al., 2001; Valencia et al., 2001). Consistent with this model, Nej1p is repressed in *sir* strains. This regulation ensures that NHEJ only functions in haploid yeast cells, and demonstrates that the role of the *sir* proteins in NHEJ is to regulate Nej1p. There are no data to indicate whether NHEJ is regulated in a similar manner in mammalian cells, although the process clearly functions in diploid mammalian cells. An Nej1p homologue has not been identified in mammalian cells.

(83) The heterodimeric Ku protein, consisting of 83 and 70 kDa subunits, has DNA double-stranded end-binding activity. Its binding to DNA ends is likely to represent an early step in the repair process. The binding of Ku to dsDNA ends serves to recruit DNA-PKcs and activate its catalytic activity. DNA-PKcs is a member of a subfamily of phosphoinositol (PI) 3-kinases, termed 'PI 3-K related protein kinases' (PIKK), that have protein rather than lipid kinase activity (Hartley et al., 1995). This potentially provides the cell with a signal transduction pathway to alert the presence of a DNA DSB. However, the function and physiological targets of DNA-PK activity are currently unclear. It does not appear to be involved in p53 activation or cell-cycle checkpoint arrest (Jimenez et al., 1999). There is mounting evidence that DNA-PK may serve to autoregulate the process of NHEJ, and one clear in-vivo substrate of DNA-PK activity is the protein Artemis, which is stimulated to cleave hairpin junctions by DNA-PK-dependent phosphorylation (Ma et al., 2002; Merkle et al., 2002). Autophosphorylation of DNA-PK also appears to be essential for NHEJ (Ding et al., 2003).

(84) XRCC4 and DNA ligase IV co-associate strongly and depend on each other for stability (Critchlow et al., 1997; Grawunder et al., 1997). XRCC4 has no obvious domains or motifs (Li et al., 1995). The crystal structure of XRCC4 reveals a globular head domain and two tails with coiled coils (Sibanda et al., 2001). DNA ligase IV has a catalytic domain at its N terminus plus two BRCT domains at its C-terminus. Interaction with XRCC4 occurs via the region between the two BRCT domains (Grawunder et al., 1998). It is the only mammalian ligase identified to date that can rejoin double-strand DNA ends. An emerging model is that Ku serves to recruit the DNA ligase IV/XRCC4 complex to the DNA end and then translocates inwards to allow LX access to the DNA end (Kysela et al., 2003).

Role of NHEJ in V(D)J recombination

(85) During B- and T-cell development, the V, D, and J segments become rearranged into contiguous units by a process that involves the introduction of site-specific DSBs by two recombination activating genes (RAG1 and 2) (Fugmann et al., 2000; Gellert, 2002; Hesslein and Schatz, 2001). In germline cells, each V, D, or J segment, termed a 'coding segment', is juxtaposed to a recombination signal sequence (RSS). The DSBs are introduced at the junctions between

an RSS and its adjacent coding sequence. This process involves the introduction of a single-strand nick and a transesterification reaction generating a blunt-ended RSS end and a hairpin coding end. Rejoining yields accurately rejoined signal junctions and coding junctions that frequently bear deletions or insertions. This re-arrangement process coupled with inaccurate rejoining of coding junctions plays a significant role in enhancing the diversity of the immune response. Thus it appears that the cell utilises the same DNA NHEJ machinery to effect re-arrangements during the V(D)J recombination process and to rejoin radiation-induced DNA DSBs.

(86) The genetic requirements for signal and coding joint formation are distinct and provide insight into the nature of the rejoining process. Rejoining of the blunt-ended signal junctions requires only Ku70, Ku80, Xrcc4, and DNA ligase IV. Thus, Artemis and DNA-PKcs are largely dispensable for RSS rejoining. In contrast, all six proteins are required for coding join formation (Moshous et al., 2001). Recently, it has been demonstrated that Artemis is activated by DNA-PKcs. Following activation, Artemis is able to cleave the hairpin coding junctions (Ma et al., 2002). This neatly explains the requirement of both DNA-PKcs and Artemis for coding join formation. What is the likely role of Artemis and DNA-PKcs in the rejoining of radiation-induced breaks? In unphosphorylated form, Artemis has 5′ to 3′ exonucleolytic activity with single-strand DNA specificity (Ma et al., 2002). Upon phosphorylation by DNA-PK, its activity changes and Artemis gains single-strand-specific endonucleolytic activity on both 5′ and 3′ overhangs as well as the ability to cleave hairpins. It is, therefore, possible that Artemis functions to modify the ends of radiation-induced breaks (Jeggo and O'Neill, 2002).

Homologous recombination

(87) HR is a high fidelity and efficient mechanism to repair DNA DSBs that utilises information on the undamaged sister chromatid or homologous chromosome to retrieve information lost at the break site. In yeast, genes involved in HR belong to the Rad 52 epistasis group (Rad50, Rad51, Rad52, Rad54, Rad55, Rad57, Rad59, Mre11, and xrs-2) (Helleday, 2003; West, 2003). Homologues of some of these proteins (e.g. Rad50, Rad51, Rad52, Rad54, and Mre11) have been identified in higher organisms. The yeast proteins Rad55 and Rad57 display sequence similarity to Rad51, and further members of a Rad51 family (termed 'Rad51-like genes') have been identified in mammalian cells, including XRCC2, XRCC3, Rad51L1, Rad51L2, and Rad51L3 (Thacker, 1999). Steps involved in HR have been characterised in yeast and *Escherichia coli,* and involve processing of the DNA ends, strand invasion, the formation of heteroduplex DNA, and a step involving resolution of the cross-over junction (Holliday junction) (outlined in Fig. 3.1) (Kanaar et al., 1998). RecA, Rad51p, and human Rad51 (hRad51) polymerise on DNA to form a nucleoprotein filament that promotes ATP-dependent homologous pairing and DNA strand exchange. hRad52 stimulates homologous pairing by hRad51, suggesting that it functions in an early stage of Rad51-mediated recombination that precedes homologous pairing

(Benson et al., 1998; New et al., 1998; Shinohara and Ogawa, 1998). In vitro, the homology searching and strand exchange reaction is facilitated by RPA (Replication Protein A), Rad55, and Rad57, although their precise roles are unknown. Resolution of the Holliday junction complex is carried out by RuvABC in *E. coli* and requires Rad51C and XRCC3 in mammalian cells (Liu et al., 2004). Mre11, Rad50, and xrs2 may play a role in early nucleolytic processing to produce ends suitable for the exchange reaction (Tauchi et al., 2002). There is also increasing evidence for roles of BRCA1, BRCA2, and BARD1 in HR. Specifically, BRCA2 can bind to Rad51 via its Brt domains and potentially plays a role in delivering Rad51 to single-stranded DNA (Pellegrini et al., 2002; Yu et al., 2003a). BARD1 interacts with BRCA1 and loss of either prevents HR from taking place (McCarthy et al., 2003; Westermark et al., 2003).

Single-strand annealing

(88) A third process for DSB rejoining identified in yeast is SSA, a mechanism that uses short regions of homology, possibly to stabilise ends prior to rejoining. The analysis of sequences at the break junctions in mammalian mutants arising after radiation in higher organisms has suggested that this mechanism also functions in mammalian cells (Morris and Thacker, 1993). This mechanism is inherently inaccurate as it involves loss of sequences around the short regions of homology. This may be the mechanism utilised when HR or NHEJ fail, and could thus potentially contribute to error-prone DSB repair. Unfortunately, little is known about the genetic requirement for this process in mammalian cells.

Contribution of HR and NHEJ to DNA DSB repair in mammalian cells

(89) Yeast mutants defective in Rad51p, Rad52p, or Rad54p are dramatically radiosensitive; NHEJ-null yeast mutants display little or no sensitivity but double mutants defective in both HR and NHEJ are slightly more sensitive than single mutants defective in HR. Thus, in yeast, HR is the major mechanism for DSB repair and NHEJ functions in its absence. Two factors may account for this. Firstly, Nej1p appears to regulate NHEJ in yeast, resulting in repression of the process in *MAT*a/*MAT*α diploids (Frank-Vaillant and Marcand, 2001; Kegel et al., 2001; Ooi et al., 2001; Valencia et al., 2001). Additionally, NHEJ appears to be regulated in some other way allowing it to function primarily in G1 phase. The situation in mammalian cells is quite different. The major radiosensitivity of NHEJ-defective mammalian cells attests to the importance of NHEJ in the repair of DNA DSBs in higher organisms. However, HR does function in higher organisms and radiosensitivity is a feature of some HR-defective cell lines. Increasing evidence suggests that in higher organisms, HR functions to repair breaks in late S and G2 phases and that NHEJ plays its major role in G1 phase (Fukushima et al., 2001; Rothkamm et al., 2003). In mammalian cells, HR utilises sister chromatids rather than a homologous chromosome as the source of undamaged template. HR, therefore, plays a particular role in the repair of breaks at the replication fork, and also appears to be essential for the efficient repair of breaks that arise from interstrand cross-links.

3.3.2. Cell-cycle checkpoint control

(90) Perturbation to DNA metabolism, arising either endogenously or through exogenous DNA damaging agents, causes arrest at one of several cell-cycle checkpoints, collectively called 'DNA integrity checkpoints'. Progression from one cell-cycle phase to the next occurs by phosphorylation or dephosphorylation of cyclin-dependent kinases, and checkpoint arrest is effected by controlling the activity of the DSBs. In addition to checkpoint controls that operate at the boundary between cell-cycle phases, there is also an S-phase checkpoint that presumably recognises a stalled replication fork. These checkpoint responses have been most widely studied using *S. cerevisiae* or *S. pombe* as model systems, but the operation of checkpoints is also evident in mammalian cells. Homologues of most of the yeast checkpoint proteins have now been identified. The checkpoint responses involve three stages: damage recognition, signal transduction, and effector proteins. A brief overview of the process in yeast will be given first, followed by a discussion of the available knowledge in mammalian cells.

DNA integrity checkpoints in yeast

(91) In yeast, there are several points where cell-cycle delay or arrest can occur: (1) G1/S that serves to prevent replication of damaged chromosomes; (2) intra S phase which slows down or delays replication; and (3) G2/M which prevents transition from G2 into M. In addition, there is a distinct response that monitors the replication status of the DNA and prevents mitosis if replication has not been completed. SpRad3 (*S. pombe* Rad3) or ScMec1 (*S. cerevisiae* Mec1) are the PIKKs that initiate the signal transduction process by phosphorylating key proteins involved in cell-cycle regulation (Furuya and Carr, 2003; Osborn et al., 2002; Rouse and Jackson, 2002). Both kinases have partner proteins, SpRad26p and ScLcd1p/ScDdc2p, which are thought to function to target the kinase to the site of damage, with recent evidence indicating that recruitment of the proteins to the break site requires initial binding of RPA to single-stranded regions of DNA (Cortez et al., 2001; Zou and Elledge, 2003). Activation of the kinases, however, requires additional complexes. One is an RFC-like protein or protein complex represented by ScRad24p and SpRad17p. The second complex contains PCNA-like proteins (ScRad17p/ScDdc1p/ScMec3p and SpRad1p/SpRad9/SpHus1). The RFC (Replication Factor C)-like proteins can target damaged sites independently of the PIKKs and are required to load the PCNA (Proliferating Nuclear Antigen)-like proteins. Downstream phosphorylation of transducer proteins in cell-cycle checkpoint control, such as the Chk1p and Rad53/Cds1 kinases, requires all the proteins described above. Through effector proteins that include the Wee1 kinase, Cdc25 phosphatase and Mik1 kinases, key cyclin-dependent kinases that control cell-cycle progression are activated or de-activated. These include the mitosis-inducing kinase Cdc2.

Checkpoint responses in mammalian cells

(92) Although the steps are less well understood in mammalian cells, the checkpoint responses are clearly conserved between organisms (Durocher and Jackson,

2001; Rouse and Jackson, 2002). However, in yeast, nearly all checkpoint signalling is carried out by the ScMec1/SpRad3 kinases which respond to a range of different DNA damages, whereas in mammalian cells, there appears to be some divergence of function with two PIKK kinases, ATM (ataxia telangiectasia mutated protein) and ATR (ataxia telangiectasia and Rad3-related protein), both contributing to damage-dependent phosphorylation events (Abraham, 2001; Bradbury and Jackson, 2003; Shiloh, 2001). ATM appears to respond primarily to DNA DSBs and, therefore, is the PIKK activated by IR. ATR, in contrast, appears to be activated by single-stranded regions of DNA arising at stalled replication forks or during processing of bulky lesions (Zou and Elledge, 2003). A further significant difference in higher organisms is the role of p53 in the signal transduction process, for which there is no functional homologue in yeast. Mounting evidence suggests that recognition complexes, similar to those found in yeast, sense damage and initiate signal

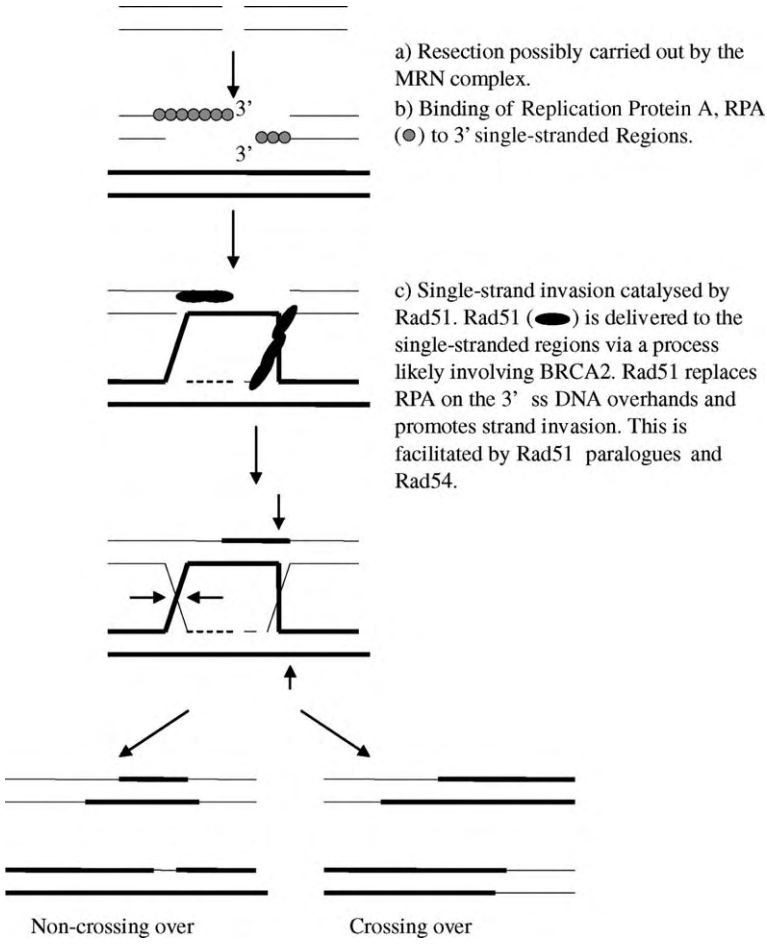


Fig. 3.2. Depiction of homologous recombination.

transduction pathways by phosphorylation (Rouse and Jackson, 2002). In mammalian cells, these pathways also target p53. The result of this is that checkpoint activation, in addition to inducing transient delays at cell-cycle transitions, can also mediate permanent cell-cycle arrest or apoptosis in mammalian cells (outlined in Fig. 3.2).

3.3.3. Early sensors of DNA damage

Role of ATM

(93) ATM is defective in ataxia-telangiectasia (A-T), a multisystem disorder associated with diverse characteristics that include cancer predisposition and clinical radiosensitivity (Taylor et al., 1996). A-T cell lines are defective in a range of damage responses following IR including an inability to arrest at the G1/S, S, and G2/M cell-cycle checkpoints (Goodarzi et al., 2003; Shiloh, 2001, 2003). Significantly, p53 levels are not elevated following radiation in A-T cell lines, suggesting that ATM functions upstream of p53, potentially as part of an early damage sensor mechanism (Kastan et al., 1992; Lu and Lane, 1993). ATM is a member of the PIKK family with homology to SpRad3 and ScMec1, although the yeast homologue of ATM is Tel1 (Savitsky et al., 1995). ATM can function as a ser-thr protein kinase both in vivo and in vitro, and can phosphorylate the serine 15 residue of p53 (Banin et al., 1998; Canman et al., 1998; Khanna et al., 1998). This residue of p53 fails to become phosphorylated in irradiated A-T cells, demonstrating that ATM functions as the major, if not the only, kinase phosphorylating this residue of p53 after irradiation. This was initially thought to provide the explanation underlying p53 induction following irradiation. However, this is clearly an oversimplification, as phosphorylation of this residue does not appear to be a key factor controlling p53 stability, ATM can phosphorylate other sites on p53, and ATM can phosphorylate other kinases such as Chk1 and Chk2, which themselves phosphorylate p53 on serine 20, which is required to stabilise p53 (see section on p53 below). Furthermore, ATM can also phosphorylate MDM2, an event that could itself influence p53 stability. Added to this complex picture, other kinases including DNA-PK and ATR can, at least in vitro, phosphorylate the S15 residue of p53. Thus, a complex picture of p53 regulation by phosphorylation emerges in which ATM clearly plays an important role either directly or indirectly. Taken together, these data suggest that ATM plays a key role in sensing DNA DSBs and, by phosphorylation, initiating signal transduction pathways that control cell-cycle arrest. ATR probably serves the same role for ultraviolet-induced lesions and stalled replication forks, and overlaps to some degree with ATM for DNA DSBs.

Role of Nbs1, hMre11, and hRad50

(94) NBS is another syndrome associated with cancer predisposition and radiosensitivity that is distinct from, but overlaps with, A-T (International Nijmegen Breakage Syndrome Study Group, 2000; Shiloh, 1997). In contrast to their somewhat distinct clinical characteristics, cell lines derived from A-T and NBS display similar phenotypes including radiosensitivity, cell-cycle checkpoint defects, and decreased

ability to stabilise p53. The gene defective in NBS has been shown to encode a protein, Nbs1 or p95 (Carney et al., 1998; Varon et al., 1998). Nbs1 interacts strongly with hMre11 and hRad50. In yeast, Mre11 and hRad 50 interact with a third protein, Xrs-2p, and mutants defective in any of these proteins share identical phenotypes (Johzuka and Ogawa, 1995). Nbs1 appears to be a functional homologue of Xrs-2p, although the two proteins share only limited sequence homology. Like other DNA repair proteins, Nbs1 has a forkhead-associated domain and a BRCT domain, which appear to be important for function (Cerosaletti and Concannon, 2003). The link between A-T and NBS has been further strengthened recently by the finding that a milder variant form of A-T called 'A-T-like disorder' (ATLD) has mutations in hMre11 (Stewart et al., 1999). hMre11 and hRad50-null mice show embryonic lethality, and the mutations in hMre11 in ATLD impair but do not inactivate hMre11 function, a feature consistent with the milder clinical features of this variant class of A-T. hMre11, hRad50, and p95 (termed the 'MRN complex') colocalise in nuclear foci which form at the sites of DSBs (Kobayashi et al., 2002). The precise role of the MRN complex is still hotly debated. In yeast and vertebrates, there is evidence that MRX functions in both HR and NHEJ (Tauchi et al., 2002). In mammalian cells, however, it is not an essential component of the NHEJ machinery (O'Driscoll et al., 2001). Importantly, current evidence also shows that MRN is required either directly for ATM activation or to aid ATM-dependent phosphorylation events (Girard et al., 2002; Uziel et al., 2003). Taken together, the findings suggest that MRN acts in concert with ATM in an early sensor complex that activates, by phosphorylation, a number of damage response mechanisms that include p53-dependent and -independent processes.

BRCA1 and BRCA2

(95) Germline mutations in these genes confer a high risk of breast and ovarian tumours, and both have been identified as genes defective in familial breast cancer patients (Miki et al., 1994; Wooster et al., 1995). Recent evidence points to the involvement of both gene products in damage response mechanisms, and cells carrying mutations in either protein show pronounced genomic instability (Venkitaraman, 2002). *BRCA1* has an N-terminal RING finger domain that mediates protein–protein interactions, and a tandem BRCT motif at its C-terminus which appears to represent a phosphor–protein binding module (Manke et al., 2003; Yu et al., 2003b). BRCA1-defective cells show marked genomic instability and impaired checkpoint responses, including impaired S and G2/M checkpoint arrest (Xu et al., 2001). BRCA1 is also localised to H2AX foci after DNA damage, and thus colocalises with MRN, 53BP1, and MDC1 (Paull et al., 2000). BRCA1 is phosphorylated after DNA damage, and emerging evidence suggests that it is required to facilitate at least some ATM-dependent phosphorylation events. This feature is also displayed by other proteins that localise to the H2AX foci (Foray et al., 2003; Lee et al., 2000). However, following irradiation, BRCA1 also colocalises with Rad51 to nuclear foci, which are distinct from the H2AX foci (Zhong et al., 1999). Consistent with this finding, BRCA1-defective cells are impaired in HR (Moynahan et al., 1999). Taken together, these results suggest that BRCA1 may have two independent

functions, one in checkpoint signalling and another in promoting HR. Thus, like p53, BRCA1 has a 'caretaker' role.

(96) BRCA2-defective cells do not appear to show cell-cycle checkpoint defects but they are impaired in HR (Moynahan et al., 2001). Rad51 foci do not form in BRCA2-defective cells, and it has been suggested that BRCA2 is required for the delivery of Rad51 to the sites of single-stranded DNA (Pellegrini et al., 2002; Yang et al., 2002). The link with DNA repair has been further strengthened by the surprising finding that *FANCD1*, a gene involved in cross-link repair and defective in some patients with Fanconi anaemia, is in fact *BRCA2* (Howlett et al., 2002).

Role of H2AX

(97) H2AX is a variant form of the histone H2A, which becomes phosphorylated in response to DNA damage and plays a critical role in the retention of repair factors at the site of DSBs (Celeste et al., 2003; Paull et al., 2000). Mice lacking H2AX are viable but show genomic instability and radiosensitivity (Celeste et al., 2002). H2AX phosphorylation is a rapid response following the introduction of DSBs, and phosphorylation rapidly extends to H2AX molecules located up to three megabase pairs within the region of the DSB (Rogakou et al., 1999). Using phosphospecific antibodies, phosphorylated H2AX (termed 'γ -H2AX') can be observed as discrete foci, and current evidence suggests that all DSBs are marked by the presence of such foci (Rothkamm and Lobrich, 2003). The analysis of such foci is promising as a tool to monitor the formation and repair of DSBs (see also Section 3.4.3).

MDC1, 53BP1, and SMC1

(98) Recent data have led to the identification of additional proteins that accumulate at the site of γ -H2AX foci and are required for an efficient checkpoint response. Lack of these proteins confers at least some level of radiosensitivity. 53BP1 was originally identified through its ability to bind to p53 via C-terminal BRCT repeats present in 53BP1 (Mochan et al., 2003; Wang et al., 2002). MDC1 was identified simultaneously by several laboratories, one of which identified it as a binding partner of the Mre11 complex (Goldberg et al., 2003; Lou et al., 2003; Stewart et al., 2003). Both proteins form foci that colocalise with H2AX and MRN foci after irradiation (Abraham, 2002; Fernandez-Capetillo et al., 2002; Goldberg et al., 2003; Lou et al., 2003; Stewart et al., 2003). SMC1 is also required for normal cell-cycle checkpoint arrest and radioresistance (Kim et al., 2002; Yazdi et al., 2002), and localises at H2AX foci after DNA damage.

3.3.4. Signal transduction after irradiation

Role of p53

(99) An early response of mammalian cells that occurs within minutes of a cell sustaining DNA damage is an increase in the levels of p53 (Kastan et al., 1991). In addition to changes in p53 levels, its ability to function as a transcriptional activator may also be increased (Ashcroft et al., 1999; Lakin and Jackson, 1999). In combination, these changes in p53 result in the transcription of key proteins involved in a number

of distinct damage response mechanisms (see below). The role of p53 in the response to radiation damage is complex as it affects some aspects of DNA repair, cell-cycle checkpoint arrest, and the onset of apoptosis (Fei and El-Deiry, 2003). The importance of p53 and the significance of the damage response mechanisms it controls are underscored by the dramatically elevated cancer predisposition in patients with mutations in p53 (Li-Fraumeni syndrome patients), and in p53 knock-out mice (Donehower et al., 1992; Malkin et al., 1990; Srivastava et al., 1990). Additionally, mutations in p53 are found in around 40% of tumours covering all the cancer types.

(100) Since p53 is so critical to the cell and to the whole organism, it is not surprising that it is subjected to stringent regulation, the complexity of which is ever-increasing (Ashcroft et al., 1999; Deb, 2003; Lakin and Jackson, 1999). A key protein controlling p53 is Mdm2 (Deb, 2003). Mdm2 binds to the amino terminus of p53 and targets it for ubiquitination and subsequent degradation by ubiquitin-controlled proteosomes (Kubbutat et al., 1998). Thus, in undamaged cells, p53 is maintained at low levels via Mdm2 binding and ubiquitin-dependent degradation. Following radiation exposure, changes to p53 and/or Mdm2 decrease their binding potential with a consequent increase in the half-life of p53. Additionally, however, Mdm2 binding represses the ability of p53 to act as a transcription activator (Momand et al., 1992). Thus, Mdm2 negatively regulates both stabilisation of p53 and its function. Knock-out mice for Mdm2 are embryonic lethal due to high endogenous levels of p53, but double-mutant p53/Mdm2 knock-out mice are viable. More significantly, mutations in Mdm2 are frequently found in tumours, particularly those tumours without p53 mutations. Mdm2 is also itself subject to controlling mechanisms that include multisite phosphorylation and sumoylation (Meek and Knippschild, 2003). Another factor influencing Mdm2 function in humans is the tumour suppressor protein $p19^{ARF}$, which is derived from an alternative reading frame of INK4a. $p19^{ARF}$ binds directly to Mdm2 in a region distinct from the p53-binding domain. It does not inhibit p53/Mdm2 binding but does inhibit p53 degradation, probably by sequestering Mdm2 into the nucleolus. The major mechanism regulating MDM2 binding to p53 is phosphorylation, both of p53 and MDM2 itself. As discussed above, ATM plays a role in both of these events.

G1/S arrest

(101) Careful analysis has demonstrated that two types of G1/S arrest can occur in mammalian cells: prolonged arrest, which is a p53-dependent response, and a more transient response (Di Leonardo et al., 1994; Little, 1968). The latter appears to be similar to the G1/S response observed in yeast. The major p53 response protein required for G1/S arrest is p21 (Wahl and Carr, 2001). Whilst p21 is transcriptionally regulated by p53, there is also recent evidence that p53 regulates the stability of p21 via another p53 protein, p53RPF (Ng et al., 2003). p21 is an inhibitor of cyclin-dependent kinases and plays its major role in G1/S arrest by binding to the cyclin D/Cdk6 complex and inhibiting its ability to phosphorylate pRb, which in turn inhibits the release of pRb from E2F, an essential step that triggers S-phase progression (Ko and Prives, 1996). Consistent with this model, neither p53- nor ATM-null cells show prolonged radiation-induced G1/S arrest. A-T cells are, however, capable

of arresting at the G1/S boundary following ultra-violet irradiation, demonstrating the specificity of the upstream signal transduction mechanism. However, the operation of this checkpoint does not necessarily serve to elevate survival to IR, since transformed fibroblasts (which normally lack this response due to p53 inactivation) as well as p53-null cell lines display elevated radioresistance compared with primary or $p53^{+/+}$ cells (Lee and Bernstein, 1993).

S-phase arrest

(102) Replication in mammalian cells is also inhibited following irradiation, which can be observed by decreased ability of replicating cells to incorporate radioactive precursors into DNA. Cells from ATM and NBS display a phenotype called 'radioresistant DNA synthesis' which is believed to be due to a failure to undergo S-phase delay (Jackson, 2002). Current evidence suggests that early S-phase arrest after irradiation is ATM dependent but, at later times, S-phase arrest is mediated via ATR (Zhou et al., 2002). Chk2 and possibly Chk1 represent strong candidate proteins involved in mediating S-phase arrest via Cdc25A degradation (Iliakis et al., 2003; Xiao et al., 2003). S-phase arrest encompasses inhibition of ongoing replication forks, stabilisation of replication forks, and the inhibition of late firing replicons (Feijoo et al., 2001; Tercero et al., 2003).

G2/M arrest

(103) Progression from G2 to M is controlled largely by the DSB–cyclin B complexes. Activation or inhibition of these complexes is controlled by opposing kinases and dephosphatases affecting the phosphorylation status of the Thr14 and Tyr15 residues of cyclin-dependent kinases. Currently, the prevailing evidence suggests that ATM phosphorylates Cds1 and/or Chk1, which in turn phosphorylates and inactivates Cdc25, the event that prevents dephosphorylation and activation of Cdc2–cyclin B. G2/M arrest after γ irradiation, although ATM dependent, is p53 independent. In earlier studies, confusion arose concerning the G2/M checkpoint due to the ability of cells to arrest in two distinct ways in G2. Normal cells in G2 at the time of irradiation show a delay in entry into mitosis, which represents the operation of a G2/M checkpoint. A-T cells in G2 at the time of irradiation show a reduced delay compared with normal cells, showing that this arrest is at least partially ATM dependent (Beamish and Lavin, 1994). However, following higher doses, asynchronous A-T and control cells can show a permanent arrest at G2/M which has recently been shown to be ATR dependent (Wang et al., 2003). The contribution of G2/M arrest to survival following radiation exposure is unclear, although the prevailing view is that arrest enhances survival and reduces the probability of genomic alterations.

Apoptosis

(104) Apoptosis is a process utilised to balance cell proliferation and cell death. It is crucial to certain developmental processes and is, for example, used during immune development to remove cells that have failed to undergo productive re-arrangements (Sohn et al., 2003). It is also utilised to remove cells damaged by exogenous DNA damaging agents. The onset of apoptosis in normal cells by radia-

tion is p53 dependent, although p53-independent routes to apoptosis have also been described (Adams, 2003). Additionally, there are significant differences between cell lineages in their propensity to undergo apoptosis following irradiation.

(105) The signalling processes leading from p53 induction to apoptosis are complex and diverse. All the pathways, however, converge in the activation of proteases termed 'caspases' (Adams, 2003; Thornberry and Lazebnik, 1998). Caspases exist as pro-enzymes that require activation and finally effect apoptosis by protein degradation that results in disassembly of cell structures such as nuclear lamin, degradation of DNA repair proteins such as PARP, ATM and DNA-PKcs, and by enhancing DNA fragmentation via the cleavage of I^{CAD}, an inhibitor of a nuclease capable of fragmenting DNA. One pathway leading to apoptosis, and probably the pathway that plays the major role following IR, involves the bax/bcl2 family (Adams, 2003), of which at least 15 members have been described. Bcl2 itself, first identified by its presence at a chromosomal translocation break site in B-cell lymphomas, is an anti-apoptotic protein, whilst Bax, with which it can dimerise, is a pro-apoptotic protein. Bcl2 family members regulate the release of cytochrome C from the mitochondria, which serves to activate caspases through an interaction with Apaf1 (Cory and Adams, 2002). Other routes to apoptosis involve death receptor proteins that activate death ligands, which in turn activate caspases (Ashkenazi, 2002).

3.4. Fidelity of DSB repair

(106) A crucial consideration for radiation protection is the level of fidelity with which DSBs are rejoined and the impact of error-prone rejoining. In this context, several factors are important: (1) the inherent fidelity achievable by the distinct DSB rejoining mechanisms; (2) the fate of unrejoined and misrejoined breaks; and (3) the ability of radiation damage to undergo accurate repair compared with other forms of DNA damage, particularly endogenous damage. These three issues are discussed below.

3.4.1. The fidelity achievable by HR and NHEJ

(107) HR is clearly a high fidelity process utilising sequence information from an undamaged template to repair coding information lost at a break site. The level of fidelity achievable by NHEJ, for either simple breaks or complex breaks, is still an open question. One difficulty in evaluating the studies on fidelity is that restriction enzymes are frequently used to induce DSBs, and these may be repaired with different fidelity to radiation-induced DSBs. Studies in *S. cerevisiae* have examined the fidelity of rejoining simple restriction-enzyme-induced breaks in the presence and absence of the individual NHEJ components. From these studies, it has been concluded that Ku-dependent NHEJ is an accurate process that can act as a barrier to an alternative error-prone end-joining mechanism (Boulton and Jackson, 1996). Recently, a

study examining repair of a transposase-induced DSB in mammalian cells also concluded that NHEJ was normally accurate (van Heemst et al., 2004).

(108) As discussed previously, the NHEJ pathway is also used during V(D)J recombination. The rejoining of these V(D)J breaks can also provide information on the accuracy of the process in mammalian cells. Although the coding joints generated during V(D)J recombination are rejoined inaccurately due to specific processing unique to lymphoid cells, the signal junctions are rejoined accurately (Gellert, 2002). In cell lines lacking components of the NHEJ machinery, both the frequency and fidelity of signal joint formation is dramatically reduced (O'Driscoll et al., 2001; Riballo et al., 2001; Taccioli et al., 1993). This suggests that for these types of breaks, if rejoining is compromised, the ends are subjected to nuclease digestion and repair is inaccurate. This suggests that NHEJ has the ability to rejoin a blunt-ended break accurately and, indeed, does so predominantly.

(109) However, the repair of radiation-induced breaks may be more demanding than the repair of the breaks discussed above. Many of the radiation-induced breaks may represent non-ligatable ends or ends that require additional processing prior to ligation. One approach that has been used to assess the fidelity of radiation-induced breaks during NHEJ is a technique that monitors the misrepair of DSBs by PFGE, a procedure that separates large DNA fragments (of the order of 10^6 base pairs) on the basis of size (Rothkamm et al., 2001). To assess the fidelity of rejoining, the gels were probed using a large unique DNA fragment generated by digestion of genomic DNA using a rare cutting restriction enzyme. Following radiation exposure, the unique restriction fragment became a smear of smaller size due to the presence of DSBs within it. Following incubation to allow repair, the band was recovered representing accurate repair. It was argued that whilst fragments smaller than the anticipated size could arise from either inaccurate rejoining or lack of rejoining, fragments larger than the anticipated size could only arise by misrejoining. When the experiment was carried out following exposure to a high dose (80 Gy), significant misrepair could be seen. Although a limitation of this technique is that it necessarily involves the use of high doses, the results demonstrate that, under such conditions, NHEJ has the potential to rejoin breaks inaccurately. Studies with NHEJ-deficient cells further suggest that the observed misrepair is, in fact, mediated by the NHEJ pathway. Using the same technique, misrepair was also examined following 80 Gy delivered at a low dose rate where radiation-induced DSBs would be less likely to be in close proximity to one another in both space and time. Under these conditions, much less detectable misrepair was observed. Taken together, these findings suggest that the accuracy of NHEJ may be influenced by the presence of neighbouring breaks, and suggest that the process has the potential to be of higher fidelity when few breaks are present in any one cell, but that its fidelity may be compromised when many breaks arise independently. Interestingly, similar experiments carried out following exposure to alpha particles showed that there was no reduction in misrepair with increasing fractionation (Kuhne et al., 2002). These data are consistent with dose and dose-rate data for the induction of chromosome alterations following exposure to IR where effects are significantly reduced for low-dose-rate exposures. It is important to note, however, that these data show that misrepair can occur at high dose

rates. They still leave open the question of whether misrepair can occur at low dose rates and doses. Exposure of mammalian cells to IR causes a linear dose-dependent increase in chromosome breaks, gaps, and re-arrangements at relatively low doses and low dose rates. Making the reasonable assumption that chromosomal re-arrangements represent erroneous DSB-rejoining events, such data would argue for misrepair mediated via the NHEJ machinery even under conditions where the distribution of radiation-induced DSBs are not in close proximity in space and time. This argument, while strong, cannot be directly tested experimentally at this time.

(110) Cells lacking components of the NHEJ machinery (e.g. xrs-6 cells) show elevated radiation-induced chromosomal aberrations relative to normal cells (Darroudi and Natarajan, 1989; Kemp and Jeggo, 1986). This suggests that in the absence of Ku, a lower fidelity rejoining process takes place. Although this finding does not directly address NHEJ fidelity, it does strongly suggest that there is elevated infidelity in the absence of Ku. In other words, Ku serves to promote accurate rejoining.

(111) Finally, recent studies have also provided evidence for a process of rejoining DSBs that involves rejoining of the breaks to dysfunctional telomeres (Bailey et al., 2004; Latre et al., 2003). These studies thus open a new pathway for misrepair that represents DSB–telomere fusions and could represent an important cause of genomic instability induced by radiation (Urushibara et al., 2004).

3.4.2. The fate of unrejoined and misrejoined breaks

(112) The role of cell-cycle checkpoints is to prevent the proliferation of damaged cells. It has been argued that a single unrejoined DSB is lethal to a cell. From the perspective of a multicell organism, this may not be unduly harmful. However, a misrejoined break may not be recognised by a cell, and therefore may pose a bigger threat as a potential oncogenic lesion. Failure of cell-cycle checkpoint control coupled with impaired DSB repair will, however, pose a particular risk. In this light, patients such as A-T and NBS patients, where the defects impair both DNA repair mechanisms and cell-cycle checkpoint control, display significant cancer predisposition. Similarly, the combination of p53 mutations with mutations in essential DNA repair genes (such as DNA ligase IV) promotes survival at the expense of elevated tumour predisposition (Zhu et al., 2002). In this light, the ability of low doses of radiation to affect cell-cycle checkpoint control is particularly important to evaluate.

3.4.3. The impact of the nature of DNA damage on repair

(113) As described in Section 3.2, the damage induced by IR is distinct from endogenous ROS-induced damage in its complexity. SSBs are repaired accurately and rapidly, and there are an array of glycosylases that recognise and initiate the excision of specific damaged bases (Scharer and Jiricny, 2001; Slupphaug et al., 2003). It is important to point out, however, that although ROS-induced damage may not directly induce DSBs, it is likely that DSBs do arise endogenously, potentially through the processing or replication of other lesions. It is also likely that such breaks will have ends that require processing prior to rejoining. The major evidence suggesting that

DSBs arise spontaneously is that cells lacking either NHEJ or HR components display elevated instability (Difilippantonio et al., 2000; Karanjawala et al., 1999).

(114) The repair of complex lesions induced uniquely by IR may pose a problem for the DNA repair machinery. Studies are now emerging on how one type of damage influences the repair of another. The current evidence suggests that the ability of glycosylases to recognise and remove a damaged base is impeded by the presence of a nearby nick on the opposite strand (David-Cordonnier et al., 2000, 2001). Since clustered base damage arises frequently after irradiation, a considerable number of additional DSBs could arise if clustering of base damage inhibits repair (Gulston et al., 2004). How the presence of a nick or damaged base affects DSB repair is entirely unknown.

(115) Classical analysis of postirradiation cell survival has also provided evidence that the highly complex lesions induced by high-LET radiation are less reparable than low-LET radiation. Most specifically, cells lacking Ku (e.g. xrs-6) are more sensitive compared with wild-type cells to low-LET radiation than to high-LET radiation, consistent with the notion that high-LET radiation has a higher non-reparable component (Thacker and Stretch, 1985). These studies have been discussed in detail in previous ICRP and UNSCEAR reports, and will not be discussed further here.

(116) As mentioned above, ROS-induced damage and the damage induced by IR frequently have damaged termini, precluding their repair by direct ligation. Recently, polynucleotide kinase (PNK), a protein that has both DNA kinase and DNA phosphatase activities, has been found to be associated with Xrcc1, one of the proteins involved in SSB repair (Whitehouse et al., 2001). Furthermore, Xrcc1 can stimulate the activity of PNK. Thus, the damaged 3′ end, which cannot be subjected to direct ligation, is first processed by PNK in the presence of Xrcc1, which then co-ordinates gap filling, if necessary, by an interaction with DNA polymerase β followed by subsequent ligation (Caldecott, 2002). This important finding demonstrates how cells use their resources to co-ordinate repair involving several distinct steps. However, these damaged termini frequently arise endogenously, which has likely provided a strong selective pressure to drive the evolution of this co-ordinated repair process. This may not be the case for other, more complex lesions unique to IR.

3.5. Impact of defects in DNA repair, checkpoint control, and apoptosis

(117) Disruption of the NHEJ components in mice results in varied phenotypes: loss of XRCC4 and DNA ligase IV causes embryonic lethality; Ku-defective mice senesce prematurely; and DNA-PKcs-defective mice grow and develop normally although manifesting severe combined immunodeficiency (Bosma et al., 1983; Frank et al., 1998; Gu et al., 1997; Nussenzweig et al., 1996). Significantly, however, DNA-PKcs-defective mice have only a small elevated incidence of spontaneous cancer. The situation with Ku is exceptionally unclear; Ku80-defective mice display no elevated tumour incidence, whereas Ku70-defective mice develop a high incidence of lymphomas. Thus the impact of the loss of NHEJ on tumour incidence in mice remains to be resolved. A defect in DNA ligase IV has been identified in a leukaemia patient who was normal until the onset of leukaemia at 14 years of age (Riballo et al., 1999). The

mutation identified in this patient significantly decreased but did not ablate ligation activity. This suggests that impairment of NHEJ can be compatible with life, and confers significant radiosensitivity without overt immunodeficiency. More importantly, the defect may confer leukaemia predisposition. The fact that this patient has decreased activity rather than totally ablated activity may be significant.

(118) Haplo-insufficiency of ligase IV has been shown to result in an increased incidence of sarcoma in ink4a/arf-/- mice (Ferguson et al., 2000; Sharpless et al., 2001). Decreased but not ablated DNA-PKcs activity has also been associated with increased sensitivity to radiation-induced lymphomas (Mori et al., 2001) and mammary tumours (Yu et al., 2001) in mice, and lung and colon cancer in humans (Auckley et al., 2001; Rigas et al., 2001). It has been hypothesised that because of the importance of the NHEJ pathway, complete loss of function of one of the components in this pathway may result in a low frequency of tumours because of significant problems with genomic integrity and stability. Cells with such significant problems would manifest substantial genomic damage and would likely be eliminated by the cell cycle and apoptotic response pathways before having the opportunity to progress to become tumours. On the other hand, with less severe defects in this pathway, the cellular effects would be less severe and it would be more likely that cells with less severe forms of damage could escape elimination (Ferguson et al., 2000).

(119) Recent evidence suggests that defects in checkpoint control or apoptosis confer a very different phenotype with significantly elevated cancer predisposition. Mice defective in p53 display elevated spontaneous tumour formation, both in the homozygous and heterozygous state. Recently, CHK2 was identified as the germline tumour suppressor loci of a small number of Li-Fraumeni families that did not have TP53 mutations. Both A-T and NBS patients display significantly elevated tumour incidence. BRCA1 and BRCA2 defects are associated with cancer predisposition. Taken together, this suggests that whilst lack of repair may simply enhance sensitivity, failure to arrest at a cell-cycle checkpoint or failure to undergo apoptosis may result in elevated carcinogenesis. The impact of these processes for radiation protection is two-fold. Firstly, although the effect of low-dose irradiation on DNA repair has been investigated, almost nothing is known about the impact of low doses on cell-cycle checkpoint arrest. Secondly, the variation in these responses between individuals is not known.

(120) It has been proposed recently that a low-dose threshold could result, not from the absence of DSBs and complex lesions at very low doses, but from the absence of repair; i.e. affected cells are unable to replicate and therefore do not contribute to carcinogenesis. That is, the affected organism, or tissue, may be genetically programmed to tolerate a certain amount of cell loss as a means of minimising the risk of mutation and cancer due to DNA misrepair. A recent study by Rothkamm and Löbrich (Bonner, 2003; Rothkamm and Löbrich, 2003) involved the irradiation of cultures of non-dividing primary human lung fibroblasts with 90 kV x rays at doses ranging from 2 Gy to 0.1 mGy. Numbers of DSBs formed were measured by immunofluorescence of foci of the phosphorylated histone γ -H2AX. The investigators found that the number of DSBs formed was linear with radiation dose, but that

DSBs induced at 1.2 mGy (0.1 foci/cell compared with 0.05 foci/cell among controls) remained unrepaired for many days, in contrast to efficient DSB repair following exposure at higher doses (0.66 and 0.22 foci/cell at 20 mGy and 5 mGy, declining to 0.1 foci/cell after 24 h). However, there is some question about the extent to which the assay can be relied upon to quantify DSB frequency following radiation exposure. For example, in this study, the assay indicated a surprisingly high frequency, and persistence over time, of DSBs in control cells, and a high persistence of radiation-related DSBs following high-dose exposure compared with findings from split dose experiments. It has been demonstrated that those proteins involved in DSB rejoining, including H2AX, translocate substantial distances along the DNA from the break, implicating other functions for these proteins (Rogakou et al., 1999). Also, Petrini and Stracker (2003) noted that although late foci of DSB repair proteins and γ -H2AX appear to be genuine reflections of DSB metabolism, it is problematic to use them to draw inferences about recruitment to DSB sites because the vast majority of DSBs are repaired by 90 min after their induction. A more recent application of the -H2AX foci assay to in vivo formation and repair of DNS DSB after computed tomography examinations found no evidence of compromised repair capacity at low radiation doses (Löbrich et al., 2005). There is also some question whether the DSBs examined by Rothkamm and Löbrich were direct or indirect effects of radiation exposure (Seymour and Mothersill, 2004). Thus, the implications of this intriguing study for low-dose risk are not yet clear.

3.6. Conclusions

(121) IR is able to produce a unique type of damage in which multiple lesions are encountered within close spatial proximity. Even a single track of IR through a cell is likely to induce these unique clustered damages. This type of damage is unlikely to be frequently generated endogenously or by other exogenous agents, and thus there may not have been a strong selective pressure driving efficient repair. Although cells have a vast array of damage response mechanisms that facilitate the repair of DNA damage and the removal of damaged cells, these mechanisms are not foolproof. Moreover, clustered radiation-induced lesions pose a particular problem, and currently emerging evidence suggests that closely spaced lesions can compromise the repair machinery. On this basis, there is no strong evidence for a radiation dose below which all radiation-induced damage can be repaired with fidelity. Whilst many of the cells containing such radiation-induced damage may be eliminated by damage response pathways involving cell-cycle checkpoint control and apoptotic pathways, it is clear from analysis of cytogenetics and mutagenesis that damaged or altered cells are capable of escaping these pathways and propagating. This further argues against the likely possibility of a threshold for radiation-induced cellular effects.

4. CELLULAR CONSEQUENCES OF RADIATION-INDUCED DAMAGE

(122) The misrepair of radiation-induced DNA DSBs and other lesions is believed to be the principal pathway for the induction of chromosome and gene alterations responsible for the killing, mutagenic, and carcinogenic effects of IR. Studies focusing on cytogenetic damage and mutagenesis were among the earliest quantitative measures of the cellular effects of IR (Sax, 1938).

(123) On a practical level, such studies have provided considerable information on dose–response relationships over a wide range of doses and on the effects of dose rate and fractionation (NCRP, 1980). On a more fundamental level, these studies have provided a substantial amount of information relevant to DNA damage after radiation, repair kinetics, and underlying mechanisms. Due to the close mechanistic relationship between chromosome aberrations, mutations, and cancer (UNSCEAR, 2000), such studies also have particular relevance to radiation risks and the question of risks at low doses.

4.1. Radiation-induced chromosome aberrations

(124) The first documented account of the cytogenetic effects of x rays described the production of dicentrics, centric rings, and deletions in plant microspores irradiated in the extended G1 phase (Sax, 1938). Using the standard staining technique, it was very difficult to observe reciprocal translocations and inversions; these aberrations are the most common in tumours of different types. This latter fact is the consequence of reciprocal translocations and inversion being transmissible from cell generation to generation, whereas dicentrics, centric rings, and deletions are cell lethal as a result of the loss of genetic material at cell division. The ability to analyse all types of chromosome aberrations has been greatly enhanced by the use of fluorescence in situ hybridisation (FISH), which is discussed in more detail below.

(125) The early studies by Sax et al. (1955) also demonstrated that the dose–response curve for dicentric aberrations fit a linear-quadratic model ($Y = \alpha D + \beta D^2$), suggesting that some dicentic exchanges were produced by one ionisation track (αD) and some by two independent tracks (βD^2). Neutrons induced the same types of chromosome aberrations, but in contrast the dose–response curve for dicentrics was linear, indicating a one-track mechanism of formation. The prediction, based on the proposed mode of formation of aberrations, was that chronic exposures to x rays would produce all types of aberrations linearly with dose, and that split doses would lead to lower aberration frequencies than the same dose given as a single exposure. These predictions were borne out in experiments with Tradescantia microspores (Sax et al., 1955), and have, of course, been confirmed in an expansive range of studies covering many cell types and species. Some of the most comprehensive studies examining low doses of radiation were those of Lloyd et al. (1992). A further prediction from these studies is that over a low dose range (and for low dose rates), the dose–response curve for chromosome aberrations is linear (αD) and time (i.e. dose rate) independent because the one-track mechanism dominates the response. Thus, the linear slope for low-dose and low-dose-rate exposures in this dose

range would be the same. This has been borne out in careful studies of the induction of chromosome aberrations over a range of dose rates to specifically test the prediction of a limiting slope at low doses and low dose rates (Cornforth et al., 2002).

(126) While details of mechanisms involved in the formation of chromosome aberrations remain under investigation, the current view is that the majority of radiation-induced chromosome aberrations are produced by the misrepair of DNA DSBs, quite possibly those involved in complex DNA lesions (multiply damaged sites). The observations presented above with respect to low-dose linearity would support this view. The repair of DSBs (described in Chapter 3) is performed by NHEJ and HR; the former is the prevalent mechanism in mammalian cells. In some cases, the pairs of DSBs required for the formation of chromosome aberrations by misrepair are produced by one or more electron tracks from a single photon, and in other cases, by two or more tracks from different photons. While DSBs are generally presumed to be produced linearly with dose for low-LET radiations, the probability of conversion into chromosome aberrations is not established. The probability of conversion will depend upon the probability of misrepair and the overall kinetics of DSB repair, and it is likely to be linear with dose given the predictable one-track/two-track nature of the dose–response curve for chromosome aberrations.

(127) The development of FISH techniques has allowed assessment of the non-lethal reciprocal chromosomal events, i.e. reciprocal translocations and pericentric inversions, as well as complex events involving multiple chromosomal exchanges that would not typically be identified by conventional staining. The dose–response relationship for reciprocal translocations is quite similar to that for dicentrics, discussed above, and involves a one-track and a two-track process (Camparoto et al., 2003). Thus, the effects of dose rate and dose fractionation are also similar to those described above for dicentrics. Low dose linearity is observed for acute and chronic low-LET exposures.

(128) The 'complex exchanges' observed with FISH are often considerably more complex than previously thought. These complex exchanges can involve multiple interactions among several chromosomes. Such complex aberrations constitute a large fraction of aberrations observed after exposure to high-LET radiations, and the fraction does not appear to vary with dose. For low-LET radiation, the fraction of complex aberrations is more dose dependent. At relatively high doses (2–4 Gy), the fraction is high, and the fraction of complex aberrations is substantially lower but still present at low doses. More precise data on the dose–response relationship and dose-rate effects for these complex aberrations at low doses will be forthcoming from ongoing studies over the coming years. The mechanisms underlying these complex aberrations are not yet clear and are under investigation. They do appear to involve interactions between sites of complex DNA damage of the type particularly prevalent after exposure to high-LET radiation. Such damage is much less prevalent as a result of low-LET irradiation, but is still present even at low doses. The significance of these complex exchanges in mutagenesis and carcinogenesis is also unclear. Many of them are probably lethal and therefore not likely to impact such endpoints. However, certain complex aberrations are potentially transmissible and could have a significant impact on mutagenesis, carcinogenesis, and the initiation of genomic

instability. As a result, understanding of the mechanisms involved in the development of these complex aberrations may provide important information relevant to low-dose risks.

(129) Thus, the prevailing view is that chromosome aberrations of all types result from the interactions of pairs (or greater number) of DNA lesions. These lesions can be induced by a single track or by combinations of two or more tracks. However, there is a possible exception to this general rule. Griffin et al. (1996) assessed the efficiency of 1.5 keV aluminum x rays at inducing complex chromosome aberrations (requiring three or more interacting lesions for their formation). Based upon the rather high efficiency of this process, the authors suggested that damaged DNA could interact with undamaged DNA to produce some of the aberrations. A proposed mechanism, similar to the production of recombinations during meiosis (Szostak et al., 1983), is not supported by data developed by Cornforth (1990) who concluded that a one-hit exchange was unlikely to occur, although it could not be ruled out at low doses. The impact of a one-hit exchange process on the shape of the dose–response curve at high doses and the exchange yields at low doses is readily apparent; a steeper slope than that described by the αD component of the linear-quadratic equation would be predicted. The question of its likelihood requires further study.

(130) Additional details of the mechanisms of formation of chromosome aberrations and the relevance of their distribution among and within cells to low-dose responses can be found in NCRP Report No. 136 (2001). These data and those presented above support the conclusion that at low doses of high- or low-LET radiation, the dose–response curves for chromosomal aberrations are linear. Predictions can be made for threshold responses, but the existing data do not support or refute them. The same conclusion applies for supralinear low-dose responses.

4.2. Radiation-induced somatic cell mutations

(131) Radiation is capable of inducing a wide spectrum of mutations, from point mutations in single genes to deletions that encompass several physically linked genes (UNSCEAR, 2000). The nature of mutation assays limits the ability to detect large deletions in certain genes because of their close linkage with sequences that are essential for survival of the cell. With this complicating factor in mind, most molecular evidence indicates that DNA deletions resulting in gene loss are the primary events responsible for the mutagenic effects of IR (UNSCEAR, 2000). It is also important to note, in this regard, that when data are available, a close relationship between radiation-induced mutations and chromosome aberrations has been found (UNSCEAR, 2000). This spectrum differs from spontaneous mutations, mutations induced by ultraviolet light, and many chemical mutagens where the majority of mutations are a result of point mutations (UNSCEAR, 2000). Interestingly, radiation-induced point mutations tend to occur randomly throughout a gene while spontaneous mutations tend to be clustered at specific sites (Grosovsky et al., 1988; Nelson et al., 1994). The data indicating a predominance of deletion-type mutations, and the distribution of

point mutations, suggest differences between underlying damage induced by IR compared with that from endogenous processes.

(132) Mutagenesis is essentially a result of the attempts of the cell to repair damage, and analyses of induced mutations can provide clues about mechanisms involved. Sequence analyses of radiation-induced deletion-type mutations have revealed that, as in the case of radiation-induced chromosome aberrations, the mutations are much more complex than originally thought. Deletions often include inversions and insertion of genetic sequences from other chromosomes, and frequently involve short direct or inverted DNA repeat sequences (Morris and Thacker, 1993; Morris et al., 1993; Thacker, 1986). Overall, these analyses support DSBs as an important initiating lesion in the pathogenesis of the large deletions characteristic of IR, and the involvement of DNA DSB repair pathways in the mutagenic process (UNSCEAR, 2000). The presence of repeat sequences suggests that illegitimate recombination associated with DSBs is often responsible for the mutagenic process when large deletions are involved. Limited studies with cells defective in specific repair pathways also suggest an important role for DNA DSB repair in the mutagenic effects of IR (UNSCEAR, 2000). While DSBs are more difficult to repair with fidelity than base damage, radiation-induced base damage is also important. It is clear that base damage can often lead to base substitutions (point mutations) and that certain repair pathways involved in base damage repair can be mutagenic.

(133) Quantitative studies on dose–response relationships for the induction of mutagenesis can be more complicated than studies of chromosome aberrations, with considerable variation depending upon the nature of the mutations that can be assayed in each system, genetic background, tolerance for large genetic changes such as deletions, and sensitivity of the system. In systems that have sufficient sensitivity to examine effects at relatively low doses, either linear or linear-quadratic dose–response relationships have been reported when a wide dose range has been examined (UNSCEAR, 2000). In either case, in the low-dose region, data are consistent with a linear dose–response relationship. This linear response is consistent with current models of mechanisms of mutagenesis involving DNA damage and its processing. Such a linear dose–response relationship has been observed down to $\sim$200 mGy by Thacker et al. (1992).

(134) Studies of the effects of dose rate are more complex. In most systems, the effectiveness of low-LET radiation at doses greater than 1 Gy is reduced, at low dose rates, by a factor of 2–4; however, there are data in which the effectiveness has remained the same or even increased after low-dose-rate exposures (Thacker et al., 1992). For example, no dose-rate effect or even an inverse dose-rate effect is observed in TK6 and other DNA-repair-deficient human cells and in many rodent cell lines at very low dose rates (Amundson and Chen, 1995, 1996; Vilenchik and Knudson, 2000). These dose-rate data are consistent with expectations when repair plays a major role in mutagenesis. Cells defective in DNA repair capacity are likely to have little dose-rate effect, and inverse dose-rate effects may be anticipated in cells with defects in damage response pathways at low dose rates (Thacker et al., 1992; UNSCEAR, 2000). A systematic study of this hypothesis would be important in clarifying mutagenic risks following protracted exposures.

4.2.1. Summary

(135) The processing and misrepair of radiation-induced DSBs, particularly complex forms, are principally responsible for chromosome/gene alterations that manifest as chromosome aberrations and mutations. Current understanding of mechanisms and quantitative data on dose and time–dose relationships support a linear dose–response relationship at low doses with no compelling evidence for the existence of a threshold dose below which there would be no effect.

4.3. Adaptive response, genomic instability, and bystander effect

(136) Recently, studies on the induction of so-called 'bystander effects' in cells that have not been directly irradiated, and the development of genomic instability in the non-irradiated progeny of irradiated cells many generations after exposure, have served to challenge the conventional view that only those cells directly traversed by radiation are targets for cellular effects of radiation, including cell killing, and the induction of chromosomal aberrations and mutations. In addition, the assumption that multiple exposures at low doses are additive has come into question as a result of studies demonstrating an adaptive response in certain cells following low-dose exposures. The concept of additivity is a result of the view that, following repair, a cell will respond similarly to a second exposure as it did to the first. Studies demonstrating an adaptive response, however, suggest that this may not always be the case; the induction and/or activation of genes likely to be involved in damage response pathways can influence, positively or negatively, the response to subsequent exposures. If these three phenomena occur in vivo, they could impact in particular on the shape of the dose–response curve for low-dose, low-dose-rate exposures in human populations.

4.3.1. Adaptive response

(137) The adaptive response was first described for chromosomal aberrations (Olivieri et al., 1984). It was observed that pre-exposing cells to a low 'priming' dose of radiation appeared to protect these cells from the effects of a second, larger 'challenging' dose. This effect was demonstrated most clearly in human lymphocytes, where a decrease of up to 50% in the frequency of aberrations induced by the challenging dose has been observed in cells pretreated with a small priming dose (Sugahara et al., 1992; Wolff, 1996). Since the appearance of the initial report over 20 years ago, literally hundreds of reports have been published describing this phenomenon in various experimental systems and for various endpoints, including micronucleus formation, mutations, and neoplastic transformation; many of these were reviewed in 1994 by UNSCEAR. Despite all of this research, the mechanisms for this phenomenon remain unclear, in contradistinction to the adaptive response to alkylation damage (Lindahl et al., 1988). The effect is not consistently seen in all cell types, and there has been considerable donor variation in studies with lymphocytes of individual humans and different strains of rodents. No or very little adaptive response

has been observed after prenatal radiation exposures (Streffer, 2004). The adaptive response is very limited after exposure to high-LET radiation.

(138) In earlier studies of the adaptive response to chromosomal aberrations in lymphocytes, low-dose-rate exposure from tritiated thymidine was used as a priming dose, although it was later shown that an acute exposure to x rays would also trigger the effect (Shadley and Wiencke, 1989). Priming doses of 5–100 mGy are generally required to induce the protective effect (Sasaki, 1995; Shadley and Wiencke, 1989). These doses are high enough to produce significant damage in all irradiated cells. Adaptation takes place within 3–6 h when the cells become resistant to the larger challenge dose, usually 1 Gy or higher. Gap-junction-mediated intercellular communication has been implicated in this process (Ishii and Watanabe, 1996). The magnitude of the effect depends on many factors including dose, dose rate, cell and tissue type, and the endpoint measured.

(139) The mechanisms for the effect remain unclear. It is now known that low doses of radiation can modulate the expression of a variety of genes (e.g. Hallahan et al., 1991; Leskov et al., 2001; Sasaki et al., 2002). Sasaki et al. (2002) found that p53 appeared to play a key role in the adaptive response, while the DNA-PKcs, ATM, and FANCA genes were not involved. They proposed that the adaptive response and apoptosis constitute a complementary defence mechanism. It has also been reported that the induction of heat shock proteins may be involved in the adaptive response (Kang et al., 2002; Lee et al., 2002).

(140) While it has been hypothesised that the phenomenon reflects the induction of some type of DNA repair process that requires a certain level of damage in the cell, no such inducible DNA repair mechanism for DNA strand breaks has been clearly demonstrated in mammalian cells. Restriction enzymes that produce DNA DSBs will induce adaptation in human lymphocytes (Wolff, 1996), and the rate of repair has been reported to be more efficient in adapted cells (Ikushima et al., 1996). Evidence has been presented to suggest the involvement of DNA repair in the adaptive response in yeast (Dolling et al., 2000), and Haber and colleagues (personal communication) have shown that when a single DSB is introduced in budding yeast cells synchronised in G1, the cells become significantly resistant to a challenge dose of MMS (methyl methane sulphonate) applied approximately 6 h later during the discrete period when repair is taking place. It is of interest in this context that the inducible repair of thymine glycols by the base excision repair process has been described (Le et al., 1998). Generally, however, DNA base damage is not thought to be the principal mechanism for the induction of mutations and chromosomal aberrations by IR. It has also been proposed that the priming dose may lead to persistent free radical activation as part of the postirradiation cellular stress response that includes the upregulation of genes associated with signal transduction and cell-cycle control (Bravard et al., 1999).

(141) A number of reports have presented evidence for an adaptive response for the induction of specific gene mutations (Kelsey et al., 1991; Rigaud et al., 1995; Sanderson and Morley, 1986; Zhou et al., 1994). In general, the mutation frequencies induced by relatively high radiation doses have been shown to be decreased by approximately 50% if the exposure is preceded by a priming dose of approximately

10 mGy 5–24 h previously. These experiments have been carried out in various different systems, although generally but not exclusively with cells of lymphoid origin (lymphocytes, established lymphoblastoid cell lines, and a human T-cell leukaemia cell line). The adaptive exposure to radiation may also decrease the frequency of neoplastic transformation either arising spontaneously or induced by a subsequent high radiation dose (Azzam et al., 1994; Redpath and Antoniono, 1998; Redpath et al., 2001, 2003). Adaptive responses have been described in human tumour cells with irradiation protocols closely resembling clinical applications (Smith and Raaphorst, 2003).

(142) Evidence is emerging for the occurrence of adaptive phenomena in vivo. These include the induction of leukaemia and lymphoma (Bhattacharjee and Ito, 2001; Ishii et al., 1996; Mitchel et al., 1999, 2003), as well as the development of heritable germline mutations (Somers et al., 2002). In one study (Bhattacharjee, 1996), pre-irradiating mice with five repeated exposures of 10 mGy/day appeared to significantly reduce the incidence of thymic lymphoma induced by a challenge dose of 2 Gy. It has been reported that short-term low-dose occupational exposures may act as an in-vivo adaptive dose for the induction of micronuclei by in-vitro irradiation of lymphocytes (Thierens et al., 2002).

(143) The adaptive response shares some similarities with the phenomenon of 'low dose hypersensitivity' described by Joiner et al. (1996), based on the multiphasic shape of the single dose survival curve for some mammalian cell lines. They observed a steep decline in cell survival in the low-dose range, followed by a plateau which they hypothesised represented induced radioresistance. In a recent study (Short et al., 2001), cells displaying a strong hypersensitivity response showed increased killing following multiple low-dose exposures. Similar to the adaptive response, it has been proposed that the phenomenon may represent the manifestation of inducible processes facilitating the repair of DNA damage (Joiner et al., 2001; Marples and Joiner, 2000). In two quite different experimental systems for the study of malignant transformation in vitro, evidence has been presented that the spontaneous transformation frequency is actually reduced by very small doses of radiation (doses as low as 1 mGy) (Azzam et al., 1996; Redpath et al., 2001, 2003). The frequency of transformation rose rapidly at higher doses.

(144) Despite such provocative findings, there are still many questions concerning the adaptive response (Stecca and Gerba, 1998; Wolff, 1998). The response for chromosomal damage has been shown to vary with the donor, with some individuals being unresponsive and others showing a synergistic effect (Bosi and Olivieri, 1989). The same is true for different cellular systems and for other biological endpoints such as cell survival (Boothman et al., 1996; Short et al., 1999; Sorensen et al., 2002). In the absence of firm knowledge of molecular mechanisms, it is difficult to evaluate the potential significance of the adaptive response for the risk from exposure to IR in human populations. Clearly, the phenomenon appears to be real in many cellular systems, and could influence the response to protracted radiation exposure. It will be important, however, to determine the extent to which it is active in vivo at relevant dose and dose-rate levels for human exposures before it can be considered as a factor in risk estimation.

(145) Adaptive responses including those in relation to radiation-induced cancer and stimulatory effects on the immune system were reviewed comprehensively by UNSCEAR in 1994, and some aspects were revised in 2000. The general conclusion from these reports was that there was insufficient information on the role and mechanisms of adaptive responses to influence judgements on low-dose cancer risk. Recent animal carcinogenesis studies relating to adaptive responses (Mitchel et al., 1999, 2003) raise the possibility that adaptive-like responses may increase tumour latency whilst having no effect on lifetime risk. These data are of scientific interest but remain of rather uncertain relevance to radiological protection. The present knowledge demonstrates that the adaptive response is very variable, it is dependent on the genetic disposition of an individual, and it apparently does not (or only to a little extent) occur during prenatal development or after exposure to high-LET radiation. Therefore, taking account of the adaptive response does not appear to be appropriate for a universal system of radiological protection.

4.3.2. Radiation-induced genomic instability

(146) The term 'radiation-induced genomic instability' refers to a phenomenon observed in a number of different cellular systems whereby radiation exposure appears to induce a type of instability in individual cells that is transmitted to their progeny, leading to a persistent enhancement in the rate at which genetic changes arise in the descendants of the irradiated cell after many generations of replication. The genetic endpoints studied have included malignant transformation, chromosomal aberrations, specific gene mutations, and cell survival. Typically, this phenomenon has been studied by examining the occurrence of such genetic effects in clonal populations derived from single cells surviving radiation exposure (Little, 2003), although some studies have relied upon the postirradiation analysis of cells in mass culture rather than clonal isolates.

(147) Early evidence for the existence of such a phenomenon was derived from an examination of the kinetics of radiation-induced malignant transformation of cells in vitro (Kennedy and Little, 1984; Kennedy et al., 1980; Sinclair, 1964). These results suggested that transformed foci did not arise from a single radiation-damaged cell. Rather, radiation appeared to induce a type of instability in 20–30% of the irradiated cell population; this instability enhanced the probability of the occurrence of a second neoplastic-transforming event. This second event was rare, occurring with a frequency of approximately 10^{-6}, and involved the actual transformation of one or more of the progeny of the original irradiated cells after many rounds of cell division. This transforming event occurred with constant frequency per cell per generation, and had the characteristics of a mutagenic event (Kennedy et al., 1984). Thus, neoplastic-transformed foci did not appear to arise from the original irradiated cell but rather from one or more of its progeny. These findings were consistent with the hypothesis that radiation induces genetic instability in cells, that enhances the rate at which malignant transformation or other genetic events occur in descendants of irradiated cells after many generations of cell replication.

(148) This hypothesis has since been confirmed in a number of experimental systems for various genetic endpoints (Baverstock, 2000; Little, 1998; Morgan, 2003a; Morgan et al., 1996; Pampfer and Streffer, 1989; Romney et al., 2001a). In terms of mutagenesis, approximately 10% of clonal populations derived from single cells surviving radiation exposure showed a significant elevation in the frequency of spontaneously arising mutations compared with clonal populations derived from non-irradiated cells (Chang and Little, 1992; Little et al., 1997). This increased mutation rate persisted for approximately 30 generations after irradiation, then gradually subsided. Interestingly, the molecular structural spectrum of these late-arising mutants resembles that of spontaneous mutations in that the majority of them are point mutations (Grosovsky et al., 1996; Little et al., 1997), indicating that they arise by a different mechanism from that of direct x-ray-induced mutations that primarily involve deletions. An enhancement of both minisatellite (Li et al., 1992) and microsatellite (Romney et al., 2001b) instability has also been observed in the progeny of irradiated cells selected for mutations at the thymidine kinase locus, which is further evidence that a subpopulation of genetically unstable cells arises in irradiated populations. It is of interest that instability as measured in minisatellite sequences of x-ray-transformed mouse 10T1/2 cells was markedly enhanced when the cells were grown in vivo compared with prolonged cultivation in vitro (Paquette and Little, 1994).

(149) An enhanced frequency of non-clonal chromosomal aberrations was reported in clonal descendants of mouse haematopoietic stem cells examined 12–14 generations after exposure to alpha radiation (Kadhim et al., 1992). Persistent radiation-induced chromosomal instability has since been demonstrated in a number of other cellular systems (Holmberg et al., 1993; Kadhim et al., 1995; Little et al., 1997; Marder and Morgan, 1993; McIlrath et al., 2003; Ponnaiya et al., 1997; Sabatier et al., 1992). Susceptibility to radiation-induced chromosomal instability differs significantly among cells from different strains of mice (Ponnaiya et al., 1997; Watson et al., 1996a), and similar differences in genetic susceptibility to radiation-induced chromosomal instability have been observed in primary human fibroblasts (Kadhim et al., 1998).

(150) It is now clear that genomic instability, both chromosomal and mutational, can be induced by high- or low-LET radiation (Belyakov et al., 1999; Evans et al., 2001; Limoli et al., 2000; Little et al., 1997), and in most normal and transformed human and rodent cases, as described above. The fact that Dugan and Bedford (2003) found no evidence for induced chromosomal instability in a normal human diploid fibroblast strain may be related to genetic factors, as described by Kadhim et al. (1998) who observed variability in the response of different strains of human diploid fibroblasts. Furthermore, delayed re-activation of p53 and a persistent induction of ROS has been reported in normal human fibroblasts (Rugo et al., 2002), as well as in human fibrosarcoma cells (Suzuki et al., 2003). Long-term instability can be induced by irradiation of cells with single alpha particles from a focused microbeam (Kadhim et al., 2001), supporting earlier observations that the instability phenotype can be activated by low radiation doses, becoming saturated at higher doses (Grosovsky et al., 1996; Kadhim et al., 1995; Little et al., 1997).

(151) Finally, a persistently increased rate of cell death has been shown to occur in cell populations many generations after irradiation (Belyakov et al., 1999; Chang and Little, 1991; Seymour et al., 1986). This phenomenon has been referred to as occurring as a result of 'lethal mutations' or 'delayed reproductive failure', but has been measured as a reduction in the ability of cells to attach and form macroscopic colonies in a classic clonogenic survival assay. In some cellular systems, an increased rate of apoptotic cell death has been shown to accompany this phenomenon (Belyakov et al., 1999; Jamali and Trott, 1996; Limoli et al., 1998). Persistent reproductive failure has been linked to chromosomal instability (Limoli et al., 1998) and malignant transformation (Lewis et al., 2001; Redpath and Gutierrez, 2001), and evidence has been presented to suggest that DNA is at least one of the critical targets in the initiation of this phenomenon (Limoli et al., 1999). Instability was attenuated by treating the irradiated cells with free radical scavengers or allowing potentially lethal damage to be repaired by confluent holding prior to analysing the subsequent development of chromosomal instability (Limoli et al., 2001). It has been proposed that oxidative stress, perhaps as a consequence of enhanced, p53-independent apoptosis, may contribute to the perpetuation of the instability phenotype in these populations (Limoli et al., 1998; Redpath and Gutierrez, 2001).

(152) Of importance in terms of radioprotection is whether this phenomenon occurs in vivo and thus may be related to the induction of cancer. A number of mouse models for genetic instability have been described (Reliene and Schiestl, 2003). The transmission of chromosomal instability in vivo has been reported in several distinct experimental models (ICRP, 2003; Pampfer and Streffer, 1989; Ullrich and Davis, 1999; Watson et al., 1996b, 2001), although not in others (Bouffler et al., 2001), and in-vivo aspects of transmissible instability are addressed in detail later in this report. Evidence for transmissible instability in irradiated human populations has not been demonstrated adequately (Nakanishi et al., 2001; Tawn et al., 2005; Whitehouse and Tawn, 2001). While it has been suggested that instability induced in x-irradiated mouse haematopoietic stem cells may be related to the occurrence of the non-specific genetic damage found in radiation-induced leukaemias in these mice (Macdonald et al., 2001), other work from the same laboratory indicates that susceptibility to radiation-induced leukaemia/lymphoma is generally separable from sensitivity to induced genomic instability (Boulton et al., 2001).

(153) In the case of murine mammary tumours induced by radiation, the link between genomic instability and early events in mammary cancer development appears to be stronger (Okayasu et al., 2000; Ullrich and Davis, 1999). In this instance, the instability appears to be directly related to a defect in the function of the DNA repair enzyme DNA-PKcs.

4.3.3. The bystander effect in irradiated cell populations

(154) The bystander effect of radiation refers to the evidence that damage signals may be transmitted from irradiated to non-irradiated cells in a population, leading to the occurrence of biological effects in cells that receive no radiation exposure. The use of this term has been interpreted broadly, however, as is evidenced by the

experimental protocols employed to study such effects in vitro. The first protocol employs monolayer cultures of mammalian cells in which a small fraction of the cells in the population are irradiated, generally by alpha particles, and the biological effect is examined in the non-irradiated, neighbouring cells. A corollary protocol involves mixing experiments in which irradiated cells are mixed with non-irradiated cells, and the biological effect is subsequently measured in the non-irradiated cohort of the population. The second protocol involves the harvesting of conditioned medium from irradiated cultures, and incubating this with non-irradiated cells; the bystander cells are thus not in physical proximity to the irradiated cells. Both mixing and medium transfer techniques permit the examination of effects with low-LET radiation as well as high-LET radiation.

(155) The experimental model employed in many of these studies has involved the exposure of monolayer cultures of mammalian cells, often confluent or subconfluent, to very low fluences of alpha particles; fluences whereby only a very small fraction of the nuclei in a cell population will actually be traversed by an alpha particle. This may be accomplished by irradiation from an external source of alpha particles (Metting et al., 1995), or by use of precision microbeam irradiators whereby specific cells can be targeted (Folkard et al., 2001; Hei et al., 1997; Prise et al., 1998, 2000; Shao et al., 2003a). A grid arrangement has also been employed to protect many cells in a population exposed to relatively high fluences of alpha particles (Lorimore et al., 1998).

(156) The first evidence for this phenomenon was derived from studies of the induction of sister chromatid exchanges (SCEs) by very low fluences of alpha particles from an external source (Nagasawa and Little, 1992). It was observed that an enhanced frequency of SCEs occurred in 20–40% of the cells exposed to fluences, whereby only about 1/1000 to 1/100 cell nuclei were actually traversed by an alpha particle. This finding was later confirmed and evidence was presented to suggest that the phenomenon involved secretion of cytokines or other factors by irradiated cells leading to the upregulation of oxidative metabolism in bystander cells (Deshpande et al., 1996; Lehnert and Goodwin, 1997; Narayanan et al., 1997, 1999). It has since been shown that an enhanced frequency of specific gene mutations occurs in bystander cells in populations exposed to very low fluences of alpha particles (Nagasawa and Little, 1999). As a result, the induced mutation frequency per alpha-particle track increases at low fluences where bystander as well as directly irradiated cells are at risk for the induction of mutations. This leads to a dose–response curve in which the slope is initially steeper than it is at higher doses. Studies with microbeam irradiation have provided evidence for an enhanced frequency of micronucleus formation, cell killing, and apoptosis in bystander cells (Belyakov et al., 2001; Prise et al., 1998, 2000; Schettino et al., 2003; Shao et al., 2003a), as well as an enhanced frequency of mutations (Zhou et al., 2000, 2001) and malignant transformation (Sawant et al., 2001a).

(157) It has also been shown that changes in gene expression occur in bystander cells in monolayer cultures; the expression levels of p53, $p21^{Waf1}$, CDC2, cyclin B1, and rad51 were significantly modulated in non-irradiated cells in confluent human diploid cell populations exposed to very low fluences of alpha particles (Azzam

et al., 1998). These experiments were carried out by Western blotting and in-situ immunofluorescence staining techniques using confocal microscopy. Although only about 1–2% of the cell nuclei were actually traversed by an alpha particle, clusters of cells showed enhanced expression of $p21^{Waf1}$. This phenomenon involved cell-to-cell communication via gap junctions (Azzam et al., 1998, 2001), as has also been shown for micronucleus formation (Shao et al., 2003b) and mutations (Zhou et al., 2001). It appears that radiation exposure itself can enhance intercellular communication as evidenced by an upregulation of connexin 43 (Azzam et al., 2003a). Evidence for DNA damage in bystander cells was provided by examining micronucleus formation, a surrogate measure of DNA damage; the hypothesis that the upregulation of the p53 damage response pathway in bystander cells was a consequence of this DNA damage is supported by the observation that p53 was phosphorylated on serine 15 (Azzam et al., 2001). Interestingly, it has been hypothesised that the apparent persistence of DNA DSBs after exposure to very-low-dose x rays may be the result of such a bystander effect (Rothkamm and Lobrich, 2003).

(158) DNA damage in bystander cells, however, appears to differ from that occurring in directly irradiated cells; whereas the mutations induced in directly irradiated cells were primarily partial and total gene deletions, over 90% of those arising in bystander cells were point mutations (Huo et al., 2001). This would be consistent with the evidence that oxidative metabolism is upregulated in bystander cells (Azzam et al., 2002; Narayanan et al., 1997), and has led to the hypothesis that the point mutations are a result of oxidative base damage occurring in bystander cells (Huo et al., 2001). A similar mechanism has been proposed for the observation that localised cytoplasmic exposure from a microbeam irradiator led to a significant increase in the frequency of point mutations which appeared to involve the generation of ROS (Shao et al., 2004; Wu et al., 1999). Bystander cells defective in the NHEJ pathway, including mouse knock-out cell lines for Ku80, Ku70, and DNA-PKcs, are extremely sensitive to the induction of mutations and chromosomal aberrations (Little et al., 2003; Nagasawa et al., 2003). Interestingly, the mutations in these repair-deficient bystander cells were primarily the result of partial and total gene deletions (Nagasawa et al., 2003), whereas those in wild-type bystander cells were predominantly point mutations. The marked sensitisation of repair-deficient bystander cells to the induction of mutations and chromosomal aberrations may be a consequence of unrejoined DNA DSBs occurring as a result of clustered damage arising from opposed oxidative lesions and SSBs. Mutations in wild-type cells arise primarily from oxidative base damage.

(159) In earlier studies, it was reported that alpha-particle irradiation could induce the intracellular generation of ROS, including the superoxide anion and hydrogen peroxide (Narayanan et al., 1997). This ROS response did not require direct nuclear irradiation, as a ROS response was induced in non-irradiated cells with conditioned medium from alpha-irradiated cells. The various studies examining the role of oxidative metabolism and gap-junction-mediated intercellular communication have been summarised by Azzam et al. (2003b). The role of oxidative stress in modulating signal transduction and micronucleus formation in bystander cells was examined in confluent monolayer populations of human diploid cells exposed to low fluences

of alpha particles (Azzam et al., 2002). The results support the hypothesis that superoxide and hydrogen peroxide produced by flavin-containing oxidase enzymes mediate the activation of several stress-inducible signalling pathways, as well as micronucleus formation in bystander cells. These include the p53 damage response pathway as well as the MAP kinase family of signalling pathways. It has also been reported that nitric oxide may initiate intercellular signal transduction pathways influencing the bystander response to radiation (Matasumoto et al., 2001; Shao et al., 2002). It thus appears that ROS may be the primary mediators of the bystander effect (Szumiel, 2003).

(160) Interestingly, this upregulation of oxidative stress in bystander cells is reminiscent of the effect associated with radiation-induced genomic instability (Limoli et al., 2001; Redpath and Gutierrez, 2001), and it has been proposed that the bystander effect may be related to the induction of an inflammatory-type response in vivo (Lorimore et al., 2001). The activation of MAP kinase proteins and their downstream effectors in bystander cells (Azzam et al., 2002) is of particular interest in terms of the recent observation that membrane signalling pathways are involved in the bystander effect in monolayer cultures (Nagasawa et al., 2002; Shao et al., 2004).

(161) Bishayee et al. (1999) and Howell and Bishayee (2002) developed a three-dimensional tissue culture model that utilised Chinese hamster V79 cells to study bystander effects caused by non-uniform distributions of radioactivity. Cells labelled with ^{125}IdUrd were mixed with unlabelled cells, and multicellular clusters were formed by centrifugation. A decrease in clonogenic survival occurred among the unlabelled cells which, based on inhibitor studies, appeared to depend upon gap-junction-mediated intercellular communication (Bishayee et al., 2001). On the other hand, when cells irradiated with carbon beams were cocultured with non-irradiated cells, cloning efficiency and proliferation of the non-irradiated recipient cells was increased (Shao et al., 2003c), reminiscent of the well-known feeder layer effect. When a mixture of ^{125}I-labelled and unlabelled human tumour cells was injected into nude mice, a distinct inhibitory effect on the growth of the unlabelled cells was observed (Xue et al., 2002). Belyakov et al. (2003) presented evidence for a bystander effect in a primary tissue explant model. Watson et al. (2000) transplanted a mixture of irradiated and non-irradiated bone marrow cells in a mouse system that allowed the discrimination between irradiated donor-stem-cell-derived cells and non-irradiated stem-cell-derived cells in vivo. They were able to demonstrate chromosomal instability in the progeny of the non-irradiated haematopoietic stem cells, providing a link between a bystander effect of IR and the induction of genomic instability in vivo.

(162) There is a long history of the apparent induction of clastogenic factors by radiation, primarily as measured in the plasma of irradiated individuals. These studies have been reviewed in detail by Mothersill and Seymour (2001). These workers have reported that the exposure of cells in culture or explants of tissue to gamma-radiation doses as low as 10 mGy can lead to the release of factors into the medium by the irradiated cells; when this conditioned medium is transferred to non-irradiated cells, their cloning efficiency is reduced and this is associated with increased levels of apoptotic cell death (Mothersill and Seymour, 1998). This phenomenon has been

associated with early changes in mitochrondrial membrane permeability and the induction of ROS (Lyng et al., 2001).

(163) Overall, however, a clear picture has yet to emerge from the experience with medium transfer experiments. There is convincing evidence that factors are released into the medium by irradiated cells that can lead to changes in the viability of non-irradiated cells incubated with such conditioned medium. The results from different laboratories, however, are not entirely consistent. Some workers have reported that incubation with conditioned medium harvested from irradiated cultures leads to a reduction in cloning efficiency of the recipient cells (Lyng et al., 2002; Sawant et al., 2002), while others have found it is enhanced (Iyer and Lehnert, 2002) or dependent on cell type (Mothersill and Seymour, 1997). The effect of medium irradiation alone is particularly controversial (Belyakov et al., 2001; Lehnert and Goodwin, 1997; Zhou et al., 2002). In terms of genetic effects, one laboratory has described a bystander effect for SCEs in conditioned medium transfer experiments (Lehnert and Goodwin, 1997), whereas another laboratory found little or no evidence for a bystander mutagenic effect under similar conditions (Zhou et al., 2002). The effect appears likely to be mediated by cytokines or ROS, but the exact nature of the factor or factors responsible for the biological effects in the non-irradiated bystander cells remains to be elucidated.

(164) In summary, the results of these studies of bystander effects clearly indicate that damage signals can be transmitted from irradiated to non-irradiated cells. In confluent monolayer cultures, this phenomenon involves gap-junction-mediated cell-to-cell communication, and appears to involve both the induction of ROS and the activation of extranuclear signal transduction pathways. Preliminary evidence suggests a role for membrane signalling. Multiple biological effects may occur in bystander cells including cell killing, the induction of mutations and chromosomal aberrations, and the modulation of gene expression. Some evidence suggests that regulation of the p53 damage response pathway may be central to this phenomenon. In addition, damage signals may be transmitted through the extracellular medium, also appearing to involve the production of ROS. Finally, preliminary studies with tissue explant models and a mouse bone marrow stem cell transplant system suggest that the effect may occur in vivo (R. Ullrich, personal communication).

4.4. Conclusions: implications for risk assessment

(165) There is increasing evidence that the development of invasive metastatic cancer involves a series of distinct genetic events, some of which can be associated with specific stages in the carcinogenic process (Fearson and Vogelstein, 1990). A question that arises is how as many as six to eight such genetic events may accumulate in a single cell lineage, given that the prevalence of most mutations is about 10^{-5}. Loeb et al. (2003) and others have postulated that early in the process of carcinogenesis, a mutation may arise in a gene that is important in maintaining genomic stability, yielding a cell lineage with a mutator phenotype. This phenotype would enhance the frequency with which spontaneous mutations arise in these cells, and thus facilitate the accumulation of the requisite number of genetic events to produce a cancer.

One such example is hereditary non-polyposis colon cancer, which is associated with a germline defect in DNA mismatch repair. While genomic instability is a hallmark of tumour cells, most types of cancer have not been associated with specific DNA repair defects.

(166) The finding that radiation itself may induce an instability phenotype has thus attracted considerable interest. It would suggest that the initial radiation-induced event may be frequent, involving as much as 10–20% of the population, rather than a rare mutagenic event. This increased level of instability, which is transmissible over many generations of cell replication, would thus enhance the rate at which multiple genetic events important to the development of cancer would arise in the cell population. However, the extent to which this radiation-induced phenomenon may be of importance in carcinogenesis is not yet clear. The fact that it appears to saturate at fairly low doses (of the order of 100–500 mGy) implies that it could influence the extrapolation to low-dose effects. On the other hand, as it may not represent an irreversible carcinogenic event such as mutation, it may be susceptible to modulation by external factors. Clearly, additional research is needed to determine the mechanisms involved in radiation-induced genomic instability, in terms of both the initiating event and how the effect is transmissible for many generations of cell replication, before its implications for the assessment of the carcinogenic risk of low-dose, low dose-rate exposure to IR can be clarified.

(167) Another area where this phenomenon could well be of significance involves potential transgenerational effects of irradiation. The sum of the available evidence suggests that such instability is induced in the germ cells of irradiated parents and their offspring (Niwa, 2003). If exposure to low levels of IR thus induces the instability phenotype in germ cells of the offspring of irradiated parents, it is entirely feasible that this instability could increase their susceptibility to cancer or other genetic effects. For example, Pils et al. (1999) reported that genomic instability manifested by lethal and teratogenic effects may be passed on to two successive generations of offspring in mice after irradiation of the zygote, while Niwa and Kominami (2001) and Dubrova and colleagues (Dubrova and Plumb, 2002; Dubrova et al., 1998) presented evidence for transmissible germline instability at mouse minisatellite loci. There is preliminary experimental evidence to suggest that such transmissible instability may lead to increased susceptibility to the induction of tumours in the offspring of irradiated mice (Lord et al., 1998; Nomura, 1982). The question of radiation-related transgenerational cancer risk in experimental animals and human populations is discussed in Section 2.1.1; the induction of transmissible genomic instability by radiation in germ cells would provide a mechanism for such transgenerational effects.

(168) The bystander effect has clear implications in terms of human exposures to very low fluences of high-LET particulate radiation, such as alpha particles from environmental radon or densely ionising galactic cosmic rays in space (Brenner and Elliston, 2001). In the case of radon, for example, only a small fraction of a person's bronchial epithelial cells, the presumed target for lung cancer, will be hit each year by an alpha particle arising from residential radon exposure. In the past, the genetic or carcinogenic risk has been assumed to be directly related to the number of cell nuclei actually traversed by an alpha particle, thus yielding a linear

dose–response relationship. The evidence that irradiated cells may transmit damage signals to neighbouring non-irradiated cells that result in genetic alterations in these 'bystander' cells would invalidate this assumption. Rather, it would suggest that the dose–response curve may be non-linear at low mean doses, yielding a greater effect than that predicted on the basis of the dose received by individual cells at low fluences of alpha particles. Preliminary data, based primarily on cell-mixing experiments, are emerging to suggest that a bystander response also occurs with low-LET radiation. However, these preliminary data are insufficient to draw any conclusions concerning the significance of this effect at low radiation doses, particularly at levels such that the track fluence is less than the number of cells in the radiation field (J.B. Little, personal communication).

(169) Evidence for the convergence of the three phenomena (adaptive response, genomic instability, and bystander effects) is also of interest (Lorimore and Wright, 2003; Morgan, 2003b; Streffer, 2004). Several different studies involving both in-vitro and in-vivo assays have shown, for example, that transmissible genomic instability may arise in bystander cells (Lorimore et al., 1998; Watson et al., 2000), and that the bystander effect may be modulated by the adaptive response (Iyer and Lehnert, 2002; Mothersill et al., 2002; Sawant et al., 2001b; Zhou et al., 2003). Defects in the NHEJ DNA repair pathway have been associated with both radiation-induced genomic instability (Okayasu et al., 2000) and the bystander effect (Little et al., 2003). It has been reported that conditioned medium from certain (but not all) unstable clones harvested many cell generations after irradiation is highly cytotoxic to unirradiated cells (Nagar et al., 2003). Finally, oxidative stress manifested by enhanced levels of ROS has been implicated in all three phenomena.

(170) When considered as a whole, the emerging results with these three phenomena raise the possibility that the dose–response relationship at low doses of IR is uncertain, and a simple extrapolation from high-dose effects may not be appropriate. In some cases, such as the induction of mutations by exposure to very low fluences of high-LET particles, or as reported for the cytotoxic effects of very low doses of x rays, the effect may be greater than predicted from a linear extrapolation. On the other hand, certain studies of malignant transformation have revealed a reduced effect for very low doses. Overall, however, these findings imply that the biological effects of radiation in cell populations may not be restricted to the response of individual cells to the DNA damage they receive, but rather that tissues respond as a whole. These three phenomena are of importance as they may influence the nature of the dose–response relationship at low doses and low dose rates. However, a better understanding of the mechanisms for these phenomena, the extent to which they are active in vivo, and how they are inter-related is needed before they can be confirmed as factors to be included in the estimation of potential risk to the human population of exposure to low levels of IR.

5. CARCINOGENIC EFFECTS OF IONISING RADIATION

5.1. Mechanisms of radiation-induced cancer

(171) Studies on the cellular and molecular mechanisms of carcinogenesis over the last several years have provided substantial insight with respect to the complex multistep nature of the process of neoplastic development (Hanahan and Weinberg, 2000; UNSCEAR, 2000). Such studies have identified a number of specific target genes and gene pathways, and also important variations among different tumour types. From such studies, tumour development is now generally viewed as a multistep clonal process of cellular evolution and selection. The conversion of a normal somatic cell into a cell with neoplastic potential is generally referred to as 'initiation' (Knudson, 2001; UNSCEAR, 2000). Subsequent to initiation, the process of neoplastic development continues via the progression phase. This phase includes clonal selection and the development of additional mutational events. As such, this stage may be viewed as the early developmental and evolutional phases of an initiated cell during neoplastic progression. Factors such as cell–cell communication, mitogenic stimulation, cellular differentiating factors, mutational processes, and cell–tissue interactions play a role in determining the probability of progression of initiated cells. Specific genetic changes involved in progression often differ among tissue types, although key related pathways are generally involved (Hanahan and Weinberg, 2000; UNSCEAR, 2000). The end phase in tumour progression is the conversion of a cell or cells to the malignant phenotype. Due to the high degree of instability associated with such cells, progression and evolution within a population of malignant cells will continue indefinitely (Loeb, 1991). Overall, it is clear that only a small fraction of cells that enter the pathway of neoplastic development as initiated cells will complete the full sequence of events leading to malignancy; a process that can require years in the human being.

(172) Although radiation-induced tumourigenesis in experimental animals and humans has been the subject of intense study for many years, direct evidence with respect to underlying mechanisms of radiation carcinogenesis has been lacking until recently and models have relied heavily on indirect inferential data. For example, it has been suggested for many years that the primary effect of radiation is principally on early events, i.e. the primary effect of radiation is as a tumour-initiating agent. This is based on several observations. First, animals and human beings are generally more sensitive to the tumourigenic effects of IR at young ages compared with older ages. This suggests that radiation effects have more to do with tumour initiation than with promotional effects that accelerate the development of pre-existing neoplasms (Clifton et al., 1986; Fry, 1992; Fry and Storer, 1987; Fry et al., 1977; UNSCEAR, 2000). Second, experimental animal data from studies of skin cancer development, specifically designed to examine the influence of radiation on different stages of tumourigenesis, show that radiation only weakly promotes the development and progression of chemically initiated tumours but has significant initiating activity (Jaffe and Bowden, 1987). Finally, it has been observed in humans and animals that single acute doses of low-LET radiation are

sufficient to produce a dose-dependent increase in cancer risk, and that dose protraction decreases that risk in quantitative animal studies. The last observation also supports the inference that the major effect of radiation is on early events in the carcinogenic process (Hanahan and Weinberg, 2000; IARC, 2000). While this inference appears to be logically based, there was no direct evidence in support of it until recently.

(173) Advances in cell biology, cytogenetics, molecular biology, and mouse genetics over the past several years have enabled more direct investigation of events in the tumourigenic process following radiation exposure. Such studies, by linking specific cell and molecular effects directly to the tumourigenic process, provide valuable insights into mechanisms as well as a better understanding of potential radiation-related risks. Of particular importance in this regard have been animal studies using newly developed models, both in inbred strains of mouse and rat and in genetically engineered rodents. Quantitative studies using mouse and rat models for radiation-induced mammary cancer and for thyroid cancer in rats have provided direct evidence to indicate that the principal effects of IR are on early events (Adams et al., 1987; Bouffler et al., 1996a,1996b, 1997; Domann et al., 1994; Ethier and Ullrich, 1984; Gould et al., 1987; Jaffe and Bowden, 1987; Mulcahy et al., 1984; Ullrich et al., 1996; Watanabe et al., 1986). Cellular, cytogenetic, and molecular data for acute myelogenous leukaemia (AML), intestinal tumours, and mammary tumours also provide evidence for clonal development of radiation-induced preneoplasms, implying an initial, single-cell target (Bouffler et al., 1997; Haines et al., 2000; Ullrich et al., 1996). Recent cytogenetic and molecular studies on the induction of AML and mammary tumours in inbred mouse strains, and of a variety of tumours in transgenic mouse models, have provided more specific information on the potential nature of these early events (Bouffler et al., 1997; Haines et al., 2000; Kemp et al., 1994; Pazzaglia et al., 2002; Selvanayagam et al., 1995; Silver et al., 1999). These studies provide direct support for the view that the critical radiation-associated events in the tumourigenic process are predominantly early events involving DNA losses targeting specific genomic regions harbouring critical genes. Since many of the radiation-associated DNA loss events in these tumourigenesis models involve large chromosomal regions within the genome, mechanisms for radiation-induced chromosome aberration induction appear to be of particular relevance to the understanding of radiation effects at low doses. The predominant importance of DNA DSB induction and postirradiation error-prone NHEJ repair for the induction of aberrations, and the apparently critical role for radiation-induced aberrations in the pathogenesis of cancer in these experimental models, would tend to argue against the proposition of a low-dose threshold in the dose–response relationship for the initiation of carcinogenesis.

(174) More recently, experimental studies have questioned whether the initiating events produced by radiation are direct chromosomal or mutational effects, or whether the mutations and chromosomal re-arrangements result indirectly as a consequence of genomic instability induced by the radiation exposure (Little et al., 1990, 1997; Morgan et al., 1996; Selvanayagam et al., 1995; Yu et al., 2001).

(175) It is well known that the development of tumours is frequently accompanied by the acquisition of genomic instability phenotypes that serve to promote the mutational evolution involved in neoplastic progression. This form of genomic instability is increasingly well understood, and many of the responsible tumour gene mutations have been identified (Loeb, 2001). This instability, however, differs from radiation-induced genomic instability described during the last decade (Selvanayagam et al., 1995b). Evidence has accumulated that, under certain experimental conditions, the progeny of cells surviving radiation appear to express new chromosomal and gene mutations over many postirradiation cell generations. The details of radiation-induced genomic instability have been discussed in detail earlier in this report. What may be unique about radiation-induced instability with respect to its potential role in tumourigenesis is that because of the high frequencies of instability observed following radiation exposure (10–50% of irradiated cells), such instability would not appear to be a result of radiation-induced mutations in a specific gene or family of genes (Kadim et al., 1991; Selvanayagam et al., 1995; Wright, 1995). On the basis of data discussed earlier on radiation-induced genomic instability, and the previously reported high frequency of neoplastic cell transformation (Kennedy et al., 1980; Selvanayagam et al., 1995b), it has been suggested that such events can serve to destabilise the genomes of a substantial fraction of the progeny of irradiated cells, and that it is the elevated postirradiation mutation rates in cell progeny rather than gene-specific initial mutations that act to drive radiation tumourigenesis (Selvanayagam et al., 1995b). The question then arises regarding the impact of this type of mechanism on assumptions with respect to low-dose risks.

(176) Instability associated with telomere dysfunction appears to be of particular relevance to tumourigenesis (Bouffler et al., 2001a; Desmaze et al., 1999, 2003; Ducray et al., 1999; Lo et al., 2002a,b; Mills et al., 2003; Morgan et al., 1996). Such dysfunction can be manifest in several forms. Telomeric repeat sequences $(TTAGGG)_n$ cap the ends of mammalian chromosomes and serve to protect against replicative erosion and chromosomal fusion; in normal human cells in culture, telomere shortening and instability is a natural feature of replicative cell senescence. Telomeric repeats are also found in subtelomeric and interstitial chromosomal locations, and there is some evidence that these loci may act as sites at which radiation-induced and other forms of genomic damage are preferentially resolved. There is also good evidence that telomeric instability is a recurrent feature of tumourigenic development. Of particular relevance to the question of unstable translocation junctions are the so-called segmental jumping translocations that have been well characterised in spontaneously arising human leukaemias. With respect to radiation-induced leukaemia, detailed cytogenetic analyses suggest an excess of complex aberrations and segmental jumping translocations in leukaemias arising at old ages in high-dose atomic bomb survivors (Nakanishi et al., 1999). Telomeric instability at radiation-associated deletion/translocation breakpoints in mouse myeloid leukaemia has also been reported, but it is not a general characteristic of such tumour-associated events. Interestingly, excess spontaneous telomeric instability is often found to be associated with deficiencies in DNA repair or damage response (Mills et al., 2003).

(177) Evidence for the involvement of telomeric sequences in the pathogenesis of at least some forms of radiation-induced instability comes from several laboratories. Early studies on the postirradiation development of chromosomal instability in in-vitro passaged human diploid fibroblasts were among the first to suggest a link between telomeres and instability. Initial studies using this in-vitro model were suggestive of instability effects in a high proportion of irradiated cells (Sabatier et al., 1989, 1992). Subsequent studies by the same research group have served to address issues related to the pathogenesis of instability and its frequency (Desmaze et al., 1999, 2003; Ducray et al., 1999; Lo et al., 2002a,b). Detailed cytogenetic analyses suggested that passage-dependent instability in cultured human fibroblasts primarily represented telomeric events expressing in cell clones naturally selected by growth rate during passage. Overall, the data obtained may be interpreted as evidence that initial radiation exposure brings forward in time the natural process of clonal telomeric instability associated with cell senescence and telomere shortening. Equally important is the suggestion that selection processes lead to an overestimate with respect to the frequency of induction of instability by radiation. Whether selection processes impact on estimates of the frequency of instability in other systems remains to be addressed.

(178) A different form of postirradiation telomere-associated instability is expressed in a hamster–human hybrid cell system where, in some clones, chromosomal instability is persistently expressed at translocations that have telomeric sequences at their junction (Morgan et al., 1996). Similar unstable structures have been observed in non-irradiated hamster cells undergoing gene amplification. Such data suggest that radiation induces genomic structures that enhance the natural expression of instability. A number of other reports have also suggested that radiation-associated chromosomal exchange can lead to the formation of unstable junctions that undergo secondary change, leading to the formation of complex chromosomal aberrations (Desmaze et al., 1999, 2003; Lo et al., 2002a,b; Morgan et al., 1996).

(179) The mechanistic role of instability in radiation tumourigenesis is not clear and the two model systems used to study this question have yielded differing results. Radiation-induced genomic instability in haematopoietic cells was first demonstrated in studies showing a persistent excess of chromatid-type aberrations in the progeny of mouse bone marrow cells irradiated in vitro with alpha particles and subsequently grown in culture (Kadim et al., 1991). Alpha particles are considered to be substantially more effective than low-LET radiation in inducing this form of genomic instability, which has also been reported in the progeny of cells that had not sustained an alpha-track traversal; i.e. induced instability may occur as a bystander effect (Lorimore et al., 1998). In-vivo post-transplantation growth of in-vitro-irradiated bone marrow cells has also been reported to result in excess chromatid aberrations. On the basis of these observations, it was proposed that such instability had a major role in radiation-induced murine AML. More recent data have not supported this hypothesis, and in fact suggest that radiation-induced instability is not involved in the initiating events in murine AML (Bouffler et al., 2001b). Of particular importance in this regard were studies demonstrating that

susceptibility to radiation-induced instability in haematopoietic cells, and susceptibility to radiation-induced AML, are not genetically linked phenotypes (Boulton et al., 2001).

(180) In contrast to these studies are data on instability and radiation-induced mammary cancer. Differences in radiosensitivity and susceptibility to induced tumourigenesis among inbred mouse strains are well recognised and there is good evidence that the BALB/c mouse is unusually sensitive to the induction of tissue injury and mammary tumours, while the C57BL/6 mouse falls into the radioresistant category (Hanson et al., 1987). Initial cytogenetic studies showed that mammary epithelial cells cultured from irradiated BALB/c mice persistently expressed substantially more chromatid aberrations during passage than those derived from irradiated C57BL/6 animals (Ponnaiya et al., 1997). In follow-up investigations, the chromatid instability phenotype of BALB/c was shown to be associated with a partial deficiency in the NHEJ repair protein DNA-PKcs, together with compromised postirradiation DNA DSB repair (Okayasu et al., 2000; Yu et al., 2001). This study, which included an intercomparison of inbred mouse strains, showed that the deficiency of DNA-PKcs and DNA DSB repair was restricted to BALB/c mice, suggesting genetic associations with persistent genomic instability and with mammary tumour susceptibility. Molecular genetic analyses showed that BALB/c mice carry a rare variant form of the gene (*Prkdc*) encoding DNA-PKcs. Subsequent analysis of recombinant mice provided strong evidence that variant *Prkdc* directly determined DNA-PKcs deficiency and postirradiation chromatid instability in mammary epithelial cells (Yu et al., 2001). On the basis of these data, it was proposed that induced genomic instability and mammary tumour susceptibility were genetically codetermined. Importantly, these investigations provide genetic evidence that a deficiency in the repair of DNA DSBs is likely to determine persistent instability. Interestingly, recent observations have suggested a link between DNA-PKcs function, telomeric integrity, and genomic instability. The question of whether such instability is a primary causal element in mammary tumourigenesis remains to be resolved (Bailey et al., 1999, 2001).

(181) While the role of radiation-induced genomic instability in radiation-induced cancer is still a matter of investigation, there are several observations that provide a framework for its potential role in cancer development following radiation exposure. In the case of radiation-associated, persistent telomeric re-arrangement and unstable chromosome translocation junctions, a strong case may be made that a certain fraction of misrepaired genomic damage after radiation may be prone to ongoing secondary change in clonal progeny. Since there is evidence that such secondary genomic re-arrangement can be a normal component of tumour development, it is reasonable to assume that instability of this type would be involved in the pathogenesis of some radiation-associated tumours. It is unclear whether it plays a major role and, if so, for which tumour types. The genetic evidence from mouse mammary studies, which implies that postirradiation instability can associate with mammary tumour development, supports a role for genomic instability in this system. Thus, in certain genetic settings, such as individuals harbouring specific types of DNA repair deficiencies, a role for postirradiation instability in tumourigenesis appears reasonable.

(182) Interestingly, recent data in the SCID and BALB/c mouse strains, both of which have defects in DNA-PKcs, suggest that telomeric instability may be the underlying mechanism for the induction of instability, and that the resulting cytogenetic instability plays an important role in early carcinogenic events in the mouse mammary carcinogenesis model discussed above. In particular, it appears that dysfunctional telomeres may tend to interact with sites of radiation-induced DSBs, increasing the probability of misrepair (Bailey et al., 1999, 2001; Mills et al., 2003). It would be predicted that mechanisms involving DNA DSBs and telomeric sequence interactions would be particularly important at low doses where DNA DSBs are in relatively low abundance. This appears to be consistent with observations that instability is induced in a dose-dependent manner at radiation doses below 0.5 Gy, whereas no dose dependence is observed at higher doses, at which the response appears to plateau. Importantly, the emerging evidence suggests a role for radiation-induced DSBs in the induction of instability and provides a mechanistic link between DSBs, chromosome aberrations, and cancer not unlike that for more directly induced effects. This linkage would also suggest that predictions of effects at low doses will be unaffected by the underlying mechanism, whether that mechanism involves direct effects of radiation or is mediated by radiation-induced instability.

(183) Observations of microsatellite instability in acute AML among atomic bomb survivors (Nakanishi et al., 2001) appear to provide only weak evidence of involvement of this phenomenon in radiation leukaemogenesis, with significantly more instability among exposed compared with non-exposed cases but with little evidence of a dose–response relationship among the exposed, or of greater involvement in cases in which radiation exposure was more likely to have played a causal role (Cox and Edwards, 2002; Little, 2002; Little et al., 2003; Plumb, 2003). The question remains open, however, and studies with greater statistical power may resolve the issue in the future.

(184) Microsatellite instability, observed in radiation-related paediatric thyroid cancers associated with human exposure to radioactive fallout from the 1986 Chernobyl accident, was significantly greater for tumours diagnosed within 6–8 years after the accident compared with those with later onsets (9–11 years); however, without individual radiation dose estimates, it was not possible to evaluate the effects of dose on instability (Lohrer et al., 2001; Nikiforov et al., 1998; Richter et al., 1999).

5.2. Tissue-modifying factors

(185) It is well known that the probability that individual initiated cells will progress to become tumours can be modulated by interactions with surrounding cell and tissue components, as well as systemic host factors (Bissell and Radisky, 2001). Studies have also provided evidence that radiation can influence these cell–cell, cell–tissue, and host factor interactions (Barcellos-Hoff, 1998, 2001; Barcellos-Hoff and Brooks, 2001; Bissell and Radisky, 2001; Park et al., 2003). There has been renewed interest in these effects as a result of recent studies that have begun to identify potential

underlying mechanisms involved in modulation of tumourigenic progression and expression (Barcellos-Hoff, 1996; Barcellos-Hoff and Brooks, 2001; Barcellos-Hoff and Ewan, 2000; Bissell and Radisky, 2001). Research in this area will be extremely important in understanding the overall processes involved in neoplastic development, but a clear understanding of their potential impact on radiation-induced cancer remains to be determined.

(186) Two key points tend to support the view that factors involved in modulation of tumour progression and expression are not likely to play a major role in determining low-dose risks. It has been demonstrated in a number of instances that an important early and ongoing event in the process of neoplastic development is the acquisition of genomic instability (Selvanayagam et al., 1995). This instability increases the rate of mutational and chromosomal changes in the cells, and increases the probability for mutations that will allow initiated cells to escape from the inhibitory effects of cell-, tissue-, and host-modifying factors. Furthermore, age-related changes in the tissue micro-environment tend to reduce the ability of normal cells and tissues to inhibit expression of neoplastic potential by initiated cells. Over time and with increasing age, therefore, it is highly likely that mutations in initiated cells and alterations in the tissue micro-environment will result in the emergence of a cell or population of cells capable of escaping or overcoming these cell-, tissue-, and host-modulating factors. As a result, it seems prudent to focus on early initiating cell and molecular events as the major determinant of risks at low doses.

(187) Studies on in-vivo tumour induction in mice and rats also suggest that early cell and molecular events represent the principal determinant of radiation-related cancer risk in tissues. In this regard, fractionation studies are particularly relevant. Comparisons of the carcinogenic effects of fractionated exposures with effects of acute radiation exposures of rat skin (Burns and Vanderlaan, 1977; Burns et al., 1975; Vanderlaan et al., 1975) and mouse lung (Ullrich, 1980, 1984; Ullrich et al., 1987) have clearly demonstrated that the greatest reduction in the carcinogenic effect is for fractions separated by times of 24 h or less. Such time periods are compatible with repair of initial damage. Longer times of up to 30 days between fractions, which would allow tissue effects to impact on cancer risk, have not been found to result in further reduction in risk.

5.2.1. Target cells

(188) In hierarchical-type tissues, where less-differentiated precursor cells produce well-differentiated and mature functional cells, cancers are generally considered to originate from tissue stem cells that possess unlimited division capacity. These tissue stem cells are transformed by carcinogenic agents, altering their differentiation patterns so that cell renewal predominates over differentiation, leading to growth of the abnormal cell population. Stem cells have been well characterised in haemopoietic, epithelial, and spermatogenic tissues (Potten, 1983, 1997). They have renewal and location characteristics that are specific to a particular tissue. They renew themselves more slowly than their dividing and differentiating daughter cells, and hence,

in protracted irradiation scenarios, receive more ionisations per cell cycle. Stem cells are often located at the static end of a polarised system of cell production, for example near the bottom of intestinal crypts, in the basal layer of epithelia, and more centrally in red bone marrow. These locations can provide some protection against exposure from short-range radionuclides deposited on (for example) epithelial surfaces or lumenally.

(189) In the case of the colon, it has been suggested that tumours may originate in cells on the intercryptal plate rather than, or in addition to, stem cells at the base of the crypt (Shih et al., 2001). This study indicated that most early neoplastic lesions of the colon contain dysplastic cells solely at the orifices of crypts and on the luminal surface between crypts. Analysis showed loss of the *APC* gene and high expression of β-catenin in such dysplastic cells, but not in cells with normal appearance within the crypts. Mutations in the *APC* gene are the earliest genetic alterations in the genesis of colorectal tumours and appear to be required to initiate clonal evolution, involving overexpression of β-catenin (Fodde et al., 2001). This suggestion of target cells on the luminal surface is contentious (Preston et al., 2003; Wright and Poulsom, 2002). In normal tissue, differentiated epithelial cells on the intercryptal surface would have a very limited lifespan of a few days, and would be destined to be lost into the intestinal lumen in the normal process of cell renewal. To develop into a tumour, these dysplastic cells would need to escape this process completely to allow time for progression to malignancy, involving a number of mutational events (Goyette et al., 1992; Vogelstein et al., 1988). Although this scenario seems highly unlikely, the possibility cannot be excluded that daughter cells of the stem cells, situated at higher cell positions in the crypt, are also target cells, perhaps to a lesser degree. For the purposes of the ICRP report on the Human Alimentary Tract (ICRP, 2006), doses are calculated to the estimated position of the stem cells. However, in considering uncertainties, the possibility that cells higher in the crypts may also be targets has been addressed, including the extreme case of target cells on the intercryptal luminal surface.

(190) There are other protective mechanisms in stem cell systems, such as the selective retention of template DNA strands in stem cells, providing protection of the stem cell genome (Cairns, 1975, 2002). An example of this is the stem cells in the crypts of the small intestinal mucosa, which divide about 1000 times during the lifespan of a laboratory mouse. However, these cells show little evidence of any decline in proliferative potential and rarely produce overt tissue abnormalities, suggesting that their genome is extremely well protected. Protection against DNA-replication-induced errors can be achieved by the selective sorting of old (template) and new DNA strands with all template strands retained in the stem cell line. Experiments have shown that the template strands in the stem cells can be labelled during development or during tissue regeneration using tritiated thymidine (3HTdR) (Potten et al., 2002). Labelling newly synthesised strands with a different marker (bromodeoxyuridine, BrdUrd) allowed segregation of the two markers to be studied. It was shown that the template strand label was retained (3HTdR), whereas the label in the newly synthesised strands (BrdUrd) was lost following the second division of

the stem cell. Random errors may still occur in the template strands owing to environmental agents.

(191) Another protective mechanism is apoptosis. Apoptosis is the non-inflammatory and 'altruistic' cell suicide that involves characteristic molecular and cytological features. It occurs naturally at a low level in many hierarchical tissues in the stem cell zone, and the frequency is enhanced by irradiation. This type of cell death is very radiosensitive. Hypotheses for the low rate of cancer in the small intestine have been proposed, based on apoptosis that deletes mutated stem cells (Potten et al., 1992). These hypotheses suggest that radiation-induced TP53-dependent apoptosis in the stem cell zone in the small intestine prevents the propagation of mutated dividing progenitor cells. This is consistent with the increased frequency of cancer in *Tp53*-null mice compared with wild-type mice. Experiments in mice show that the level of apoptosis saturates after acute doses above 100 mGy, there is no detectable dose-rate effect (Hendry et al., 1982), and the incidence of apoptosis is repeatable after each dose in a series of small radiation exposures. This provides a potential mechanism in this tissue for the often purported presence of a threshold dose for carcinogenesis. Higher doses are capable of inducing tumours, as found in rats given irradiation to a temporarily exteriorised loop of small intestine (Osborne et al., 1963). In the large intestine, there is also natural and radiation-induced apoptosis. However, *Tp53* is not expressed in the stem cell zone, and *bcl-2* expression promotes cell survival and allows the development of mutated progenitor cells (Merritt et al., 1995). Hence this potential protective mechanism does not operate in the colon. Also, carcinogenesis in the colon may be exacerbated by the longer presence of fecal contents containing carcinogens.

(192) In other organ systems such as lung and thyroid, cell renewal is very slow and a much greater proportion of the total cell population may be target cells. In these cases, the above mechanisms are very unlikely to apply, and the long-lived target cells would accumulate multiple mutations in the conventionally described multistage process of carcinogenesis (Goyette et al., 1992; Vogelstein et al., 1988).

(193) An important question with respect to protective mechanisms in target cells and the removal of damaged cells via apoptosis is the persistence of radiation-initiated cells once the initial damage has been produced. Hoshino and Tanooka (1975) examined the persistence of latent carcinogenic damage in irradiated mouse skin, and found that radiation-initiated cells could persist as latent carcinogenic damage for up to 400 days. In studies examining the interaction of radiation and hormones in breast cancer development, Yokoro et al. (1977) found that latent radiation-initiated cells persisted for a substantial portion of the rats' lifetimes.

5.3. Radiation-induced cancer in animals

(194) On the basis of the discussion of cellular and molecular mechanisms above, it can be predicted that the dose–response and time–dose relationships for radiation-induced cancer would be similar to those for radiation-induced chromosomal aberrations. Specifically, at low doses, a linear dose–response relationship would be anticipated. There are, however, relatively few studies on animal carcinogenesis

where the data are sufficient to address the issue of dose–response relationships or the issue of dose-rate effects, protraction, and/or fractionation effects, and rigorously test these predictions. Those studies where such analyses are possible are mainly limited to rodent studies, principally studies in mice. A further caveat is the applicability of animal data to human risks. The pathogenesis of certain tumours in experimental animals appears to involve unique mechanisms for induction that do not appear to be compatible with known mechanisms of cancer development in humans. This section will describe the available data and its applicability to understanding of low-dose risks and risks following low-dose-rate or protracted exposures. This is not meant to be a comprehensive review but is limited to those data sets that focus on effects at low-dose (<0.5 Gy) and low-dose-rate exposures following external irradiation. Data from studies using internal emitters are not included because of the dosimetric issues that complicate interpretation. Likewise, studies with low statistical power in the low-dose range have also been excluded.

(195) At first glance, an examination of available animal data suggests a high degree of complexity in that a variety of dose–response relationships have been observed ranging from threshold responses to linear or linear-quadratic responses. However, a more systematic examination of the data with a view towards the underlying biology involved in the pathogenesis of individual tumour types reveals a clearer picture. In this regard, it is useful to first separate the discussion of the data into that for induction of leukaemia and solid tumours.

5.3.1. Leukaemia

(196) The induction of leukaemia and lymphoma has been examined in two murine systems: thymic lymphoma and AML. The dose–response relationship for induction of thymic lymphoma is complex, and reducing the dose rate results in a large reduction in the effectiveness for radiation-induced thymic lymphoma (Ullrich and Storer, 1979a). The applicability of these data to human risk estimates is unclear. The development of thymic lymphoma in mice following irradiation is an extremely complex process largely mediated through indirect mechanisms (Kaplan, 1964, 1967). Importantly in this regard, expression of thymic lymphoma can be substantially reduced or eliminated by protection of a small fraction of bone marrow stem cells from radiation-induced cell killing. The complex nature of the pathogenesis of murine thymic lymphoma involving substantial bone marrow cell killing, and the lack of a comparable counterpart in humans, argues against thymic lymphoma as an appropriate model for the understanding of dose–response and time–dose relationships in humans.

(197) In contrast, data on the biology and pathogenesis of murine AML suggest strong similarities between mouse and human. Such data support its applicability to radiation-induced leukaemogenesis in humans with respect to studies of mechanisms and potential low-dose risks (Rithidech et al., 1999, 2002; Silver et al., 1999; Tenen, 2003). For murine AML, the most comprehensive data on the dose–response relationship and dose rate or fractionation pertain to radiation-induced myeloid leukaemia in CBA mice and RFM mice (Mole and Major, 1983; Mole et al., 1983;

Ullrich et al., 1987; Ullrich and Preston, 1987; Upton et al., 1970). The CBA mouse has also been used to dissect underlying radiation-induced molecular events (Bouffler, 1996a, 1996b, 1997). Over the 0–3-Gy dose range (the lowest dose used was 250 mGy), the dose–response relationship for both strains could be described by a pure quadratic relationship, although linear-quadratic and simple linear dose–response relationships also provided an adequate fit to the data sets. After fractionation or protraction of the dose, there was a reduction in the leukaemogenic effects of radiation at doses of 1.5 Gy and higher, resulting in a linear dose–response relationship over a wide range of doses in both strains. Barendsen (1978) analysed the RFM data set including acute high-dose-rate, fractionated, and low-dose-rate exposures and concluded that a linear-quadratic model derived from the high-dose-rate data adequately predicted the low-dose-rate and fractionation effects. Importantly, these data and the analysis by Barendsen are fully compatible with predictions based upon the known role for aberrations/deletions in chromosome 2 in the pathogenesis of murine AML, and predictions based upon data for induction of chromosome aberrations by radiation.

5.3.2. Solid tumours

(198) Data from experimental studies examining dose–response relationships following whole-body external exposures are also available for a limited number of solid cancers. The tumour types for which sufficient data are available include Harderian gland, pituitary, and ovarian tumours in female RFM mice (Ullrich and Storer, 1979a,b), and lung and breast cancers in female BALB/c mice (Ullrich, 1983; Ullrich et al., 1987). Data are also available in female Sprague-Dawley rats for mammary tumours (Burns and Vanderlaan, 1977; Burns et al., 1975; Finkel and Biskis, 1968; Hulse and Mole, 1969; Shellabarger et al., 1980), for skin in mice and rats, and for bone tumours in mice. The data for skin and bone tumours involve localised exposures as the induction of these tumours generally requires radiation doses that are too high to be well tolerated when given as whole-body exposures.

(199) The observation that high radiation doses are required for induction of skin and bone tumours supports the view that a threshold may exist for induction of these tumours. However, this does not imply that low doses of radiation cannot and do not result in the initiation of skin and bone cells. Studies in mouse skin clearly demonstrate that low doses of radiation can initiate cells that have the potential to progress to become tumour cells (Jaffe and Bowden, 1987). Rather, these data suggest that, for these tissues, factors influencing tumour progression play an important role in determining whether or not initiated cells progress and ultimately express their tumourigenic potential. The high doses required suggest an important role for radiation-induced cell killing, resulting in disruption of cell–cell and cell–tissue interactions as well as the recruitment of growth factors, all of which may participate in the progression of initiated cells in these systems. It is important to note that skin and bone are not considered to be highly sensitive to radiation-induced cancer in humans. By far the greatest contribution to estimates of radiation risk comes from tissues that are more sensitive to tumour induction, and for which risks at low doses are of more concern.

(200) The apparent lack of sensitivity of bone and skin at low doses does not mean that risks can be ignored. Exposure to ultraviolet light has been shown to be an effective promoting agent following exposure of the skin to IR (Shore et al., 1984). Such exposure allows the expression of initiated cells that would not be expressed otherwise. As a result, the relationship between the dose of IR and skin tumour development shifts from one with an apparent threshold to a much more linear response. This effect underscores the argument made previously in this section that it is important to focus on early initiating cell and molecular events as the major determinant of risks. An apparent threshold cannot be assumed to indicate that there is no increased risk to an individual who may be exposed to other agents with promoting effects, or for whom intrinsic risk factors could exist which could allow expression of initiated cells that would not normally be expected.

(201) Data from studies using RFM and BALB/c mice and Sprague-Dawley rats are most applicable with respect to low-dose and low-dose-rate effects because of the sensitivity of these tissues to radiation-induced cancer and the dose range over which data has been obtained. Again, caution must be exercised in the application of data derived from all tumour types without regard to the underlying biology involved in tumourigenesis. The most dramatic example is that for ovarian cancer in mice. Ovarian cancer in the mouse following whole-body irradiation appears to be a result of an indirect mechanism involving oocyte cell killing, and subsequent alterations in the pituitary–ovarian hormonal interactions leading to ovarian tumourigenesis (Foulds, 1975). Due to the close association between cell killing and ovarian cancer in mice, and because mouse oocytes are uniquely sensitive to the killing effects of radiation (LD50 for oocyte killing is approximately 50 mGy), ovarian tumours at high frequencies are observed following very low doses. Consistent with an indirect mechanism mediated by cell killing, a threshold dose–response relationship has been observed for the induction of ovarian tumours. Lowering the dose rate increased the threshold dose from approximately 110 mGy to 700 mGy (Ullrich and Storer, 1979b,c). There is no evidence for similar indirect mechanisms for radiation-induced cancer at any site in human studies. Therefore, radiation-induced ovarian tumourigenesis will not be included in the discussions below.

(202) Data for the induction of Harderian gland and pituitary tumours in female RFM mice, and lung and mammary cancer in female BALB/c mice, generally support the linear-quadratic model over a dose range from 0.1 to 2 Gy (Ullrich and Storer, 1979a,b; Ullrich et al., 1987), while the induction of mammary tumours in Sprague-Dawley rats tends to be more linear over this dose range (Shellabarger et al., 1980). For these tumour types, it has also been found that reducing the dose rate or fractionating the dose into small fractions reduces the risk for development of radiation-induced cancer in the manner predicted by the linear-quadratic model. At high doses (>1 Gy), the risk of cancer development is reduced primarily as a result of the diminution of the quadratic portion of the dose–response relationship, resulting in a limiting linear slope over a wide dose range that is equivalent to the linear slope of the high-dose-rate dose–response relationship in the low-dose range. At lower total doses, radiation effects are time independent. Therefore, the incidence of tumours increases linearly with dose.

(203) Overall, relevant animal tumour data tend to support a linear response with no threshold at low doses.

5.4. Life shortening

(204) A large number of studies in mice and dogs have been conducted using lifespan shortening as a means to quantify late radiation effects (Carnes et al., 1989, 2002, 2003; Grahn and Hamilton, 1964; Grahn and Sacher, 1957, 1958; Grahn et al., 1963; Lesher et al., 1960, 1965; NCRP, 1980; Sacher et al., 1958, 1976; Storer and Ullrich, 1983; Storer et al., 1979, 1982; Thomson and Grahn, 1988, 1989; Thomson et al., 1981a,b, 1983, 1985, 1986). While it has been argued that life shortening can serve as an integrated measure of the deleterious effects of radiation, the interpretation of these studies is not straightforward. A large variation in life shortening is observed as a function of strain, species, gender, and physiological status of the animals. This variation is largely a result of differences in the spectra of spontaneous and induced disease, and the age distribution of disease occurrence. For example, a high degree of life shortening is observed in animals susceptible to the induction of radiation-induced cancers that tend to occur early in life, such as thymic lymphoma or AML. Studies using animals that are not susceptible to such typically early-developing neoplasms but which tend to develop late-occurring solid tumours following radiation exposure have observed considerably less life shortening at the same radiation dose. Regardless of the degree of life shortening observed, analyses of experimental studies indicate that at low doses of radiation and for radiation delivered at low dose rates, radiation-induced life shortening is almost entirely due to radiation-induced cancer (Carnes et al., 2002; Lesher et al., 1960; NCRP, 1980; Storer et al., 1979, 1982). Life shortening attributable to non-neoplastic effects has only been observed at single acute doses in the range of 500 mGy and higher, and no such effects have been observed following low-dose-rate or protracted exposures to low-LET radiation (Carnes et al., 2002; Storer et al., 1979, 1982).

(205) Experiments designed to address questions of risk following low-dose-rate or protracted exposures have also been performed. With few exceptions, dose–response relationships derived from data following single acute radiation doses, fractionated exposures, and terminated low-dose-rate exposures all suggest linear dose–response relationships over a wide range of doses (Carnes et al., 2003; NCRP, 1980; Storer et al., 1979; Tanaka et al., 2003; Thomson and Grahn, 1988, 1989; Thomson et al., 1981a,b, 1983, 1985, 1986). This is not surprising as the dose–response relationship for life shortening represents the integrated dose–response relationships for a variety of tumour types whose individual dose–response relationships may vary widely. The primary effect of fractionating the radiation dose or reducing the dose rate at which the dose is delivered is to reduce the slope of the linear response. Importantly, experiments using multiple low-dose-rate terminated exposures suggest a limiting linear slope in all cases. Once this limiting linear response is reached, no further reduction in effect is seen if dose rate is reduced further. Protracting exposures over the entire lifespan can result in a further reduction in life shortening

per unit dose. There are two confounding factors in protraction studies that must be considered. First, in such studies, radiation injuries induced very late in life often do not have sufficient time to be expressed. Second, it is difficult to determine the dose at which specific effects have been induced because the exposure continues even after the processes involved have been initiated. Both factors tend to result in an overestimation of the dose required to produce a specific degree of observed life shortening (NCRP, 1980). This overestimation of the dose reduces the slope of the dose–effect relationship beyond the limiting slope obtained following terminated exposures.

5.5. Summary

(206) Studies on the cellular and molecular mechanisms of carcinogenesis over the last several years have provided substantial insight with respect to the complex multistep nature of the process of neoplastic development and on radiation-induced cancer. These studies provide direct support for the view that the critical radiation-associated events in the tumourigenic process are predominantly early events involving DNA losses targeting specific genomic regions harbouring critical genes. Since many of the radiation-associated DNA loss events in these tumourigenesis models involve large chromosomal regions within the genome, mechanisms for radiation-induced chromosome aberrations appear to be of particular significance. The predominant importance of DNA DSB induction and postirradiation error-prone NHEJ repair for the induction of aberrations, and the apparently critical role for radiation-induced aberrations in the pathogenesis of cancer in these experimental models, would tend to argue against the proposition of a low-dose threshold in the dose–response relationship.

(207) More recently, experimental studies have questioned whether the initiating events produced by radiation are direct chromosomal or mutational effects, or whether the mutations and chromosomal re-arrangements result indirectly as a consequence of genomic instability induced by radiation exposure. However, at this point, the mechanistic role of instability in radiation tumourigenesis is not clear. Data thus far suggest that in certain genetic settings, such as individuals harbouring specific types of DNA repair deficiencies, a role for postirradiation instability in tumourigenesis appears reasonable, but its general applicability and its impact on low-dose risks remain matters of investigation.

(208) Factors that modify the progression and persistence of initiated cells must also be considered when addressing low-dose risks. It is well known that the probability that individual initiated cells will progress to become tumours can be modulated by interactions with surrounding cell and tissue components as well as systemic host factors. Data thus far, however, suggest that such factors are not likely to play a major role in determining low-dose risks. Another important question is the persistence of radiation-initiated cells once the initial damage has been produced. It has been hypothesised, for example, that apoptosis could be a protective mechanism that removes potentially neoplastic cells and could, in effect, result in a threshold at low radiation doses. Two studies using different experimental systems (skin and mammary gland) have addressed this issue and found that latent radiation-initiated

cells could persist for a substantial portion of the rats' lifetimes. At present, therefore, it seems prudent to focus on early initiating cell and molecular events as the major determinant of risks at low doses.

(209) On the basis of the discussion of cellular and molecular mechanisms in this chapter, it can be predicted that the dose–response and time–dose (i.e. fractionation and protraction) relationships for radiation-induced cancer would be similar to those for radiation-induced chromosomal aberrations. Specifically, at low doses, a linear dose–response relationship would be anticipated. There are, however, relatively few studies on animal carcinogenesis where the data are sufficient to address the issue of dose–response relationships or the issue of dose-rate effects, protraction, and/or fractionation effects, and rigorously test these predictions. Those studies where such analyses are possible are mainly limited to rodent studies, principally studies in mice. Overall, these animal tumour data tend to support a linear response at low doses and dose rates with no threshold.

(210) A large number of studies in mice and dogs have been conducted using life-span shortening as a means to quantify late radiation effects, and it has been argued that life shortening can serve as an integrated measure of the deleterious effects of radiation. Support for this argument comes from the observation that, regardless of the degree of life shortening observed, radiation-induced life shortening is almost entirely due to radiation-induced cancer. Life-shortening experiments have examined risks following low-dose, low-dose-rate, or protracted exposures. The primary effect of fractionating the radiation dose or reducing the dose rate at which the dose is delivered is to reduce the slope of the linear response. Importantly, experiments using multiple low-dose-rate terminated exposures suggest a limiting linear slope in all cases, adding further support to the view that effects at low doses are consistent with a linear, non-threshold model.

5.6. Conclusions: implications for radiation-related cancer at low doses

(211) Models of radiation action as well as a wide range of molecular, cellular, and animal data have been used to argue that data on radiation-induced cancer in human populations derived from studies following acute radiation exposures tend to overestimate radiation risks at low doses and dose rates (ICRP, 1991; NCRP, 1980). In this regard, a number of advisory groups have used a similar approach to quantify the degree to which extrapolation of acute high-dose data may tend to overestimate risks at low doses and low dose rates. Essentially, the effectiveness per unit dose for acute exposures has been determined using a linear interpolation of data in the 2–3-Gy dose range and control data at 0 Gy. Effects per unit dose following low-dose-rate exposures were derived by calculating the slope of the entire dose–response relationship (not just in the 2–3-Gy dose range). By dividing the tumourigenic effectiveness per unit dose of acute exposures using the high-dose data and low-dose-rate exposures, an effectiveness ratio (DDREF) was obtained. The rationale for using only the high-dose data and not data at lower doses was based on the assumption that this would simulate analyses of risks from epidemiological studies where most of the available data were for single acute exposures at relatively high doses. Since the actual

dose–response relationship for most radiation-induced tumours following single acute exposures has generally been found to be linear quadratic (see discussion above), this procedure would tend to overestimate effects for single acute low doses (in the dose range where the response is predominantly linear) and for low-dose-rate exposures over a wide range of total doses.

(212) In spite of its apparent simplicity, the derivation and application of DDREFs must be performed with caution. Tumours for which there is evidence (from knowledge of their mechanisms) that they are unlikely to be applicable to radiation carcinogenesis in human populations should not be considered. This leaves a limited data set upon which to base DDREF calculations. These data sets include AML and a few solid tumours including Harderian gland (for which there is no comparable tissue in humans), lung adenocarcinomas, and mammary tumours. All the data sets for AML support a reduced carcinogenic effect when comparing high- and low-dose-rate exposures over the 0–3-Gy dose range. Calculation of DDREF values using the procedures described above yields estimates of the order of 2–6 with most values in the range of 4–5. For lung adenocarcinomas and Harderian gland tumours, DDREF values of approximately 3 have been calculated over the 0–2-Gy dose range. For mammary tumours, all of the data suggest a DDREF value of less than 2 and most are close to a value of 1 when effects of high- and low-dose-rate exposures are compared in the 0–2-Gy dose range. Thus, it appears that AML is probably more sensitive to dose-rate effects than solid tumours.

(213) It should be emphasised that these values are based upon extrapolation of data from acute doses of 2–3 Gy, and may represent maximum DDREF values (NCRP, 1980). Total dose-dependent dose-rate effects have also been reported and quantified for cytogenetic endpoints by Sorensen et al. (2000). The impact of dose range must be considered when applying DDREF factors to human risk estimates for which there are now reliable data at and below 1 Gy.

(214) It has been argued that life-shortening data may be a more appropriate measure of overall risk. Therefore, the use of these data is a better approach to the derivation of a single DDREF value. The complications of life-shortening data have been described in an earlier section including changes in disease spectrum as a function of dose and dose rate, and complications associated with terminated compared with lifetime exposures. These complications notwithstanding, DDREF values determined from terminated radiation experiments indicate maximum DDREF values following extrapolation of acute effects in the 2-Gy dose range of the order of 2. Protraction of the radiation exposure over a significant portion of an animal's lifetime tends to reduce the effectiveness of the exposure more than that observed following a simple reduction of dose rate to specific total doses. However, as discussed earlier, this experimental approach makes the determination of true effects per unit dose difficult if not impossible. As a result, the application of these large (i.e. >2) protraction factors to human risks is problematic.

6. QUANTITATIVE UNCERTAINTY ANALYSIS

6.1. Overview

(215) Chapter 2 described the epidemiological basis for estimation of radiation-related cancer risk in exposed populations, including various uncertain factors that must be considered when applying epidemiological risk estimates from one population to another, especially when the base data are as yet incomplete and must be projected forward to end of lifetime of the study population. The discussion was focused on uncertain biases introduced by random dose-reconstruction error in the first population, population differences in baseline cancer rates, and extrapolation of estimates, derived largely from moderate-to-high dose data, to situations of low-dose and very-low-dose exposure. The topic of the present chapter is quantitative uncertainty analysis of estimated cancer risk associated with low-dose, low-LET radiation exposure, illustrated in terms of the application of atomic bomb survivor risk coefficients to the population of the USA.

(216) Quantitative uncertainty analysis (QUA) was developed in a decision-theoretic framework and has been extensively applied to nuclear reactor safety (US Nuclear Regulatory Commission, 1975, 1990) and ecological risk assessment (Gilbert et al., 1996; IAEA, 1989; Warren-Hicks and Moore, 1998). It involves the application of Bayesian probability methods to estimates and decision rules based on uncertain statistical and subjective information. As stated by Warren-Hicks and Moore (1998), benefits of quantitative uncertainty analysis include improved transparency and credibility, avoidance of worst-case assumptions, a focus on critical areas of uncertainty that may benefit from further data collection, and improved decision support. Limitations of the method include the practical inability to consider all possible sources of uncertainty, the possibility that the method may be used incorrectly, and lack of universal awareness and acceptance of the methodology.

(217) The approach (i.e. QUA) is used here, not to reach a particular decision but to illustrate the implications for radiation protection of the various types of (mostly uncertain) information that contribute to our estimates of radiation-related risk. The emphasis on uncertainty is appropriate because the need for radiation protection is driven by the likelihood and magnitude of exposure-related risks, because estimates based on statistical data and realistic assumptions are uncertain, and because radiation protection is a political process that must take account of the diverse interests and viewpoints of individuals and population subgroups affected by implementation of radiation protection policies. To be successful, the development of such policies requires accommodation and consensus. It must be seen to be done fairly and openly, on the basis of facts and assumptions accessible to and challengeable by all of those affected by implementation. An important aspect of the information relevant to the political process of radiation protection is the uncertainty of estimates of radiation-related risk derived from a combination of statistical and largely subjective information sources.

(218) Different people have different points of view about risk. For example, a risk-averse person may tend to focus on how high the risk from exposure may

reasonably be (e.g. on its upper 90% uncertainty limit), while a person who is primarily averse to the costs of exposure reduction may tend to demand proof that the risk is high enough to worry about, e.g. may focus on its lower uncertainty limits. A complete uncertainty distribution for estimated risk summarises all the uncertainty information inherent in the statistical data used, and in the consensus estimates of crucial assumptions needed to apply the statistical data to the matter at hand. That summary is highly relevant to both of these points of view and to others as well.

(219) Radiation-related cancer risk is among the subjects most suitable for QUA. It is highly quantified and a number of major sources of uncertainty have been explored (CIRRPC, 1988; EPA, 1999; NCI/CDC, 2003; NCRP, 1996, 1997; NIH, 1985; Sinclair, 1994). Knowledge of uncertainty is highly relevant to radiation protection philosophy and practice, and it can be at least as important as knowing the value of a single-valued 'best estimate'. For example, a point estimate of one lifetime excess cancer death per 1000, with 90% probability (uncertainty) limits of 0.5–2.0/1000, has different implications for, say, a risk–benefit analysis than the same point estimate with probability limits of 0.1–10/1000. In the second case, assuming a log-normal uncertainty distribution, the likelihood that the risk per 1000 is between 0.5 and 2.0 is only 38% and the likelihood that it is greater than 2.0 is 31%.

(220) Statistical analyses of epidemiological or experimental observations on radiation carcinogenesis are usually concerned with quantifying risk in the context of a particular study. Applications of the original risk estimates in other contexts, without adjustment, may be misleading for a number of reasons discussed earlier in this chapter. Adjustment requires other steps and assumptions about which the original study may not be informative. The incorporation from other sources of additional information, which may be uncertain, may modify the resultant risk estimate and its uncertainty.

(221) Uncertainty analysis is concerned with such changes and their implications for the ultimate application of (in the present case) risk estimates. The approach has been extensively applied in assessments of environmental contamination (NCRP, 1996). The 1985 NIH radioepidemiological tables report (NIH, 1985) was possibly the first formal application to radiation-related cancer risk. The approach was subsequently taken a step further, at the request of the United States Department of Veterans Affairs, by the Committee on Interagency Radiation Research and Policy Coordination (CIRRPC, 1988). The following discussion is based primarily on the following sources: NCRP Commentary 14 (1996) discusses uncertainty analysis applications to assessment of dose and risk related to environmental contamination; NCRP Report 126 (1997) was derived in part from Sinclair (1994) and is specifically concerned with applications of radiation-related mortality risk estimates to low-LET radiation protection; an EPA report (1999) deals with the same subject; and a recent revision of the 1985 NIH radioepidemiological tables report (NCI/CDC, 2003) is concerned with applications to adjudication of compensation claims for radiation-related cancer morbidity.

(222) When one estimates the radiation-related cancer risk associated with a particular low-dose exposure history, what is it that one is estimating? Some possibilities include:

(a) An increase in lifetime cancer rate, e.g. from r to $r' = r \times (1 + x)$, for a particular population specified by age, sex, lifestyle, etc. Note that this increase can theoretically be verified by observation of cancer rates among exposed and non-exposed members of the population. Estimation requires information on:

(i) Dose-related risk in a population (or group of populations), and the variation of that risk by sex, age, etc. Generally, this information will pertain most directly to doses and dose rates higher than those of immediate interest. For radiation-related risk, there is a substantial body of epidemiological information, the most comprehensive of which is based on follow-up of the survivors of the atomic bombings of Hiroshima and Nagasaki, Japan.

(ii) How to transfer risk estimates for the informative population to the population of interest, which may differ from the first population in specified ways such as baseline cancer rate, smoking prevalence, patterns of reproductive history, or other possible dose–response modifiers. Also, random and biased errors in dose reconstruction for the first population, which should not affect risk estimates for members of the first population, may bias the application of dose-specific risk estimates to the second population. A similar problem exists for biased ascertainment of cancer cases, e.g. because of inaccuracies of death certificates.

(iii) How to extrapolate risk from high to low doses and from high to low dose rates, including DDREF and departures from the LNT theory such as hormesis and low-dose threshold.

(b) The likelihood that a particular individual will develop cancer as a result of his or her exposure. Note that this likelihood is not verifiable at the individual level; the individual either will or will not develop cancer, and the estimate of the individual's probability, or excess probability, of developing cancer is verifiable only if one assumes that information on a population also pertains to the individual.

(223) Thus, (b) reduces to (a), and is addressed as follows:

(i) Identify the individual as a member of a population with the exposure history and other characteristics of the individual insofar as the relevance of these characteristics to risk is known or estimated.

(ii) Estimate the exposure-related increase in cancer rate for that population.

(iii) Treat the individual as a randomly sampled person from the population, i.e. a possible cancer event is treated as a Bernoulli random variable with probability $p = r'$ as given in (a) above. Note that r' is itself an uncertain quantity.

(224) The types of required information discussed under (a) are qualitatively different. Many of them are subjective in nature, requiring expert judgement.

6.2. Sources of uncertainty

6.2.1. Statistical estimate of excess risk per Gy

(225) The epidemiological information from a radiation-exposed population is summarised by a statistical estimate of excess EAR or ERR, the uncertainty of

which can be expressed by confidence limits or, more comprehensively, by a probability distribution derived from the statistical likelihood contour of the estimate. This probability distribution defines likelihood-based statistical confidence limits at all confidence levels, and may depend upon sex, exposure age, attained age, and other identifiable risk modifiers. Fig. 6.1 represents an example of a likelihood-based statistical uncertainty distribution for ERR of cancer at 50 years of age or older following a 1-Gy, whole-body acute exposure at 40 years of age. The estimate is based on a linear-model dose–response analysis of LSS tumour registry cancer incidence data (Thompson et al., 1994) for males, re-analysed in the context of adjudication of compensation claims for possibly radiation-related cancer (NCI/CDC, 2003). In that analysis, it was found that most variation of ERR by exposure age was confined to ages under 30 years, and that most variation by attained age occurred at ages under 50 years. A model was used based on log-linear splines in exposure age and attained age such that there was no variation in ERR per Gy by exposure age after 30 years and by attained age after 50 years. The resultant statistical uncertainty distribution for ERR per Gy at older exposure ages and attained ages is approximately lognormal with 5th and 95th percentiles (90% confidence limits) of 0.18 and 0.43.

(226) This statistical uncertainty distribution is the basis for the numerical demonstration presented below. However, summary results are also given, later in this chapter, for calculations based on the fitted estimate for a female population, with a lognormal statistical uncertainty distribution and 90% confidence limits of 0.45 and 0.72, and for a population evenly divided by sex, for which the confidence limits are 0.33 and 0.53.

(227) Estimates of EAR for age-specific risk, or for lifetime risk starting from 50 years of age, can be obtained by scaling the ERR distributions by the appropriate age-specific or lifetime baseline cancer rates. However, since the population of interest is not the LSS population and the exposure of interest is not to an acute dose of 1 Gy in most applications, it is computationally convenient to develop the ERR estimate for the population and exposure of interest and then convert it to EAR.

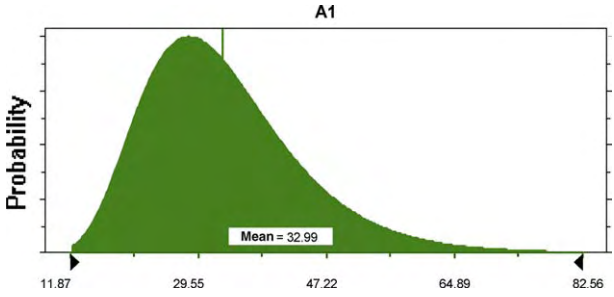


Fig. 6.1. Lognormal distribution with 90% confidence limits of 18–43%, representing statistical uncertainty about percentage cancer excess relative risk per Gy.

6.2.2. Diagnostic misclassification

(228) Based on autopsy-based analyses by Sposto et al. (1992) of misclassification of cancer as non-cancer on death certificates, NCRP Report 126 (1997) introduced an uncertain correction factor for combined-site cancer mortality risk estimates, subjectively distributed as normal with 5th and 95th percentiles of 1.02 and 1.18, respectively. No correction factor was deemed necessary, however, for cancer morbidity as determined by the RERF Tumor Registry, and none is applied in the present exercise (or 90% 'probability limits', here used as a general term to include statistical confidence limits and uncertainty limits for distributions that have a subjective component).

6.2.3. Dose-reconstruction errors

(229) Application of epidemiological information from one radiation-exposed population to a second population is problematic because errors in dose reconstruction for the first population are unlikely to be repeated in the second. Therefore, dose-specific risk estimates should be corrected before being applied to the second population. Also, lifestyle, environmental, and other factors may differentially modify the radiation dose–response relationships in the two populations.

(230) NCRP Report 126 (1997) treated bias correction for dose-reconstruction error in the atomic bomb survivors, involving five different factors: random errors in individual dose estimates [following Pierce et al. (1991)]; uncertainty about the magnitude of the neutron component of dose in Hiroshima; uncertainty about the relative biological effectiveness weight, relative to gamma dose, applied to the neutron component of individual dose; uncertain neutron dose; and uncertain gamma dose. A full rationale is given in NCRP Report 126 (NCRP, 1997) to which the reader is referred for details. With the implementation of a new atomic bomb survivor dose reconstruction system, designated DS02 (Preston et al., 2004), the details will change. For present purposes, it is enough to note that dose reconstruction is a source of bias and uncertain error that can contribute to the uncertainties of risk estimates and should be taken into account. For illustration, the subjective uncertainty distribution of the combined correction factor, described in Fig. 3.6 of NCRP Report 126 (1997) and redrawn for Fig. 6.2 of this report, has been used, which was calculated as approximately normal with a mean of 0.84 and 90% uncertainty limits of 0.69–1.0. The resulting corrected uncertainty distribution for ERR at 1 Gy is approximately lognormal with a mean of 0.26 and 90% limits of 0.15 and 0.46 (Fig. 6.3).

6.2.4. Transfer between populations

(231) Also uncertain is the relationship between radiation-related excess risk and baseline cancer rates in the two populations. This is an important consideration if population baseline rates differ substantially. For example, current age-specific incidence rates for female breast cancer are substantially higher in the USA than in

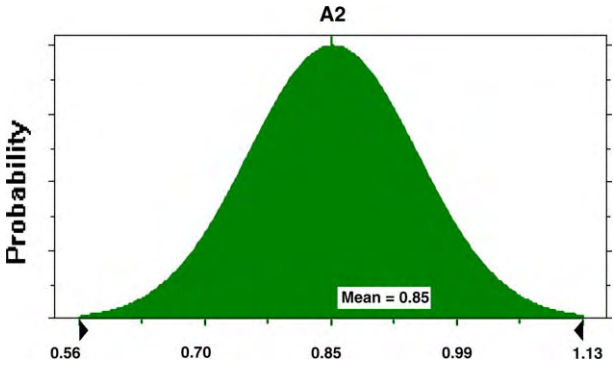


Fig. 6.2. Normal uncertainty distribution for dosimetry bias correction factor, with a mean of 0.84 and 90% uncertainty limits of 0.69–1.00.

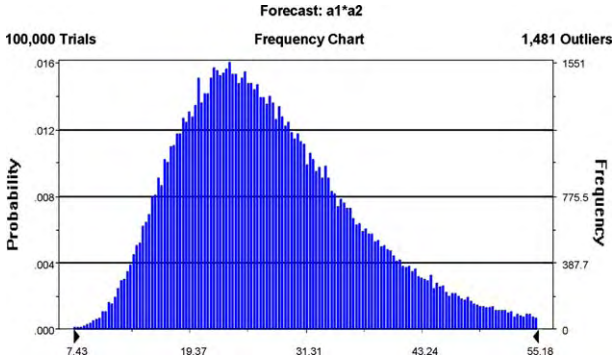


Fig. 6.3. Approximately lognormal uncertainty distribution for excess relative risk per Gy corrected for dosimetry bias, with a mean of 0.26 and uncertainty limits of 0.15–0.46.

Japan, according to tumour registry data from Hiroshima and the US SEER Registry (Parkin et al., 2002) (Fig. 6.4). In Fig. 6.4, breast cancer risk among female atomic bomb survivors exposed to a breast tissue dose of 1 Gy at 15 years of age is represented as a constant multiple of age-specific baseline risk beginning at 25 years of age. The two dashed curves tracking the US age-specific baseline rates represent two of many different ways of transferring the atomic bomb survivor estimate to a US population. The lower of the two dashed curves was calculated as the sum of the US baseline rate plus the radiation-related excess (absolute) rate in the atomic bomb survivors (additive transfer). The higher curve was calculated as the product of the US baseline rate times the estimated radiation-related relative risk among the atomic bomb survivors (multiplicative transfer). If the baseline rate curves were the same, the additive and multiplicative transfer methods would give the same solution. As the baseline rates are so different, the lifetable-averaged (over age) estimates of excess risk differ by three-fold.

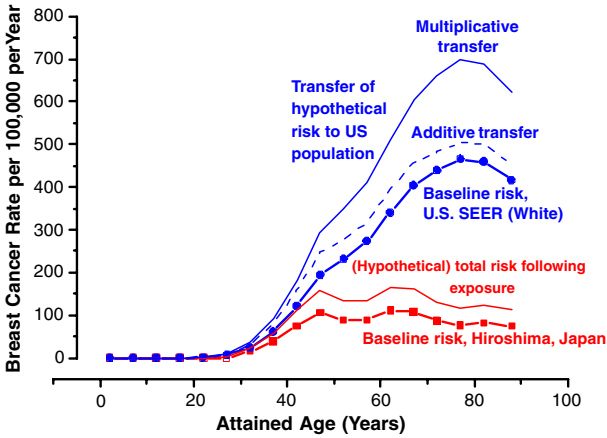


Fig. 6.4. Comparison of age-specific baseline rates for female breast cancer incidence in Japan and the USA (lower and upper polygonal lines with data points, respectively), estimated rate following a hypothetical radiation exposure of a Japanese population at 15 years of age (lower solid polygonal line without data points), and estimates for a US population obtained by additive (broken curve) and multiplicative transfer (upper solid curve) of estimated excess risk from the Japanese to the US population.

(232) In the case of breast cancer, there is epidemiological evidence that the additive transfer model is more realistic than the multiplicative model (Land et al., 1980; Little and Boice, 1999; Preston et al., 2002), but there is not enough evidence to rule out alternatives. For stomach cancer, there are some data favouring multiplicative transfer (Boice et al., 1988; Carr et al., 2002; Inskip et al., 1990). For most other site-specific cancers, there is little or no relevant information on transfer between populations. NCRP Report 126 (NCRP, 1997) only considered total cancer mortality, which is about 40% and 80% higher in the USA than in Japan for males and females, respectively (Pisani et al., 1999). In NCRP Report 126, subjective uncertainty about population transfer was expressed as an uncertain multiplicative correction factor, distributed as lognormal with 5th and 95th percentiles at 0.70 and 1.65, respectively, to be applied to the multiplicative transfer model estimate (NCRP, 1997).

(233) For site-specific cancers, a more detailed approach is needed because standardised rates may differ between the two countries by as much as 10- to 15-fold in either direction (e.g. for liver, stomach, prostate), although rates are more comparable for most sites. The approach used for the updated NIH radioepidemiological tables report (NCI/CDC, 2003) for most cancer sites was to weight equally all possible linear combinations of the multiplicative (M) and additive (A) model estimates, $p \times M + (1 - p) \times A$, by assuming p to be a random variable distributed approximately uniformly over the unit interval. This subjective approach was motivated by: (1) the consideration that differences in baseline rates may reflect differential exposure to both cancer initiators (consistent with additive transfer) and cancer promoters (consistent with multiplicative transfer); and (2) an almost complete lack of relevant epidemiological information for most cancer sites. The general EPA

approach for site-specific cancer risk was similar but on a logarithmic scale. The logarithm of the excess risk was assumed to be a linear mixture between the logarithms of the multiplicative and additive transfer model estimates (EPA, 1999), where the uncertain mixture parameter p was assumed to be uniformly distributed over the unit interval. The EPA approach tends to yield somewhat lower risk estimates than the NCI/CDC approach. For the few sites where information on population transfer was available, the NCI/CDC approach was to favour one simple transfer model over the other, e.g. for breast cancer, a probability of 0.5 was placed on additive transfer and a probability of 0.5 on the uniform model; for stomach cancer, a probability of 0.33 was placed on multiplicative transfer and a probability of 0.67 on the uniform model.

(234) For all cancers except skin, as a group, the sex-/age-standardised ratio of American to Japanese rates was assumed to be 1.3 (Parkin, 2002). Multiplicative transfer of LSS-based ERR would involve applying the same ERR to US baseline rates, whereas for additive transfer, the LSS-based ERR would be divided by 1.3 to obtain the same absolute excess in the two countries. The resulting uncertainty distribution for ERR at 1 Gy in a US population, after application of the NCI/CDC approach, is approximately lognormal with 90% limits of 0.13–0.41 and a mean of 0.25 (Fig. 6.5).

6.2.5. Dose and dose-rate effectiveness factor

(235) In general, epidemiological estimates of overall and site-specific cancer risk related to radiation exposure are statistically consistent with a linear dose–response relationship (leukaemia, with a linear-quadratic dose–response relationship, is an exception). For the same reasons that data restricted to low doses tend to be uninformative about radiation-related excess risk, this apparent linearity does not rule out, on statistical grounds, the possibility of increased, decreased, or even absent excess risk per unit dose at very low doses. For various reasons discussed in Chapters 2 and 3, linear-model estimated excess risk is often divided by a DDREF at low doses and low dose rates. The ICRP (1991) recommended a DDREF of 2 for radiation

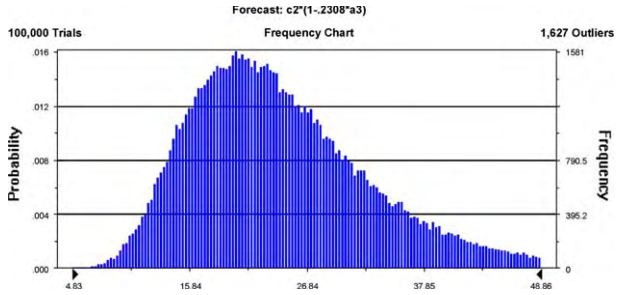


Fig. 6.5. Monte Carlo simulation of the uncertainty distribution for cancer excess relative risk (in %) at 1 Gy, after transfer to a US population: the simulated distribution is approximately lognormal with a mean of 0.25 and 90% probability limits of 0.13–0.41.

protection purposes, and the United Nations Scientific Committee on Effects of Ionizing Radiation (UNSCEAR, 1993) recommended that the chosen DDREF should be applied to chronic exposures at dose rates less than 6 mGy/h averaged over the first few hours, and to acute exposures at total doses less than 0.2 Gy. This recommendation was adopted by the EPA (1999). Continuous, subjective uncertainty distributions for DDREF were used in uncertainty analyses carried out for NCRP Report 126 (NCRP, 1997), the EPA (1999), and by an expert committee advising the Colorado Department of Public Health and Environment (Grogan et al., 2001) (Fig. 6.6). The Grogan uncertainty distribution differs from the NCRP distribution mainly in allowing a small probability that risk per unit dose may increase at very low doses. Thus, the NCRP and EPA distributions allowed for the possibility of DDREF values between 1 and 5, while the Grogan et al. distribution included DDREF values as low as 0.2. The uncertainty analysis for the revised NIH radioepidemiological tables report postulated a discrete subjective uncertainty distribution for DDREF, with non-zero probabilities assigned to 0.5, 0.7, 1.0, 1.5, 2.0, 3.0, 4.0, and 5.0 (Fig. 6.7).

(236) Application of a DDREF greater than 1 reduces estimated risk, and an uncertain DDREF introduces additional uncertainty in estimated risk. Applying the different DDREF assumptions summarised in Figs. 6.6 and 6.7 to the adjusted uncertainty distribution for risk in Fig. 6.5 resulted in roughly lognormal uncertainty distributions for ERR per Gy at low doses and dose rates, with mean values substantially less than the mean value of 0.25 for ERR at 1 Gy for acute exposures corresponding to the uncertainty distribution in Fig. 6.5, and upper 95% uncertainty limits somewhat less than the value of 0.41, also from Fig. 6.5. Means and upper limits were 0.12 and 0.20, respectively, for the EPA DDREF, 0.11 and 0.23 for the

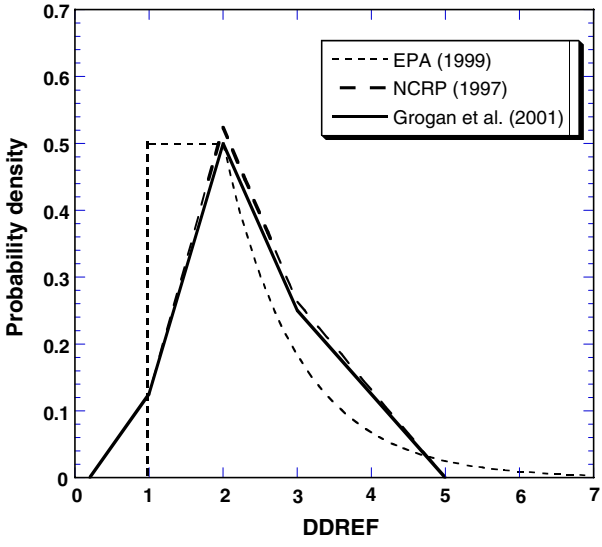


Fig. 6.6. Continuous subjective uncertainty distributions for dose and dose-rate effectiveness factors (DDREFs) used in recent analyses (F.O. Hoffmann, pers. comm.).

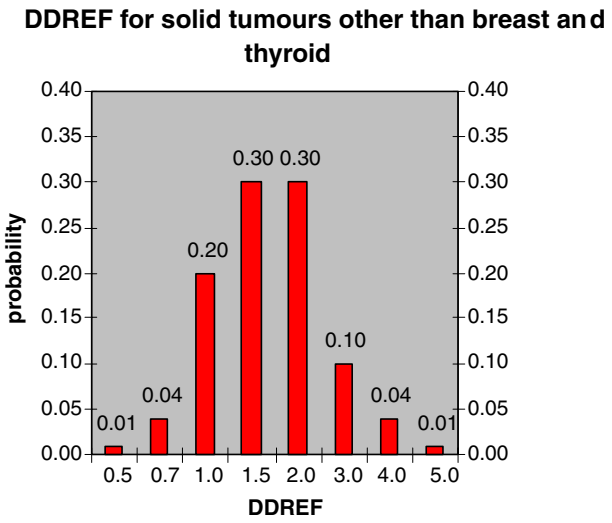


Fig. 6.7. Discrete uncertainty distribution for dose and dose-rate effectiveness factors (DDREFs) used in the NCI/CDC (2003) analysis.

NCRP model, 0.12 and 0.28 for the Grogan et al. model, and 0.17 and 0.36 for the NCI/CDC model (Fig. 6.8).

6.2.6. Variation by sex

(237) The above results apply to males. Carrying out the same calculations based on the statistical uncertainty presented in Section 6.2.1 for a female population yields an ultimate uncertainty distribution using the NCI/CDC DDREF model, with a mean of 0.355 and a 95th percentile of 0.69. For a population divided equally by age and sex, the mean is 0.26 and the upper limit is 0.50.

6.2.7. Expression of excess risk in absolute terms

(238) For US males, the lifetime baseline cancer risk, tabulated by the National Cancer Instituteã CPÖs SEER program (use 'FastStats' under http://seer.cancer.gov/statistics) from 50 years of age (given cancer-free survival to 40 years of age) is 45.3%. Thus, the estimated lifetime excess cancer risk per Gy associated with a low-dose, low-LET, whole-body radiation exposure is roughly lognormal with a mean of $0.17 \times 45.3\% = 7.7\%$ and a 95^{th} percentile of $0.36 \times 45.3\% = 16.3\%$; the 5th percentile is $0.066 \times 45.3\% = 1.1\%$. For females, the corresponding baseline risk is 35.5%, and the uncertainty distribution for lifetime EAR per Gy has a mean of $0.355 \times 35.5\% = 12.6\%$ and 90% uncertainty bounds of 0.146 and $0.69 \times 35.5\% = 5.2\%$ and 24.5%. For a population evenly divided by sex, the baseline risk from 50 years of age given survival to 40 years of age is 40.4%, and lifetime EAR per Gy is roughly lognormal with a mean of 10.5% and 90% bounds of 3.8% and 20.1%.

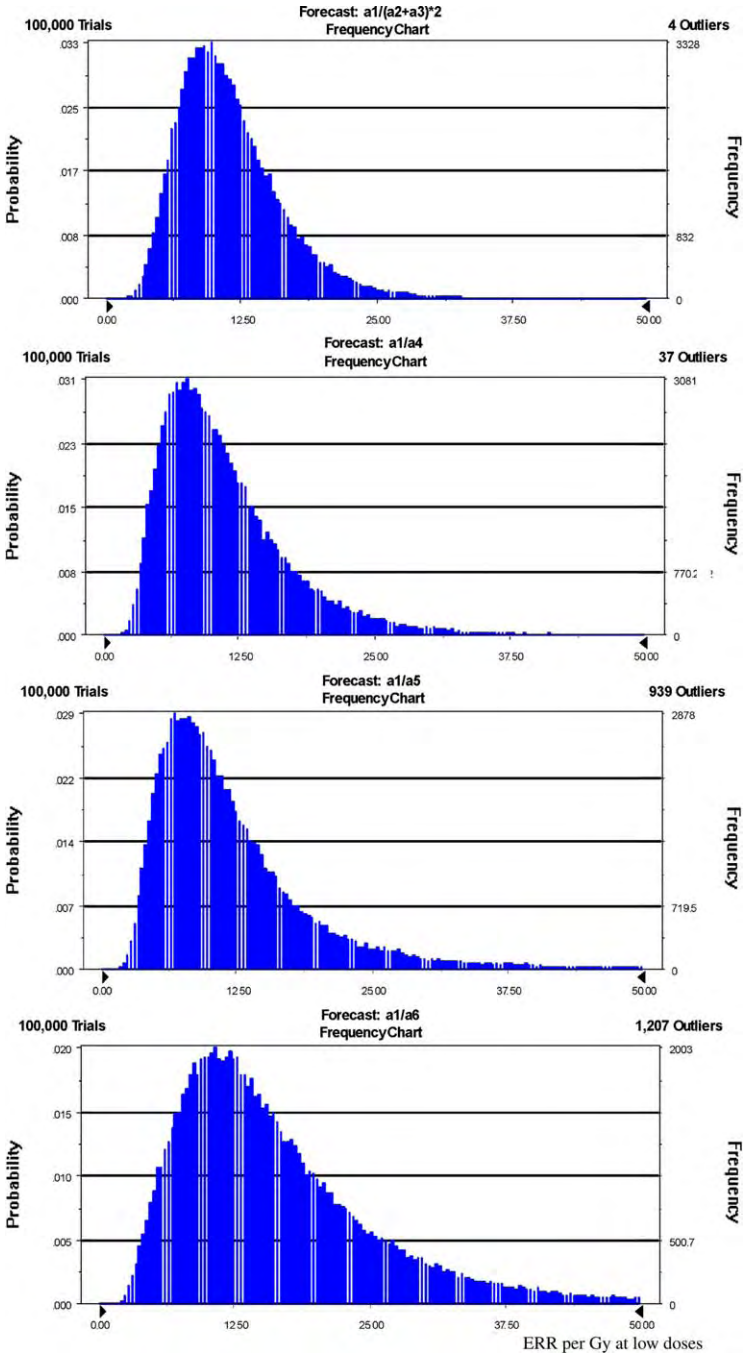


Fig. 6.8. Influence of dose and dose-rate effectiveness factor assumptions on uncertainty for excess relative risk (ERR) per Gy (%).

6.2.8. Gradualism in DDREF and threshold effects

(239) A rule that a DDREF should apply at acute doses below (say) 0.2 Gy and not at 0.2 Gy and above, or at dose rates less than 6 mGy/h but not at dose rates marginally higher than that value, is contrary to experience with stochastic phenomena, and would be difficult for practical applications, e.g. in adjudicating compensation claims for radiation-related cancer. Accordingly, in the recent revision of the NIH radioepidemiological tables report (NCI/CDC, 2003), DDREF was gradually phased in, from 1 to its (uncertain) full value, over an interval of decreasing dose of acute exposure. Similarly, a threshold dose, below which there is presumed to be no radiation-related risk, is generally not thought of as a value associated with the abrupt disappearance of risk, but a (possibly uncertain) value greater than 0 Gy at which the gradual disappearance of excess risk with decreasing dose becomes complete. Thus, a threshold or possible threshold would, like the DDREF, be phased in gradually with decreasing dose.

(240) For simplicity of presentation, phasing in DDREF and/or a threshold is ignored in the following discussion.

6.3. Allowing for the uncertain possibility of a threshold

(241) The threshold concept only has practical importance if the threshold dose is high enough to justify ignoring, for radiation protection purposes, a substantial range of exposures that would otherwise be of concern. A reasonable way to include the threshold concept in an uncertainty analysis is to multiply the uncertain dose-specific ERR, adjusted for the DDREF and other factors discussed in the preceding paragraphs, by a threshold factor distributed as a Bernoulli random variable taking value zero with probability $p(D)$ and value one with probability 1 - $p(D)$, where 0 # $p(D)$ # 1 and p is a possibly uncertain, decreasing function of radiation dose D. Some examples will illustrate the impact of uncertainties regarding whether a threshold exists or the dose level of that threshold.

(242) Example 1 – threshold and dose level certain. Known threshold at 10 mGy: $p(D) = 1$ for D#10 mGy and $p(D) = 0$ for D>10 mGy (for simplicity, the threshold is not phased in as a function of D). Thus, the uncertainty distribution for excess risk assigns probability 1 to the value 0, below 10 mGy, and is the same as that without a threshold (e.g. the NCI/CDC distribution in Fig. 6.8) above 10 mGy. The mean and 95% upper probability limit on ERR per Gy are unchanged above 10 mGy, but they are both zero below that dose level. This example represents the common conception held by those who believe that there is a threshold, albeit the putative threshold dose level may differ from 10 mGy.

(243) Example 2 – threshold uncertain but threshold dose level certain. A threshold may exist at 10 mGy; this possibility is assigned subjective probability p, where p is a known value such as 5%, 20%, 50%, or 80%. The uncertainty distribution of ERR per Gy risk below 10 mGy assigns probability P to zero and, for all other possible values of ERR per Gy, $1 - p$ times the probability that would be assigned if there were no threshold. For doses below 10 mGy, the mean of the uncertainty

distribution is $1 - p$ times the mean of the uncertainty distribution for ERR per Gy if there were no threshold (i.e. if p were 0). The 95% upper uncertainty limit is given by limit = $F^{-1}[(0.95 - p)/(1 - p)]$ for $p < 0.95$, and limit = 0 for $p \exists 0.95$, where F^{-1} is the inverse cumulative distribution function of the uncertainty distribution in the absence of a threshold (Land, 2002). Plots of the mean and upper 95% limit, as functions of p, are shown in Fig. 6.9 for the approximate lognormal uncertainty distribution for ERR per Gy according to the NCI/CDC model as represented in Fig. 6.8. This example shows that when the probability of a dose threshold is uncertain, the central estimate of the ERR per Gy for low doses decreases linearly with an increasing probability that there is a threshold, but the 95% upper limit remains quite high until the probability of a threshold reaches 80–90%, after which it falls sharply. This indicates that unless there is consensus agreement that a threshold is very likely, the potential for an appreciable low-dose risk cannot be ruled out.

(244) Example 3 – threshold certain but its dose level uncertain. A threshold is known to exist somewhere between 5 and 25 mGy, but otherwise is completely uncertain: $p(D;D_0) = 1$ for $D\# D_0$, and = 0 for $D>D_0$, where D_0 is an uncertain (random) quantity uniformly distributed between 5 and 25 mGy. Estimated ERR per Gy is 0 below 5 mGy, but the probability assigned to non-zero values by the uncertainty distribution for risk at dose D increases linearly from 0 at D = 5 mGy to 1 (or to the value assigned in the absence of a threshold) at D = 25 mGy. The uncertainty distribution for ERR per Gy assigns probability 1 to 0 for D below 5 mGy, 100% to the non-threshold distribution for doses above 25 mGy, and probability (25–D)/20 to 0 and probability (D–5)/20 to the non-threshold uncertainty distribution, for

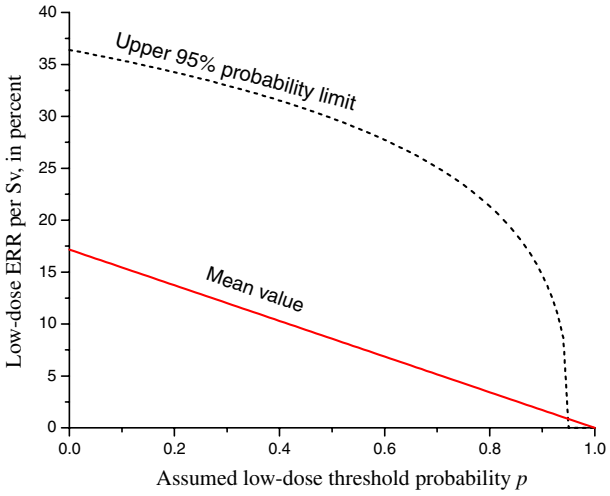


Fig. 6.9. Mean and upper 95% probability limit for excess relative risk (ERR) per Gy as functions of threshold probability p, given (in the absence of a threshold) a lognormal uncertainty distribution with a mean of 0.17 and an upper 95% limit of 0.36.

$5 < D < 25$. The mean and upper 95% uncertainty limit at dose D are as given in Example 2, and shown in Fig. 6.9, for $P = (25–D)/20$.

(245) The third example illustrates an important point: even when one is certain that there is a dose threshold but is still uncertain as to the dose level at which it occurs, the low-dose ERR per Gy behaves very similarly to the result for Example 2 (which had a fixed threshold dose but uncertainty regarding whether there was a threshold). Specifically, there is still some probability that the low-dose ERR per Gy is appreciable.

(246) Example 3a – there is a threshold for each individual in a population, but the dose level varies by individual. Thus, for a randomly chosen individual from the population, there is a threshold, but its dose level is uncertain. Mathematically, this example is essentially the same as Example 3.

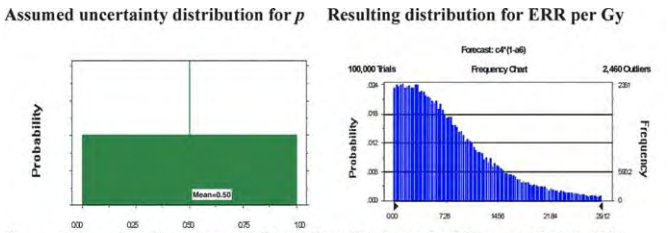
(247) Example 4 – threshold probability very uncertain but its dose level, conditional on existence of a threshold, is certain. A threshold may exist at 10 mGy, with uncertain probability. Enough is known (or there is a consensus among experts, which may be a compromise) to characterise the subjective uncertainty distribution of $p(D)$ for $D < 10$ mGy; for example, as:

(i) uniform between 0 and 1: U(0, 1);
(ii) triangular between 0 and 1 with peak at 0: Tr(0, 0, 1);
(iii) Tr(0, 0.25, 1) (peak at $p = 0.25$);
(iv) Tr(0, 0.5, 1);
(v) Tr(0, 0.75, 1); and
(vi) Tr(0, 1, 1).

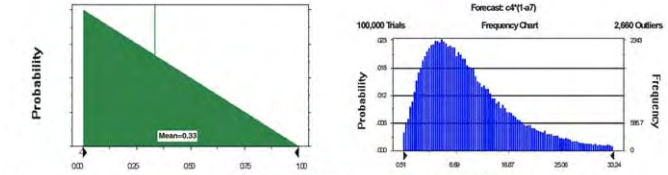
(248) In Example 4, the proportion of the uncertainty distribution for ERR per Gy assigned to zero is randomly distributed over the unit interval, and the mean and upper 95% limit of the resulting distribution depends on the assumed distribution of$p$. Fig. 6.10 shows Monte Carlo estimates of the resulting uncertainty distributions for ERR per Gy for the six cases, again using the NCI/CDC non-threshold distribution from Fig. 6.8, and the corresponding means and upper 95% uncertainty limits.

(249) The probability distributions in Fig. 6.10 show, not unexpectedly, that if the consensus uncertainty distribution of p gives a high weight to the likelihood of a threshold (e.g. subjective distribution *vi*), the distribution of the low-dose ERR per Gy is weighted toward small values, whereas the opposite is true when the probability of a threshold is less likely [e.g. subjective distributions (ii) or (iii)]. Nevertheless, even for distribution (vi), the mean expected low-dose ERR per Gy of 5.7% is about one-third as great as under the LNT theory (ERR per Gy = 17%), and it is between 40% and 70% of the LNT value for distributions (i)–(v).

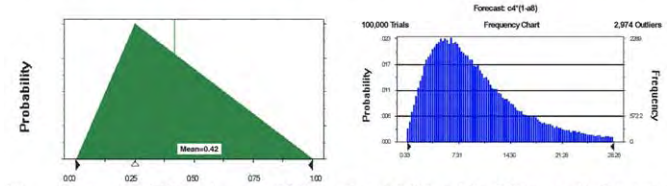
(250) Example 5 – dose-dependent uncertain probability of a threshold. Suppose that the uncertainty distribution for a threshold at 10 mGy corresponds to Example 4, distribution (ii), i.e. Tr(0, 0, 1), and that the uncertainty distributions for thresholds at 1 mGy and at 0.1 mGy correspond to Example 4, distributions (iv) [Tr(0, 0.5, 1)] and (vi) [Tr(0, 1, 1)], respectively. Then the subjective means and upper uncertainty limits for ERR per Gy would be 11.5% and 27%, respectively, at 10 mGy, 8.6% and 21% at 1 mGy, and 5.7% and 17% at 0.1 mGy. The corresponding values



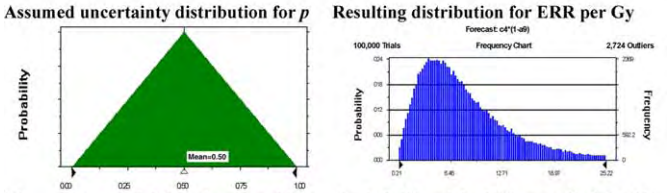
i) For $p \sim U(0,1)$, the mean ERR per Gy is 8.6% and the 95% upper limit is 23%.



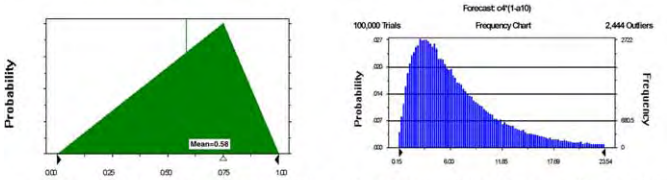
ii) For $p \sim T(0,0,1)$, the mean ERR per Gy is 11.5% and the 95% upper limit is 27%.



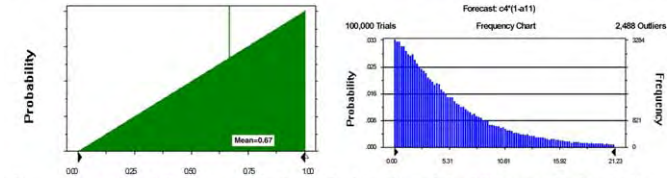
iii) For $p \sim T(0,0.25,1)$, the mean ERR per Gy is 10.4% and the 95% upper limit is 24%.



iv) For $p \sim T(0,0.5,1)$, the mean ERR per Gy is 8.6% and the 95% upper limit is 21%.



v) For $p \sim T(0,0.75,1)$, the mean ERR per Gy is 7.2% and the 95% upper limit is 19%.



vi) For $p \sim T(0,1,1)$, the mean ERR per Gy is 5.7% and the 95% upper limit is 17%.

Fig. 6.10. Effect of uncertain threshold probability on the uncertain distribution for low-dose excess relative risk (ERR) per Gy.

of ERR would be 0.115% and 0.27% at 10 mGy, 0.0086% and 0.021% at 1 mGy, and 0.00057% and 0.0017% at 0.1 mGy. The mean and 95% upper limit for ERR at 0.1 mGy can be compared with the mean of 0.0017% and upper limit of 0.0036% according to the LNT theory.

(251) Of the five examples above, Example 5 probably best reflects our present state of knowledge about low-dose risk, namely that we are uncertain about the likelihood of a dose threshold, and that in addition, if there should be a dose threshold, we are uncertain about what dose level it would be. However, as a counter to an agnostic viewpoint, it should be noted that the mechanistic and experimental data discussed in this monograph tend to give weight to a non-threshold model, as do the solid tumour data in the Japanese atomic bomb study. In addition to apparent linearity of the dose–response relationship down to doses below 100 mGy, an analysis by Pierce and Preston (2000) found that a threshold above 60 mGy would be statistically inconsistent with LSS dose–response data for all solid cancers combined.

6.4. Conclusions

(252) Information on radiation-related cancer risk is needed: (1) as guidance for radiation protection efforts; (2) as a basis for informed consent by people who may be asked to accept a certain level of exposure in the interests of medical research, economic progress, or some other social good; (3) for adjudication of claims and disputes concerning cases of disease possibly related to past radiation exposure; and (4) for risk–benefit analyses of public policy initiatives related to radiation. As mentioned previously in this report, these issues are essentially political in the sense that different people have different interests and points of view, and these must be taken into consideration when policies are developed. Moreover, implementation of such policies inevitably involves accommodation and consensus, and it is important that the policies are seen to be derived fairly and openly on the basis of facts and assumptions that are wholly accessible to those affected by implementation.

(253) Information useful for these purposes includes central estimates of dose-specific risk, but also lower and (especially) upper probability bounds on risk. Probability bounds can reflect both statistical uncertainty, estimated by fitting a mathematical model to observational data, and subjective uncertainty that may take into account model assumptions that are necessary to calculate estimates but are themselves uncertain. Probability bounds provide a level of transparency substantially beyond that provided by a point estimate, such as the expected (mean) value of the uncertainty distribution for estimated excess risk. A lower probability bound (e.g. a 95% lower confidence limit or uncertainty limit) greater than zero is evidence that there really is an excess risk; however, the carcinogenicity of IR exposure is already well established. A lower bound corresponding to a risk that is intolerably high would, of course, be evidence in support of diversion of financial resources for exposure reduction, even from the viewpoint of those who would bear the expense.

(254) From the viewpoint of those who would bear the risk, if any, associated with exposure, and of those responsible for their protection, the questions of interest concern: (1) the extent to which risks associated with a given level of exposure are

low enough to be tolerated in view of competing risk and loss of benefits associated with avoidance of that exposure; and (2) whether we can conclude that there is no risk at all associated with a given exposure. An upper probability bound, if less than some 'tolerable' level of risk, can be used to help justify a favourable risk–benefit assessment for a particular exposure, and can provide a margin of safety in decisions regarding risk protection or informed consent related to possible hazards of radiation exposure. An upper probability bound of zero or less would be evidence in favour of a threshold or, more likely, a beneficial effect of low-dose radiation.

(255) The implications of a possible, but uncertain, low-dose threshold for radiation protection are summarised by the dependence of the mean value and the upper 95% probability limit on the presumed threshold probability value (Fig. 6.9), or on the uncertainty distribution for that probability (Fig. 6.10). The mean value of estimated ERR per Gy is proportional to $1 - P$ for known threshold probability P and proportional to 1–E(p) for an uncertain threshold probability p with expected value E(p). Thus, the effect on the mean value is the same as that of an assumed constant DDREF equal to $1/P$ or 1/E(p). The effect on the upper 95% probability limit is less drastic, unless the assumed probability of a threshold is high. As shown in Fig. 6.9, the upper limit decreases with increasing P, but not nearly as steeply as for the mean until P approaches the probability level of the upper limit, e.g. about 0.85 in the case of a 95% limit. Obviously, the lower 95% limit (the 5th percentile of the distribution) is zero for $P \geqslant 0.05$.

(256) As mentioned earlier in this chapter, an established, universal, or near-universal, low-dose threshold for radiation-related cancer risk would obviate concern about risks from exposures at doses lower than the threshold value. Our present information, summarised in NCRP Report 136 (NCRP, 2001) and the present report, offers little support for the existence of a universal low-dose threshold, but it cannot be ruled out as an uncertain possibility. Two very recent, authoritative surveys, by committees of the French National Academy of Sciences and National Academy of Medicine (Tubiana et al., 2005; see also Tubiana, 2005) and the United States National Academy of Sciences/National Research Council (NRC, 2005) reached opposite conclusions about the likelihood of a universal low-dose threshold. The French committee concluded that a threshold was very likely, whereas the U.S. committee concluded that it was very unlikely, but noted that the risk of radiation-induced cancers at low doses will be small. However, the implications of the uncertain possibility of a threshold are qualitatively not much different from those of an uncertain DDREF: central values and upper uncertainty limits are reduced somewhat, but they do not become zero. Moreover, the argument that radiation protection standards should be relaxed 'because it is possible that there may not be any risk at low doses' is unlikely to be persuasive to people who are concerned about the possibility that risk associated with very low doses may be unacceptably high, and it may undermine the more realistic argument that the risk, which is understood rather well compared with that associated with other common carcinogens, is almost certainly less than some stated value which may be considered tolerable, for various reasons such as economic benefits or consideration of risks associated with alternative strategies involving less exposure.

7. CONCLUSIONS

(257) Epidemiological studies of cancer risk following radiation exposure provide the primary basis for estimation of radiation-related risk in human populations. These studies demonstrate the existence of a dose–response relationship and its modification by other factors, and show some variation by cancer site and by histological subtypes within sites. At low and very low radiation doses, statistical and other variation in baseline risk tends to be the dominant source of error in both epidemiological and experimental carcinogenesis studies, and estimates of radiation-related risk tend to be highly uncertain both because of a weak signal-to-noise ratio and because it is difficult to recognise or to control for subtle confounding factors. Thus, extrapolation of risk estimates based on observations at moderate to high doses continues to be the primary basis for estimation of radiation-related risk at low doses and dose rates.

(258) There is no direct evidence, from either epidemiological or experimental carcinogenesis studies, that radiation exposure at doses of the order of 1 mGy or less is carcinogenic, nor would any be expected because of the considerations outlined above. There is, however, limited epidemiological evidence, unlikely on the whole to be an artifact of random variation but nevertheless subject to the possibility of some bias, linking increased cancer risk to in-utero exposures at doses of the order of 10 mGy. Excess breast cancer associated with multiple fluroscopic examinations at doses averaging $\sim$10 mGy/fraction is also relevant to this low-dose issue but these data cannot be taken as direct epidemiological evidence of proportionality between dose and risk down to a few tens of mGy because of the possibility that higher-dose fractions may have contributed disproportionally to the risk estimates. The atomic bomb LSS provides good evidence of radiation cancer risk down to doses of 100–150 mGy with an approximately linear dose–response relationship. Mixed evidence of curvilinearity in this dose–response relationship has some bearing on the level of the linear component of the dose–response relationship but poses little challenge to its existence.

(259) Overall, relevant animal tumour data from experimental carcinogenesis studies tend to support a dose–response relationship that, at low doses, is linear with no threshold. This inference does not conflict with experimental evidence for reductions in excess risk per unit dose at low doses or with fractionation and/or protraction of dose. Recent cytogenetic and molecular studies provide direct support for the view that the critical radiation-associated events in the tumourigenic process are predominantly early events involving DNA losses targeting specific genomic regions harbouring critical genes, although later radiation-associated events connected with tumour promotion cannot be excluded and may be possible. The predominant importance of DNA DSB induction and postirradiation error-prone NHEJ repair for the induction of aberrations, and the apparently critical role for radiation-induced aberrations in the pathogenesis of cancer in these experimental models, would argue against the proposition of a low-dose threshold in the dose–response relationship for carcinogenesis in most organs and tissues.

(260) There is evidence from both epidemiological and experimental studies that specific tissues and cancer sites may, for various reasons, vary from the general rule articulated above, in the sense that radiation carcinogenesis is markedly and disproportionately less likely to occur at low doses than at high doses, and may even suggest a threshold. Examples are the small intestine, rectum, bone, and skin. However, experimental studies of radiation-related life shortening, which represent the integrated dose–response relationships for a variety of tumour types, suggest linear dose–response relationships over a wide range of doses.

(261) Ionising radiation is able to produce a unique type of damage in which multiple lesions are encountered within close spatial proximity. Even a single track through a cell is likely to induce these unique clustered damages. This type of damage may not be frequently generated endogenously or by other exogenous agents, and thus, there may not have been a strong selective pressure driving efficient repair. Although cells have a vast array of damage response mechanisms that facilitate the repair of DNA damage and the removal of damaged cells, these mechanisms are not foolproof. Moreover, clustered radiation-induced lesions pose a particular problem and currently emerging evidence suggests that closely spaced lesions can compromise the repair machinery. On this basis, there is no strong evidence for a radiation dose below which all radiation-induced damage can be repaired with fidelity.

(262) Although many of the cells containing such radiation-induced damage may be eliminated by damage response pathways involving cell-cycle checkpoint control, apoptotic pathways, and immune responses, it is clear from analysis of cytogenetics and mutagenesis that damaged or altered cells are capable, in a probabilistic sense, of escaping these pathways and propagating. This further argues against the likely possibility of a threshold for radiation-induced cellular effects.

(263) The processing and misrepair of radiation-induced DSBs, particularly complex forms, are probably responsible for chromosome/gene alterations that manifest as chromosome aberrations and mutations. Current understanding of mechanisms and quantitative data on dose and time–dose relationships is consistent with a linear dose–response relationship at low doses with no compelling evidence for the existence of a threshold dose below which there would be no effect. However, this question has not been answered scientifically and remains open.

(264) When considered as a whole, the emerging results with regard to a radiation-related adaptive response, genomic instability, and bystander effects suggest that the risk of low-level exposure to IR 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 inter-related 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 IR. It should be recognised that information from direct epidemiological measure of cancer risk will, by definition, include any potential contribution from these mechanistic processes, and may therefore provide insights about them, subject to the constraints of low statistical power at low doses.

(265) Probability limits on risk provide additional information relevant to radiation protection. In particular, a high lower limit attests to the reality of danger associated with a given exposure, and a low upper limit provides assurance regarding the relative safety, and presumably the acceptability, of the exposure when seen in the context of other hazards of daily life. The information reviewed in this report, from epidemiology and from experimental studies of animal, cellular, and molecular models, is consistent with proportionality between radiation-related cancer risk at low doses and at low dose rates, including the dose delivered by a single photon. It is also consistent, given uncertainties about the roles played by repair and apoptosis at very low doses, with the existence of a dose threshold at a dose level so low that radiation-related risk under the LNT theory would be statistically indistinguishable from random variation in baseline risk. However, the uncertain possibility of a threshold does not drastically reduce either central estimates or upper probability limits for low-dose risk compared with those obtained using the LNT theory, unless that possibility is assumed to be very likely. Uncertainties on the existence or otherwise of a true low-dose threshold for cancer risk of, say, a few mGy of low-LET radiation may never be resolved. The LNT theory remains the most prudent risk model for the practical purposes of radiological protection.

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Erratum

Erratum to "ICRP *Publication 98*: Radiation safety aspects of brachytherapy for prostate cancer using permanently implanted sources" [Ann. ICRP 35(3)]

The publisher and ICRP regret that the name of Professor E. Vañó was inadvertently omitted in the last line of the table on page 2 of this report.

Please accept our apologies for any inconvenience caused.

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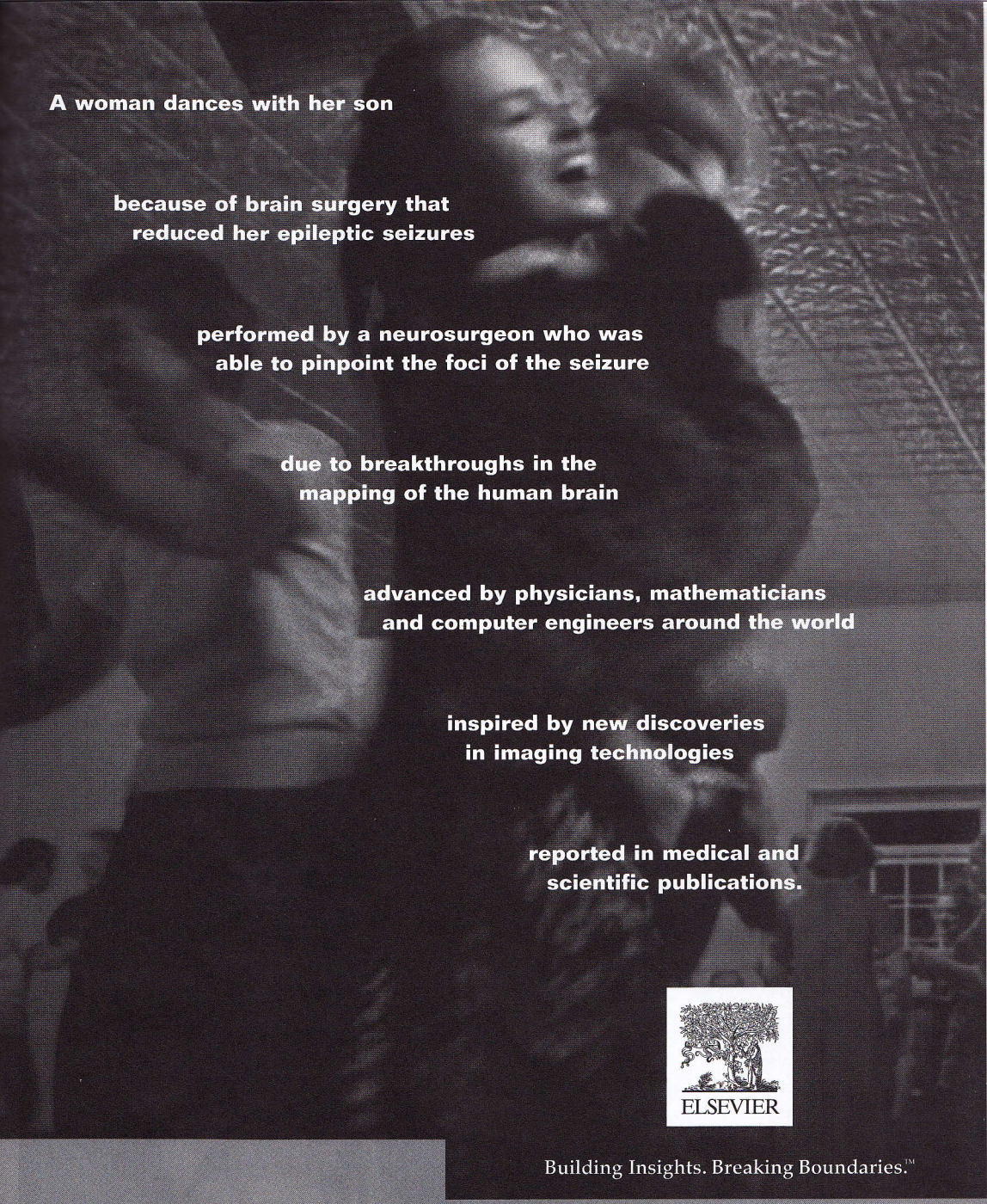

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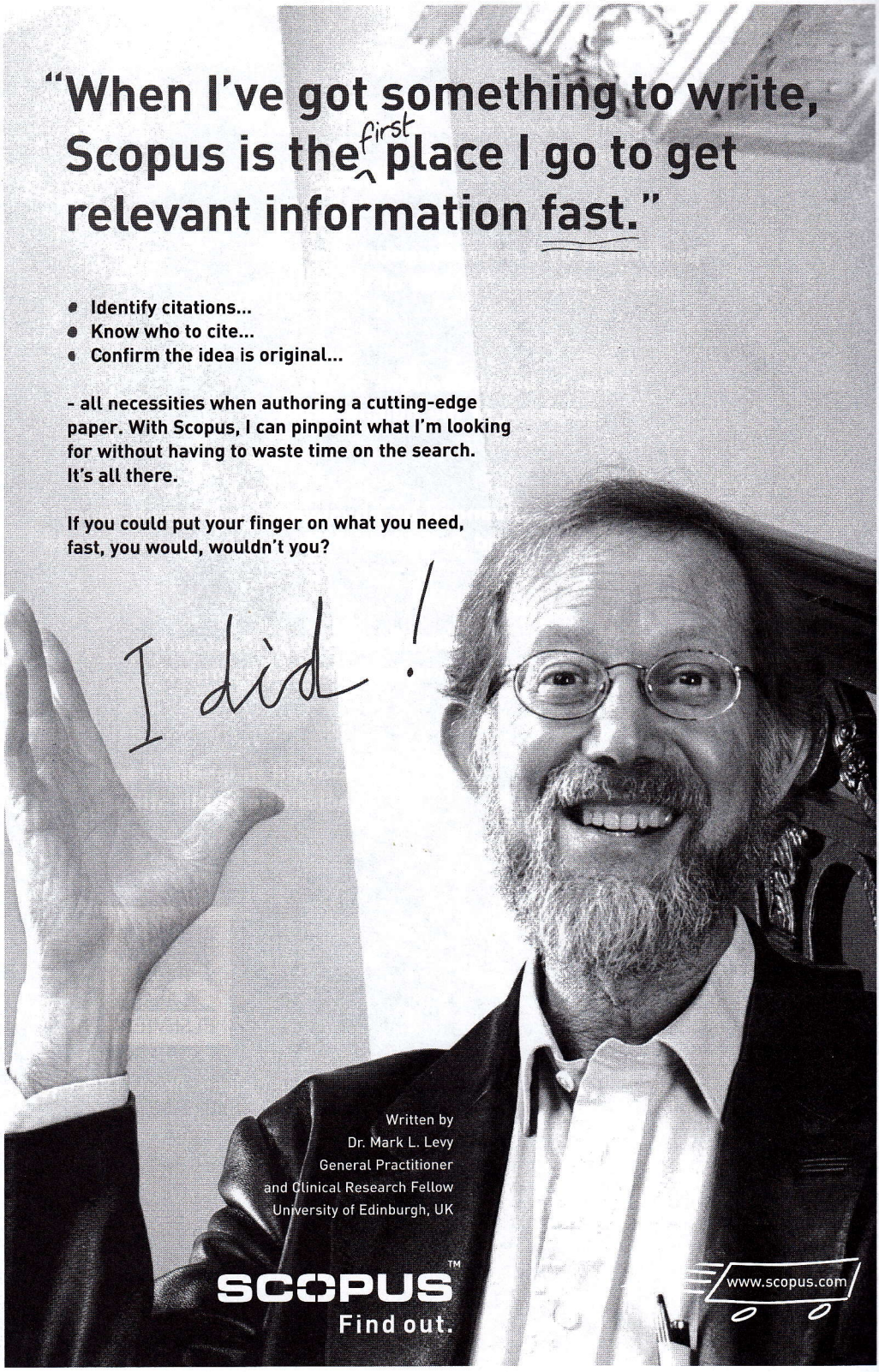
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