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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.

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

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.

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.