ICRP ref: 4904-3744-8231

Annals of the ICRP

ICRP PUBLICATION XXX

Scientific Evidence Relevant to the Assessment of Solid Cancer Radiation Risk at Low Dose and Low Dose Rate

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PUBLISHED FOR

The International Commission on Radiological Protection

by



Please cite this issue as ‘ICRP, 20xx. Scientific evidence relevant to the assessment of solid cancer radiation risk at low dose and low dose rate. ICRP Publication XXX. Ann. ICRP xx(x).’

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**Scientific Evidence Relevant to the Assessment of Solid Cancer Radiation Risk at Low Dose and Low Dose Rate**

ICRP PUBLICATION XXX

Approved by the Commission in MMMMM 20XX

**Abstract**

**–**The current System of Radiological Protection uses a dose and dose rate effectiveness factor (DDREF) with a numerical value of 2 when applying estimates of radiation risk derived from high doses and dose rates to settings involving low doses and/or low dose rates. The concept combines the low dose effectiveness factor (LDEF) when interpolating estimates of risk across dose levels, and the dose rate effectiveness factor (DREF) when extrapolating risk estimates from studies involving populations exposed to high dose rates to those exposed to low dose rates. In this report the current scientific evidence on the biological and health effects at those doses and dose rates is reviewed, with emphasis on human solid cancer incidence and mortality. Numerical evaluations of both DREF and LDEF are considered from studies of somatic cell mutation, cell transformation and cytogenetic endpoints. Life-shortening and all solid cancers combined are evaluated from historical studies on experimental animals (mice). A meta-analysis is described where risk estimates deduced from 29 human cohorts exposed to low dose rates were compared with those from the atomic bomb survivors (to address DREF), and a reanalysis of the curvature in the mortality data from the Japanese atomic bomb survivors on all solid cancers combined (to address LDEF) is presented. Finally, mechanistically-based ways to combine biological evidence with epidemiological data are considered. While considerable uncertainties remain, the ranges of LDEF and DREF values obtained here are narrower than those obtained in previous evaluations, and are largely consistent amongst the various sources of data reviewed. The overall conclusion of this report is that, based on current scientific evidence, an LDEF of much greater than 3 are not supported, and much less than 1 likewise. Similarly, it is concluded that a DREF value much larger than 3 or less than 1 is also unlikely.

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*Keywords:* DDREF, DREF, LDEF, Low-dose effects, Low-dose-rate effects, Cellular response, Animal experiments, Epidemiological cohorts, Biologically-motivated mechanistic models

MAIN POINTS

This report evaluates the current scientific evidence on low-dose and low-dose-rate biological effects of ionising radiation, in terms of the low dose effectiveness factor (LDEF) and the dose rate effectiveness factor (DREF). The report reviews results on endpoints related to the risk of all solid cancer, at sub-cellular, cellular, tissue and organism, and population levels. In this report, low doses are those below 100 mGy, and low dose rates are those below 0.1 mGy min-1 when averaged over about an hour, for low linear energy transfer (LET) exposures.

The concept of DDREF (combination of LDEF and DREF)), which basically represents an approach to be applied for radiological protection purposes, is not the focus of this report. In particular, the rationale behind this approach and its implication for the system of radiological protection is not discussed here.

For somatic cell mutation, cell transformation and cytogenetic endpoints, numerical evaluations of both DREF and LDEF provide values of around 4 and below.

Recent pooled analyses of data from experimental animals mostly suggest an LDEF close to 1 and DREF between 1 and 2 for life-shortening and for all solid cancers combined, with considerable variation depending on tumour type.

Recent meta-analyses of epidemiological data for all solid cancers point toward DREF values between about 1 and 3, taking account of the uncertainties involved in these estimates.

Analyses on curvature in the incidence and mortality data from the Japanese atomic bomb survivors find consistent evidence of curvature, so that evaluated population risks per Gy for all solid cancer mortality evaluated at 1 Gy are about twice those evaluated at 0.01 Gy. They tend to support a sex-averaged LDEF value of between 1 and 2 for all solid cancers combined, with some indication of variation between different cancer sites.

While considerable uncertainties remain, the ranges of LDEF and DREF values obtained here are narrower than those obtained in previous evaluations. The overall conclusion of this report is that, based on current scientific evidence, LDEF and DREF values much larger than 3 or less than 1 are unlikely. These ranges appear largely consistent for the various sources of data reviewed in this report.

EXECUTIVE SUMMARY

1. Since the discovery of x-rays by Conrad Roentgen in 1895, the biological effects of ionising radiation have been studied at the sub-cellular and cellular levels, and at the tissue and organism levels encompassing data from experimental animals, a range of cellular systems and human cohorts. Based on the available scientific evidence, radiation protection recommendations have been regularly updated by ICRP.
2. In its ICRP 60 recommendations, ICRP introduced the dose and dose rate effectiveness factor (DDREF) with a numerical value of 2, to extrapolate radiation risk from high doses and dose rates to low doses and/or low dose rates (ICRP, 1991). The concept combined the low dose effectiveness factor (LDEF) to extrapolate from high to low doses, and the dose rate effectiveness factor (DREF) to extrapolate from high to low dose rates (ICRP, 1991). In 2007, the Commission confirmed this approach in the ICRP103 recommendations (ICRP, 2007).
3. The concept of DDREF (combination of LDEF and DREF), which basically represents an approach to be applied for radiological protection purposes, is not the focus of this report. In particular, the rationale behind this approach and its implication for the system of radiological protection is not discussed here. Furthermore, the report does not discuss endpoints related to the induction of leukaemia, as ICRP does not recommend application of a DDREF for this endpoint.
4. This report describes a systematic review of the current scientific evidence on low-dose and low-dose-rate biological effects of ionising radiation, in terms of the LDEF and DREF factors. Low doses are considered as below 100 mGy, and low dose rates are those below 0.1 mGy min-1 when averaged over about an hour, for low linear energy transfer (LET) exposures (UNSCEAR, 2012). Low-LET refers to radiation with LET-values less than 10 keV μm-1 (ICRP, 2007).
5. Studies of cellular and molecular processes considered most relevant for the induction of cancer were included in the analysis. Numerical evaluations of both DREF and LDEF are available from studies of somatic cell mutation, cell transformation and cytogenetic endpoints. Values of around 4 based on chromosomal aberration (pooled stable and unstable) studies are towards the higher end of values based on the wider range of endpoints reviewed in this report. However, because much time elapses between induction of the relevant cellular and molecular events and clinical presentation of cancer, many biological processes are likely to modulate this cancer indication after the initial radiation-associated events. Thus, LDEF and DREF values deduced for these processes are unlikely to be fully representative of those values to be applied to stochastic effects among humans. We note that evaluations of LDEF and DREF tend to be higher for the cellular endpoints than those based on experimental animal studies or epidemiological data (see below). This provides evidence that there are processes beyond the direct induction of gene mutations and chromosomal aberrations that modulate carcinogenesis in animals and humans.
6. For all solid tumours combined, recent pooled analyses of data from historical studies on experimental animals (mice) mostly suggest LDEF and DREF values close to 1, with considerable variation depending on tumour type, while a single study suggests DREF value of about 3 and above. In contrast, for life-shortening pooled analyses suggest DREF values of about 2. Thus, the current evidence from such studies implies that values of LDEF and DREF greater than about 3 and lower than 1 are unlikely.
7. Recent meta-analyses of epidemiological data from mortality and non-redundant incidence studies, where solid cancer risk estimates deduced from 29 human cohorts exposed to low dose rates were compared with those from the atomic bomb survivors, reported a central estimate of the DREF value of 1.9, largely driven by the Mayak worker cohort. Exclusion of the Mayak worker cohort or of its portion with plutonium exposure led to DREF values of about 1.3 to 1.5, respectively, while exclusion of any other single cohort did not change the result substantially. Taking account of the appreciable statistical and methodological uncertainties involved in these estimates, the epidemiological evidence points toward DREF values in the range of about 0.9 to 3.0.
8. Reanalysis of the curvature in the mortality data from the Japanese atomic bomb survivors on all solid cancers combined suggest some curvature implying values greater than 1 for the LDEF depending on dose range considered. A range of values is, however, observed for individual cancer sites, so that for breast cancer there is less evidence for an LDEF above 1. The mortality data for most cancer endpoints suggest upward curvature over the 0-2 Gy range, although only for male solid cancer was this curvature significant. Indications of linearity and curvature reported in some studies should still be interpreted with care. The current scientific evidence on curvature in the incidence and mortality data from the Japanese atomic bomb survivors tends to a sex-averaged LDEF value of between 1 and 2 for all solid cancers combined, with some indication of variation between different cancer sites.
9. Combining biological evidence on the process of carcinogenesis with epidemiological data offers a more mechanistically-based way of extrapolation from high doses and dose rates to low doses and dose rates. Available knowledge on carcinogenesis and the mechanisms responsible is too limited to allow for a plausible quantitative mechanistic account of the process. Current assumptions made in radiological protection including those on low-dose and low-dose-rate effects are not in contradiction to what is presently known about the process of cancer development.
10. Taken together, there is currently more scientific evidence from experimental and epidemiological studies on low-dose and low-dose-rate biological effects of ionising radiation than was available in the 1990s when the DDREF concept was developed and applied for the purpose of radiological protection. In particular, continuously growing scientific evidence has become available from epidemiological studies with longer follow-up periods at low-dose exposures (i.e. at doses below about 100 mGy) yielding direct evidence of low-dose risk and of LDEF. Comparison of risks from a number of different radiation exposed groups (exposed at high dose rate and low dose rate) provide information on DREF, although there may be difficulties in inferring DREF via comparison of risks derived from populations with substantially different underlying cancer rates and other characteristics. There are also uncertainties associated with the different radiation energies in the groups being compared, which will impact on the relative carcinogenic effectiveness of the relevant exposures.
11. While considerable uncertainties remain, the ranges of LDEF and DREF values obtained here are narrower than those obtained in previous evaluations. The overall conclusion of this report is that, based on current scientific evidence, an LDEF of much more than 3 is not supported, and much less than 1 likewise. Similarly, it is concluded that a DREF value much larger than 3 or less than 1 is also unlikely. These ranges appear largely consistent amongst the various sources of data reviewed in this report.
12. The present report provides an update of the scientific evidence that was used to derive the DDREF in *Publications 60* and *103* (ICRP 1991, 2007). The conclusions of this report represent an important element in the process of review and revision of the System of Radiological Protection launched by ICRP (Clement et al., 2021). Specifically, the results described in this report will be considered in the review of the calculation scheme of radiation detriment.

# INTRODUCTION

## Background

1. Epidemiological studies provide reasonably robust evidence for elevation of human solid cancer risk at doses of 100 mSv and above (UNSCEAR, 2008a), and there is emerging evidence at lower doses. In contrast, there is a lack of direct evidence from human population studies that ionising radiation exposure causes hereditary effects. Such effects are assumed to occur in exposed populations on the basis that mouse studies provide clear evidence for the induction of hereditary mutations. There is general consensus that low doses are those below 100 mGy, and low dose rates are those below 0.1 mGy min-1 when averaged over about an hour, for low linear energy transfer (LET) exposures (UNSCEAR, 2012). Low-LET refers to radiation with LET-values less than 10 keV μm-1 (ICRP, 2007). The current report continues to use these definitions. For a more detailed discussion of these definitions see (Lowe et al., 2022).
2. The evaluation of low-dose and low-dose-rate radiation exposure risk draws on epidemiological evidence of human cohorts exposed to ionising radiation, animal studies, and mechanistic understanding at the cellular and molecular levels of the processes that contribute to the associated health effects. The health effects of concern, currently considered in radiological protection to be relevant for low-dose and low-dose-rate exposure, are cancers in a range of organs, and hereditary effects. Other non-cancer diseases and effects such as diseases of the circulatory system, cataract and cognitive disorders may also occur at low doses, although they are not included in the current system of radiological protection regarding low-dose and low-dose-rate effects; however, the shapes of the dose response relationships for these conditions and their underlying mechanisms are not well understood.
3. The Dose and Dose Rate Effectiveness Factor (DDREF) is a concept used in radiological protection and is an attempt to provide an overall estimate of how risk will vary with dose and dose rate, in the context of radiological protection (ICRP, 1991). The value of DDREF is a judgement that is based on evaluation of calculations of low dose effectiveness factor (LDEF) and dose rate effectiveness factor (DREF).
4. Cancer and hereditary effects are defined as stochastic effects that are based on genetic or epigenetic changes in cells that are not eliminated as a consequence of radiation-induced damage (ICRP, 2007). Radiation-induced stochastic effects are believed to lack a threshold of dose below which the probability of their occurrence is 0. In contrast, radiation-induced tissue reactions are caused by cell death or functional inactivation. Tissue reactions follow a sigmoidal dose response relationship with a tissue-, and effect-specific dose threshold, because they occur only after a certain number of cells have been eliminated/inactivated. Reducing the dose rate generally results in sparing effects on cell death and associated molecular events such as unstable-type chromosomal aberrations or micronuclei.
5. In most cases, reliable data on the biological effects of ionising radiation – whether from radiobiological or epidemiological studies – have been obtained from exposures to moderate and high doses and high dose rates (examples are given further below), whereas exposure situations of concern in radiological protection often include low doses and low dose rates. An example of particular importance are the data obtained from the atomic bomb survivors in Hiroshima and Nagasaki, Japan, which continue to be the gold-standard in radiation epidemiology (although high quality data are also being produced from other human cohorts exposed to ionising radiation from various sources). In the following section, the cumulative doses and typical dose rates for some human populations are summarized. It is noted that these populations are exposed to radiation fields that may include a considerable fraction of high-LET radiation. A more detailed discussion with more examples is given in (Rühm et al., 2018).

### Exposures of the Atomic Bomb Survivors

1. The survivors of the atomic bombings of Hiroshima and Nagasaki in Japan were exposed to a mixed gamma and neutron radiation field. This field comprised several components: prompt primary gamma and neutron radiation produced by the fission processes during the nuclear detonation; prompt secondary gamma radiation produced by prompt primary neutrons due to their interaction with nuclei in the atmosphere and in soil (i.e. inelastic scattering and thermal neutron capture); and delayed gamma and neutron radiation produced by fission products in the fireball.
2. In terms of free-in-air (FIA) kerma, the exposure of the atomic bomb survivors in Hiroshima was dominated by delayed gamma radiation, prompt secondary gamma radiation, and prompt neutron radiation, while in Nagasaki it was dominated by delayed gamma radiation, prompt secondary gamma radiation, and prompt primary gamma radiation.
3. Depending on their distance to the hypocenters and individual shielding conditions, cumulated gamma and neutron weighted organ doses to the atomic bomb survivors (where gamma absorbed organ dose was added to a neutron absorbed organ dose multiplied by a factor of 10 to take account of the increased biological effectiveness of neutrons) were up to several Gy at about 1,000 m from the hypocenters, and a few mGy or less at large distances from the hypocenters (Young and Kerr, 2005; Cullings et al., 2006, 2017). For example, the mean cumulative weighted colon dose for members of the Life Span Study (LSS) cohort is 114 mGy including distances to the hypocenters of up to 10 km. In terms of free-in-air kerma, total gamma doses by far exceeded total neutron doses. A recent study of the data from the LSS of atomic bomb survivors suggested the relative biological effectiveness (RBE) of neutrons to be higher than 10 (Cordova and Cullings, 2019). However, the issue of inter-city difference in cancer rates driving inferences on neutron RBE is an important aspect, as highlighted by previous analysis of this issue (Little, 1997).
4. Whatever radiation component is considered, the duration of exposure of the atomic bomb survivors during and shortly after the explosions was short (not much longer than 10 s) (reviewed in (Rühm et al., 2018)). Specifically, the typical duration of the radiation exposure from prompt primary gamma and neutron radiation was less than about 1 µs, from prompt secondary gamma radiation about 200 ms, and from delayed gamma and neutron radiation about 10 s. For this reason associated dose rates were high. For example, at a distance of 2,000 m from the hypocentre of Hiroshima the dominating sources of radiation dose were associated with estimated FIA kerma dose rates of about 4 mGy s-1 for delayed gamma radiation (corresponding to cumulated FIA kerma of 40 mGy), 170 mGy s-1 for prompt secondary gamma radiation (corresponding to cumulated FIA kerma of 35 mGy), and 40 Gy s-1 for prompt neutron radiation (corresponding to cumulated FIA kerma of 0.4 mGy assuming that the spread in time of prompt neutrons on the ground is about 10 µs), respectively. Dose rates were higher for survivors at distances of less than 2,000 m from the hypocentre.

### Other Radiation Exposed Groups

1. The global annual population-weighted mean effective dose from all natural sources of ionising radiation is about 2.4 mSv (UNSCEAR, 2000). This includes contributions from cosmic radiation, external terrestrial radiation, inhalation exposure and ingestion exposure. Levels of exposure depend on various factors such as soil and rock composition of the land, latitude, altitude, etc., so the mean effective dose varies locally between 1 and 10 mSv per year (UNSCEAR, 2000). Accordingly, associated mean effective dose rates are between 0.1 and 1 µSv h-1 (UNSCEAR, 2000). The upper end of this range of dose rates includes high background radiation areas such as those in Kerala, India, and Yangjiang, China. The corresponding mean cumulative effective doses might reach several hundred mSv depending on the years of exposure.
2. Without radon, external annual effective doses for the general population include 0.39 mSv per year (typical range: 0.3 – 1.0 mSv y-1) from cosmic radiation and cosmogenic radionuclides, and 0.48 mSv per year (typical range: 0.3 – 0.6 mSv y-1) from terrestrial radiation (UNSCEAR, 2000).
3. As an upper limit for occupational exposure, based on the annual effective dose limit of 20 mSv recommended by ICRP and typical 2,000 working hours per year, a mean average effective dose rate of 10 µSv h-1 can be estimated for a worker whose exposure was delivered at a constant dose rate. For a total career of 40 years, this would correspond to life-time effective dose of 800 mSv. Due to effective radiation protection measures, however, such high values are rare today.
4. For example, the International Nuclear Workers Study (INWORKS) which represents a pooled study of nuclear workers from the US, UK, and France, reported a mean cumulative colon dose to study participants of about 21 mGy, with a maximum value of 1,332 mGy. Given the mean length of work in that study and assuming an annual working time of 2000 h and continuous exposure, this would correspond to a mean dose rate of about 1 µGy h-1 although the dose rates were higher in early years (Richardson et al., 2015).
5. Aircrew are exposed to an elevated level of cosmic radiation, and their occupational effective dose can add up to several mSv per year (UNSCEAR, 2022d). Thus, total accumulated career doses could be 100 mSv or more. The corresponding dose rates are typically 2 – 7 µSv h-1 depending on altitude, latitude, and solar activity (Bottollier-Depois et al., 2009, 2012; Mares et al., 2009; ICRP, 2016). Dose levels are even higher for astronauts, for example mean dose rates of about 20 µGy h-1 were reported for Apollo astronauts (Cucinotta et al., 2016).
6. During the Soviet Union’s nuclear weapons programme, workers at various nuclear reactor, radiochemical and plutonium facilities, and auxiliary utilities, were exposed to ionising radiation. During the first years of operation of the Mayak facility in the early 1950s, estimated dose rates from external exposures to workers were highest and estimated to be about 150 µGy h-1, based on annual personal dose equivalent values of about 300 mGy and an assumed continuous exposure over 2,000 working hours per year. Individual dose rates could be higher if exposure was during a shorter period in time, and might have reached up to several mGy s-1. Mean cumulative personal dose equivalent values from external sources were reported to be 510 mGy with a maximum of 6.8 Gy. Absorbed dose rates to the liver from incorporated plutonium – largely alpha exposure – was estimated to be 1.7 µGy h-1, during the early phase of operation, while mean cumulative absorbed liver doses were 310 mGy with a maximum of 36 Gy (Khokhryakov et al., 2000; Hunter et al., 2013; Rühm et al., 2018).
7. In the aftermath of the Chornobyl accident on April 26, 1986, clean-up workers received mean external doses of 161 mGy, 81 mGy and 35 mGy from that date to April 25, 1987, from April 26, 1987, to January 31, 1988, and from February 1, 1988, to December 31, 1990, respectively. (It is emphasised, however, that certain individuals were exposed to higher doses above 500 mGy during certain clean-up operations.) These values would correspond to dose rates of 320 µGy h-1, 200 µGy h-1, and 110 µGy h-1, respectively, if continuous exposure over the whole days of the mission is assumed (Bouville and Kryuchkov, 2014; Ivanov et al., 2017, Rühm et al., 2018). The mean effective dose to all recovery workers at Chornobyl was ~120 mSv and the collective effective dose was ~61,000 person Sv (UNSCEAR, 2022b).
8. The mean thyroid dose among 6.4 × 106 persons living in the contaminated areas of Belarus, Russia and Ukraine was ~100 mGy, and the mean effective dose was ~13 mSv (UNSCEAR, 2022b). For the 9.8 × 107 persons living elsewhere in these three republics the mean thyroid dose was ~20 mGy and the mean effective dose was ~2 mSv; for the 5 × 108 persons living elsewhere in Europe the mean thyroid dose was ~1 mGy and the mean effective dose was ~0.4 mSv (UNSCEAR, 2022b).
9. For those persons exposed in childhood in the heavily contaminated parts of Ukraine and enrolled in a screening study the 131I thyroid doses spanned a range 0.001-41.556 Gy (Tronko et al., 2017). For a similar thyroid screening study in Belarus the thyroid doses spanned a range 0.00054 – 33 Gy (Little et al., 2015).
10. Among the 135,000 persons evacuated the mean collective dose is estimated to be 1.6 × 104 man Sv (Gonzalez, 1996). The mean external dose (by settlement) to evacuees from various villages in the 30 km exclusion zone were 1.4 – 130 mSv (Likhtarev et al., 1994). Mean doses to Pripyat evacuees were in the middle of this range, 11.5 mSv (Likhtarev et al., 1994), compatible with mean gonadal doses (taking into account both internal and external dose) that have been estimated for a recent study of transgenerational effects in parent-offspring Trios, 7.7 mSv and 13 mSv for Pripyat fathers and mothers respectively (Chumak et al., 2021).
11. During the early phase of the nuclear weapons programme of the Soviet Union (1948-1956), radioactive releases from the Mayak Production Association into the near-by Techa river led to considerable external and internal exposures of the population living downstream by the river. For example, mean red bone marrow (RBM) doses from external exposures reached 40 mGy in 1951, the year of largest releases, corresponding to a mean RBM dose rate of 4.3 μGy h-1, while those from internal exposures reached 125 mGy and 14 μGy h-1, respectively, if continuous exposure is assumed. Mean cumulative RBM doses were estimated to be about 400 mGy with maximum of 9,000 mGy, for this cohort (Krestinina et al., 2013; Rühm et al., 2018).
12. Numerous measurements of dose rates made outside the Fukushima nuclear power plant have been reported. For example, at Fukushima and Minamisoma, ambient dose rates of about 25 μGy h-1 were measured and reported for the early phase after the accident (March 12 – March 17, 2011), and then decreased continuously (UNSCEAR, 2013). This suggests exposure to the population with low dose rates, in terms of the UNSCEAR definition (UNSCEAR, 2012). It is noted that on the site of the power plant, higher dose rates were measured up to 12 mGy h-1 at the main gate, with single higher values measured at certain contamination hot spots (UNSCEAR, 2013). During the first year after the accident, cumulative average effective doses were in the range from 0.079 – 3.8, 0.10 – 4.5, and 0.12 – 5.3 mSv, for age groups adult, 10-year-old- and 1-year-old, respectively, who continued to live in Fukushima prefecture. Corresponding absorbed doses to the thyroid were in the range of 0.48 – 11, 1.0 – 17, and 1.2 – 21 mGy, respectively. (UNSCEAR, 2013).
13. A survey of medical procedure doses by country suggested that there was wide variation by income levels, so that the mean annual per caput dose for the period 2009-2018 was 1.71 mSv, 0.46 mSv, 0.31 mSv and 0.13 mSv for high, upper-middle, lower middle- and low-income countries respectively (UNSCEAR, 2022a). The breakdown in annual estimated collective dose for the period 2009-2018 per diagnostic procedure type were 9.55 × 105 person Sv for conventional radiology, 1 × 104 person Sv for dental radiology, 2.556 × 106 person Sv for computed tomography, 3.34 × 105 person Sv for interventional radiology, 2.97 × 105 person Sv for diagnostic nuclear medicine (UNSCEAR, 2022a). There has been some tendency for doses for diagnostic procedure to decrease over the decade although the annual collective dose is very little changed (UNSCEAR, 2022a).

### Exposures in Animal Experiments

1. In the past, several large-scale animal experiments have been performed in various countries all over the world. The aim of these studies was to investigate biological effects of exposures to various radiation qualities on the induction of cancers and other pathologies, and reduction of lifespan. Investigated species included mice, rats, dogs and others. Recently, databases have been established in the US and in Europe, where results of many of those experiments are stored in an effort to make these unique data available to the scientific community. Some of these studies were done with high LET radiations, but the focus in this work is low LET studies. Some publications examining both high and low LET radiation are included in this report.
2. In the US Janus archive, for example, data on mice exposed to gamma radiation include dose rates between 1.54 × 10-3 to 0.378 Gy min-1, where accumulated gamma radiation doses ranged from 0 to 49 Gy (Grahn et al., 1995).
3. In the European Radiobiological Archives (ERAs) gamma radiation dose rates for mice and rats ranged – for experiments using low LET radiation and providing relevant information for the DDREF discussion – from 1.35 × 10-3 to 240 Gy h-1, with typical dose ranges between 0.02 and 68.2 Gy for gamma radiation, and from 2 to 60 Gy h-1 with typical dose ranges between 0.02 and 15 Gy for X-rays, respectively (Birschwilks et al., 2011).
4. Currently, an animal experiment on mice in Japan includes doses of 20 mGy typical of the dose limit recommended by ICRP for workers per year, or doses of 400 mGy that astronauts might receive in space. The corresponding dose rates in the experiment are 0.05 mGy day-1 and 1 mGy day-1, respectively (Tanaka et al., 2003; Kinugawa et al., 2024).

### Exposures in Molecular and Cell Experiments

1. Molecular and cell studies on dose-rate effects typically use gamma-ray sources (mostly 60Co and 137Cs sources), while those on low-dose effects tend to use X-ray sources. Endpoints related to induction of DNA damage and kinetics of damage repair have been used with doses in the range from 1 mGy up to several 100 mGy, the lower doses delivered at low dose rates. Endpoints such as chromosomal aberrations and mutations used doses up to several Gy and dose rates as low as 1 – 10 mGy h-1. These studies are reviewed in detail in (Brooks et al., 2016).

## Scope and objective

1. This report reviews the scientific evidence of biological effects induced by low-dose and low-dose-rate exposures of ionising radiation. In particular, the report examines whether it is still appropriate to estimate radiation-induced solid cancer risks at low doses and low dose rates by assessing the slope of a linear dose response over a wider dose range and then applying a DDREF reduction factor of 2 as proposed in ICRP 1991 and confirmed in 2007 when the ICRP recommended a value of 2 to be ‘*…retained for radiological protection purposes …*’ (ICRP, 1991). Consequently, the present report is focused on dose and dose-rate effects for solid cancer, and related cellular endpoints associated with low LET radiation exposure. For most studies cancers were of adult-onset; nevertheless a few studies concerned cancers in childhood (age < 15). While not the main focus studies of cancer after prenatal exposure are mentioned briefly. These are the subject of another ICRP publication (ICRP, 2003). Hereditary effects were not considered in this report.
2. The variation of cancer risk with dose and dose rate is assumed to be a continuous function of dose and dose rate, and will also likely vary by endpoint even within the group of solid cancers (Cahoon et al., 2017; Brenner et al., 2018; Utada et al., 2018; Sadakane et al., 2019; Sugiyama et al., 2020; Mabuchi et al., 2021). DDREF is an attempt to provide useful guidance on how risk will vary with dose and dose rate, useful in the context of radiological protection.
3. The biological effects reviewed in this report include the molecular and cellular endpoints which are considered most relevant for cancer induction, those observed among irradiated animals, and those observed in human cohorts exposed to various sources of ionising radiation. Concepts based on biologically-motivated models of radiation-induced diseases such as cancer that might allow for a more reliable extrapolation to low doses and low dose rates are also reviewed.
4. In addition to the review of existing literature, a number of dedicated scientific analyses on certain topics were initiated and performed. These topics included pooled studies on life-shortening and cancer induction among rodents using data from radiobiological archives which became available recently, meta-analyses of recent epidemiological data from various human cohorts exposed to ionising radiation, and re-analyses of curvature in the data from the atomic bomb survivors.
5. This report focusses mainly on solid cancer induction, and related cellular endpoints at low doses and low dose rates of predominantly low LET radiation exposure. The report does not discuss endpoints related to the induction of leukaemia, as ICRP does not recommend application of a DDREF for this endpoint, because the data from the atomic bomb survivors on leukaemia incidence and mortality suggest a linear-quadratic dose response, which inherently indicates lower risks per unit dose at low doses as compared to high doses. A review of dose-rate effects observed in studies of radiation-induced leukaemia might be a useful further step, in the future. It was also decided to focus on all solid cancers combined (which is considered the most important outcome for practical radiological protection), although it is acknowledged that scientifically, carcinogenesis of certain tumours might be different at low doses and low dose rates implying different values of the LDEF and DREF for specific cancer sites/tissues.
6. The report does not challenge the concept of applying a DDREF for radiological protection purposes per se; but focusses – as the title implies – on the current scientific evidence behind the use of the DDREF for health risk inference. Consequently, conceptual, ethical, philosophical and other aspects involved in the derivation of DDREF values, although important, are not discussed in this report.

## Structure of this publication

1. Section 2 presents a historical review of knowledge available on the effects of low doses and low dose rates of ionising radiation, beginning with the first report of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) published in 1958 (UNSCEAR, 1958). Section 3 reviews the molecular and cellular data available based on literature published since the last review of UNSCEAR on that topic (UNSCEAR, 2010), with emphasis on specific endpoints considered most relevant for cancer induction. Further and complementary information may be found in a recent UNSCEAR report on [biological mechanisms relevant for the inference of cancer risks from low-dose and low-dose-rate radiation](https://www.unscear.org/unscear/uploads/documents/unscear-reports/UNSCEAR_2020_21_Report_Vol.III-CORR.pdf) (UNSCEAR, 2022c). The section also includes a discussion on why it is appropriate to discuss low-dose and low-dose-rate effects separately. In section 4, considered animal studies included not only cancer endpoints but also life-shortening, because previous work (such as BEIR VII) had used life-shortening as the relevant endpoint. The section describes the results of recent efforts of the Task Group to pool data from past animal experiments, both in terms of the low dose effectiveness factor (LDEF) and the dose rate effectiveness factor (DREF). Section 5 describes the results of a meta-analysis performed by the Task Group where most recent radiation-induced risk estimates from epidemiological data on low-dose-rate exposures are compared with those obtained from the Japanese atomic bomb survivors. This analysis provides information on DREF. Section 6 includes the results of a re-analysis of curvature in the most recent cancer mortality data from the Japanese atomic bomb survivors performed by the Task Group. This analysis provides information on the LDEF. Finally, section 7 reviews the use of biologically based mechanistic models fitted to epidemiological data and discusses whether the use of such an approach provides more reliable extrapolations from high-dose and high-dose-rate exposures to low-dose and low-dose-rate exposure.

# HISTORICAL DEVELOPMENT

## Definition of LDEF, DREF, and DDREF

1. Different terms and quantities are used in the literature, to infer risk observed in studies at high doses and high dose rates to those at low doses and low dose rates. These include, for example, a ‘dose rate effectiveness factor’, a ‘linear extrapolation overestimation factor’, a ‘linear risk overestimation factor’, a ‘low dose extrapolation factor’, and a ‘risk ratio’. A detailed review is given in SENES (2017).
2. The concept behind the development of a DDREF arises naturally from theoretical consideration of a number of distinct types of dose response, and can be decomposed to some extent into separate consideration of dose-rate effects and dose effects. It is not limited by the dose response shape of the measured effect. It should be noted that dose-rate effects are observed in a variety of radiobiological data in which purely linear dose responses have been observed (Ullrich and Storer, 1979). To facilitate an explanation of the concept, the probability of occurrence of a radiation-induced biological outcome of interest, p, with a linear-quadratic (LQ) dose response relationship is considered.

(1)

where *D* is – in this example – the acute dose applied, *α* the coefficient of the linear component, and *β* the coefficient of the quadratic component.

LDEF

1. A linear extrapolation from *D* to zero dose results in a slope . Division of this slope by the initial slope of the LQ dose response relationship at low dose given by the α coefficient, yields the low dose effectiveness factor (LDEF) (sometimes also called low dose extrapolation factor):

(2)

Where *β/α* denotes the curvature parameter which offers a measure of deviation from linearity; for example, at a dose of *α/β* (corresponding to the reciprocal curvature parameter) the numerical value of the LDEF is 2, and the linear and the quadratic component of the dose response curve contribute equally to the effect considered.

1. In this report, estimates of LDEF are made based on the application of the LQ model to various data including those from subcellular, cellular, animal and human data. In some cases, the mathematical description of a dose response curve at high doses might include an additional term to account for cell killing. For example, estimates for LDEF for solid cancer mortality among the Japanese atomic bomb survivors were obtained by analysing the curvature in the dose response using the LQ model with an additional cell killing term (Section 6). As an alternative, the cell-killing term might be omitted if the analysed data set is restricted to doses where cell killing does not play a dominant role.

DREF

1. If, for example, only half the dose *D* is applied (i.e. *D*/2) followed by an exposure-free time period long enough to allow irradiated cells to repair any radiation-induced damage, then exposure to the second fraction of *D*/2 will result in a radiation-induced effect again governed by the LQ relationship. In this example, after the total dose *D* was delivered, the overall effect will then be less than that obtained when the dose *D* was delivered in one fraction. In the limiting case of an infinite number of very small dose fractions (corresponding to continuous low-dose-rate exposure), the dose response of the overall effect will then be defined by . Division of the effect observed at an acute dose *D* by the effect observed at low dose rates will result in the dose rate effectiveness factor (DREF):

DREF → (3)

1. Thus, in this simplified scenario, the LDEF and DREF are very similar. This and other considerations prompted ICRP to combine both factors for practical radiological protection purposes and introduce the dose and dose rate effectiveness factor DDREF (ICRP, 1991, 2007).
2. In the present report, estimates for DREF were obtained by comparing groups of animals or humans exposed to low dose rates, with those exposed to high dose rates, at similar cumulated doses. For this purpose, in most cases, the slopes of linear dose response models were compared (see Section 4 on animal data, and Section 5 on human data).
3. The importance of the LDEF and DREF factors becomes evident if one recalls that current ICRP recommendations involving stochastic effects (e.g. cancer, leukaemia) are largely based on data from the atomic bomb survivors of Hiroshima and Nagasaki, Japan, who were exposed to rather high dose rates (Section 1.1.1.). Analysis of curvature in the dose response relationships observed among the data from the atomic bomb survivors might therefore provide information on the LDEF. Comparison of the effects reported for the atomic bomb survivors with those reported for cohorts exposed to low dose rates (e.g. nuclear workers) might provide information on the DREF. Both approaches are considered in this report. More detailed conceptual considerations are given in (Chadwick, 2017, Gonzales, 2018).

## Positions of National and International Organisations – Historical Context

1. The effects of ionising radiation on cellular, tissue and organism level are governed by many factors. This has been appreciated for many decades, and the first comprehensive UNSCEAR report published in 1958 already stated that ‘*Among the physical factors are the type of radiation …, its distribution in time (whether given during a short or a long period or repeatedly), …*’. As far as the effects of low doses of ionising radiation are concerned, the report noted that ‘*An understanding of the basic mechanisms by which the damage is produced may be the only way of making any rational assessment of the damage produced at very low doses.*’. Accordingly, the report concluded that ‘*… Our knowledge of the biological effects of low radiation levels is meagre because of experimental difficulties and the lengthy observations necessary to obtain results in this field. At present opinions as to the possible effects of low radiation levels must be based only on extrapolations from experience with high doses and dose rates.*’ (UNSCEAR, 1958).
2. The second comprehensive UNSCEAR report stressed the importance of both dose rate and total dose for the biological effects induced by ionising radiation. Because information from the atomic bomb survivors was still limited (the available data on leukemia, for example, did not yet show a clear dose response curve, and there were only first and preliminary observations that some forms of cancer other than leukemia were elevated among survivors who were close to the hypocentres), experiments on animals were considered important. However, their usefulness was judged limited ‘*by the difficulty of making valid extrapolations from one species to another, particularly to man from animals with a much shorter life-span*’. Consequently, the importance of investigations of possible mechanisms of carcinogenesis was highlighted for an assessment of the risk at low doses and it seemed ‘*reasonable to expect proportionality between doses and corresponding incidence of tumours down to the lowest doses*’, although other shapes of the dose response were not ruled out. It was observed that induction of mutations in mice depend on dose rate which was suggested by the presence of repair mechanisms. The report concluded saying that ‘*… we still know very little about the frequency with which such effects are likely to occur, particularly following small doses of radiation received at low dose-rates.*’ (UNSCEAR, 1962).
3. In its section on radiation carcinogenesis in man, UNSCEAR continued in 1964 to favour a linear dose response relationship, which was supported at the time by the incidence of leukemia among atomic bomb survivors (in the dose range from 100 to 900 rads) and thyroid cancer among individuals therapeutically irradiated during childhood (in the dose range from 100 to 300 rads). It was felt that – with a linear extrapolation from high to very low doses – an underestimation of the radiation-induced risk at very low doses was unlikely. However, this approach was followed with care, and the need was emphasised for ‘*progress in our understanding of the fundamental mechanisms of carcinogenesis, the mode of action of radiation, and its interaction with other carcinogenic agents in the environment.*’ (UNSCEAR, 1964).
4. Two years later UNSCEAR focused on the genetic risk of ionising radiation and concluded that ‘*the genetic hazard will be less per unit dose of radiation when the exposure is spread out in time, is delivered in small dosage, or when a long interval occurs between irradiation of the female germ cell and conception.*’ (UNSCEAR, 1966).
5. By 1969, new developments in cytogenetics made possible a quantitative assessment of radiation-induced chromosome aberrations (CAs) in human cells, in-vitro and in-vivo, allowing for investigation of dose and dose-rate effects. Various dose response relationships were established in vitro, but a quantitative evaluation turned out difficult, due to lack of standardization between laboratories. Furthermore, an increase in aberration yields was observed for example among radiation workers who were exposed to doses of a few rads (corresponding to a few tens of mGy). Caution was, however, advised because the ‘*incidence of CAs and that of tumours both increase with increasing dose, but the relationship between the two effects is complex*.’ (UNSCEAR, 1969).
6. The UNSCEAR 1972 report already estimated radiation-induced gene mutations among females conceiving shortly after radiation exposure to be a factor 3 less at low doses than at high doses, while they were estimated to be a factor 20 less at chronic low doses than at acute high doses. This was in line with the results of animal experiments which also indicated ‘*that radiation given continuously or in several fractions is usually less carcinogenic than if administered in a single dose within a short period of time ...*’. At the same time, ‘*… a clear increase of mortality from malignancies other than leukaemia and lung and breast cancers with increasing dose …*’ was found among the atomic bomb survivors (UNSCEAR, 1972).
7. Although experimental animal data remained an important source of knowledge and, for example, reduction factors between 2 and 20 were reported when acute and fractionated or protracted doses of low-LET radiation were compared for a number of different endpoints, the Committee made clear that ‘*the only secure basis for quantitative estimates of the frequency with which harmful effects may be produced in man must depend upon surveys of human populations who have been exposed to known doses of radiation*’ (UNSCEAR, 1977).
8. A similar reduction factor was discussed by the National Council on Radiation Protection and Measurements (NCRP) in the US. This body introduced what they called a dose rate effectiveness factor (DREF) which they calculated as the ratio αL/α1 of two slopes: one was the slope αL of a linear no threshold fit to high-dose and high-dose-rate data, while the other was the slope α1 of the linear no threshold fit to low-dose-rate data. For a variety of endpoints such as tumours and life shortening in animal models, values between 2 and 10 were observed. It was felt that these values might represent somewhat higher values than what was evident from human exposures (NCRP, 1980).
9. In 1986, UNSCEAR published a detailed review on dose-response relationships for a number of radiation-induced endpoints in experimental systems (on cellular and sub-cellular levels), in experimental animals, and in man (leukaemia, breast cancer, thyroid cancer, cancer of the respiratory tract, bone sarcoma) (UNSCEAR, 1986). Although this report acknowledged that at that time not enough was known on the mechanisms of radiation carcinogenesis to allow for a complete description of the physical and biological factors relevant for the induction of cancer, a number of functional relationships of radiation action in relation to dose were discussed including those with a linear, a linear-quadratic and a quadratic shape.
10. For induction of point mutations and CAs by low-LET X and gamma radiation most of the dose-response curves published at that time showed a linear-quadratic behaviour. When these curves were linearly extrapolated from 1 or 2 Gy down to 0 Gy, the effect would typically be overestimated by a factor of up to 5. The report emphasized that ‘*for cancer induction, however, only fragmentary information supports the notion that similar quantitative relationships with the dose might apply*’ (UNSCEAR, 1986).
11. No major new findings were published between 1977 and 1986 on cancer induction in experimental animals, and the observation that in most cases ‘*dose-response relationships for X and gamma rays tend to be curvilinear and concave upward at low doses*’ was still valid. Again, a linear extrapolation from higher to lower doses would thus lead to an overestimation of the considered radiation-induced effect at low doses and dose rates (UNSCEAR, 1986).
12. From the review on human cancer types induced by low-LET radiation the Committee concluded that ‘l*inear extrapolation from about 2 Gy down would not overestimate the risk of breast and possibly thyroid cancer. It would slightly overestimate the risk of leukemia, and would definitely overestimate the risk of bone sarcoma. For lung cancer, lack of direct evidence does not permit any assessment to be made of the magnitude of the over-estimate*’. For other tumour types human data were not sufficient, and data on experimental animals generally showed pronounced dose rate and fractionation effects. As already mentioned above, if applied to human tumours, a linear extrapolation of risk coefficients obtained at higher acute doses down to low doses and low dose rates would result in an overestimate of the real risk, possibly by a factor of 5 (UNSCEAR, 1986).
13. Two years later, UNSCEAR explicitly emphasized that risk coefficients deduced for a number of human tumour types after acute exposure to low-LET ionising radiation at high doses should be reduced by a certain factor, when applied to low doses and dose rates: ‘*The Committee considered that such a factor certainly varies very widely with individual tumour type and with dose rate range. However, an appropriate range to be applied to total risk for low dose and low dose rate should lie between 2 and 10*’ (UNSCEAR, 1988).
14. In 1991 ICRP developed the concept of Dose and Dose rate Effectiveness Factor (DDREF) (ICRP, 1991). This factor was introduced to ‘*interpret data for low LET radiation at high doses and high dose rates to give estimates of the probability of effects at low doses and low dose rates*’. ICRP suggested a value of 2 for this factor, to be used for all exposures resulting from absorbed doses below 0.2 Gy, or for exposures from higher absorbed doses when the dose rate is less than 0.1 Gy per hour. It was acknowledged that the chosen value of 2 might be somewhat arbitrary, and it was felt that it may be conservative. Already at that time ICRP expressed the view that, if more information becomes available, the specific value of DDREF might be subject of change (ICRP, 1991).
15. UNSCEAR specified this reduction factor in more detail for the first time in the UNSCEAR 1993 report where – based on radiobiological information, animal data from experimental investigations, and human data from epidemiological studies – a value of about 2 was also suggested. It was acknowledged, however, that this value was associated with substantial uncertainties and that ‘*epidemiology results do not exclude this value, but except for leukaemia, they do not support it*’ (UNSCEAR, 1993). The suggested factor should be applied for doses below 0.2 Gy. For higher doses the factor should be also applied if the dose rate is less than 6 mGy per hour averaged over a few hours.
16. The uncertainties involved in any value given to this reduction factor were obvious, for example due to the fact that epidemiological studies on different human cohorts provided different quantitative results. For example, UNSCEAR (1994) analysed risk estimates of cancer induction among nuclear workers in the US and UK. It was noted that – without applying any reduction factor – for all cancers combined the point estimates of the risk coefficients from the combined workers studies were close to those from the Life Span Study. In contrast, the Committee also cited a Russian study on Mayak workers where a reduction factor 2.7 was found when compared to the atomic bomb survivors. The Committee noted, however, that these results must be interpreted with care (UNSCEAR, 1994).
17. The UNSCEAR 2000 report emphasized the uncertainties involved in any specific value for the reduction factor, in particular because the effects of dose rate on cancer risks ‘*may differ among cancer types*’. Overall, the report confirmed the conclusion of the previous UNSCEAR 1993 report in saying that ‘*based on both epidemiological and experimental evidence, a reduction factor of less than 3 when extrapolating to low doses or low-dose rates, still appears to be reasonable in general*’ (UNSCEAR, 2000).
18. A report of the French Academy of Sciences and the French National Academy of Medicine focused on dose-effect relationships and estimation of the carcinogenic effects of low doses of ionising radiation (Tubiana et al., 2005). The authors reviewed epidemiological studies, studies on animals, and biological data. The report concluded that the biological data available at the time showed that the efficacy of cellular defence mechanisms such as DNA repair and programmed cell death is modulated by dose and dose rate and, consequently, that the linear no-threshold (LNT) model was no longer considered plausible.
19. In contrast, a report from the US National Academy of Sciences on the health risks from exposure to low levels of ionising radiation (NAS, 2006) deduced an estimate for DDREF by using information from mouse experiments including cancer risk and life-shortening, and information on curvature of the solid cancer incidence data from the Japanese atomic bomb survivors available at that time. The applied Bayesian analysis resulted in a probability density for the DDREF. Combining the animal and the Japanese LSS data resulted in a posterior median for the DDREF of 1.5 with a 95% Bayesian posterior probability interval of 1.1 – 2.3. In doing that the Committee recognised ‘*the limitations of the data and the uncertainties in estimating the DDREF*’.
20. UNSCEAR 2006 report continued to emphasize that a major source of uncertainty in radiation risk ‘*relates to extrapolation from the moderate dose but high dose-rate exposures received by the Japanese atomic bombing survivors to low doses and dose rates*’. In particular, the report stressed that at low doses and dose rates, ‘*the effects of ionising radiation on the immune system may be suppressive or stimulatory*’. Annex A of this report provided a detailed summary of DDREF history, and it also included a systematic discussion and comparison of risk estimates deduced from studies involving high doses and high dose rates with those from fractionated or protracted exposures. The comparison showed that the values obtained for the excess relative risk ‘*from the LSS do not markedly underestimate risks in the nuclear worker studies. There is no strong evidence for a DDREF greater than 1, although the substantial uncertainties are certainly consistent with a DDREF of 2 (or indeed infinity)*’ (UNSCEAR, 2008a).
21. An alternative and related concept, derived by analysing the shape of the dose response relationship obtained from epidemiological studies, corresponding to deduction of a low dose effectiveness factor (LDEF), has also been much discussed, in particular using the data from the atomic bomb survivors available at that time. From this analysis UNSCEAR 2008 Annex A concluded that the results obtained were consistent with ‘*a value of 2 for DDREF recommended by the ICRP*’. The report specified in more detail that ‘*values of DDREF much greater than 2 would not be consistent with the LSS data. Moreover, a value for DDREF of 1 would also be consistent with these data*’ (UNSCEAR, 2008a).
22. In the 2006 report, UNSCEAR for the first time pursued an approach to fit the data from the atomic bomb survivors as a function of dose using linear-quadratic and linear-quadratic-exponential dose-response functions that included both a quadratic component allowing for low-dose curvature and an exponential component allowing for high-dose turnover. In this way the chosen models ‘*implicitly take account of extrapolation of dose (if not dose rate), so that to some extent they take account of DDREF*’, and an extra adjustment for chronic exposure is not needed. It was concluded that ‘*values of DDREF of about 2, recommended by others (ICRP60), are consistent with the dose protraction effects predicted by these models and with a large body of epidemiological and experimental data*’ (UNSCEAR, 2008a).
23. At the time of the UNSCEAR report publication epidemiological studies on low-dose-rate exposures did not allow for a numerical estimate of DDREF. Based on gene and chromosomal mutation studies that suggested a range of values between 2 and 4, and on animal studies on cancer induction and life shortening that suggested a range of values between 2 and 3, ICRP confirmed in 2007 the use of a DDREF for solid cancer and recommended a value of 2 to be ‘*…retained for radiological protection purposes …*’ (ICRP, 2007).
24. The US National Research Council (NRC) requested that the National Aeronautics and Space Administration (NASA) revisit their space cancer risk model and, among other issues, NASA re-examined the use of DDREF (Cucinotta et al., 2012). Based on the earlier BEIR VII approach of combining results of various DDREF studies by use of Bayesian methods (BEIRVII, 2006), but taking into account improved animal cancer data, additional analyses of nuclear worker studies, and information on cellular biomarkers of cancer risk, NASA decided to use a central estimate for the DDREF of 1.5, with a 95% confidence interval of 1.0 – 3.2.
25. When assessing the health consequences due to the radioactivity released during the Fukushima accident in Japan, the World Health Organization (WHO) did not apply a DDREF, due to lack of epidemiological evidence. They argued that it is ‘*prudent to base risk calculations on models derived from the atomic bomb survivors cohort without applying any modification factor for low dose or low dose rate’. By this approach WHO wanted to avoid any underestimation of radiation-induced risk, but acknowledged that this ‘represents a departure from standard practice in radiation risk assessment*’ (WHO, 2013).
26. UNSCEAR commented that the WHO decision was ‘not incompatible’ with the Committee’s own estimates of radiation-induced cancer risk, but emphasized that experimental evidence points towards DDREF values greater than 1 for high-dose exposures at low dose rate (UNSCEAR, 2014).
27. In 2014, the German Commission on Radiological Protection (SSK) reviewed the scientific evidence for application of a DDREF (SSK, 2014). They came to the conclusion that although radiobiological studies on cell cultures are useful to understand mechanisms of radiation action, they do not provide a clear picture, for example because dose and dose-rate effects observed depend on the endpoint considered. Results of animal studies were also considered of limited value, as determination of dose-response relationships is difficult, in particular at low doses and low dose rates. Recent epidemiological evidence does not support a DREF value higher than 1. The SSK recommended ‘*abolishing the DDREF or adjusting it to bring it into line with more recent findings*’,and adapting‘*in parallel all of the other parameters pertaining to the detriment to the latest scientific findings*’.This should be done based on international consensus.
28. Recently, UNSCEAR emphasized that the DDREF represents a radiation protection concept. From the pure scientific point of view, however, UNSCEAR clarified that ‘*reduction of radiation-induced effects per unit dose at low doses and low dose rates relative to acute exposures with moderate or high doses cannot be expressed by a single value*’ because dose response relationships depend on a large number of factors (UNSCEAR, 2017).
29. In their latest radiation protection recommendations, NCRP continued ‘*to use a DDREF factor of two to account for differences in effect from acute to protracted exposures*’ and that ‘the DDREF is taken into account in determination of the radiation detriment’ (NCRP, 2018a).

## Selected Recent Relevant Publications

1. In the previous section the positions made by a number of national and international advisory bodies were summarized. In contrast, in this section additional considerations or analyses to evaluate DDREF models, mostly by various national and international groups, are reviewed. These studies surveyed a number of methods used by various groups, including use of animal data; clearly less weight must be attached to these reviews as compared to those described in the previous section, although they do represent a reasonable overview of the literature and make a number of valid points.
2. In 2017 a report by Trabalka and co-workers re-evaluated the use of DDREF for low-LET radiation, to be used in the determination of probability of causation of diagnosed cancers of individuals exposed to ionising radiation. Based on results from epidemiological mortality and incidence studies in humans, these authors deduced values for DREF and LDEF for solid cancers and, based on a subjective evaluation of the relevance of these values, derived a preferred probability distribution of DDREF. This distribution is characterized by a geometric mean of 1.3 with a geometric standard deviation of 1.8. In order to extrapolate risk estimates from high doses and dose rates to low doses and dose rates, however, the authors proposed to use the harmonic mean of this distribution rather than the arithmetic mean and proposed a value of 1.1 (SENES, 2017; Kocher et al., 2018). This approach was critically discussed by Wakeford and co-workers who ‘*expressed concerns about a number of aspects of the approach adopted by Kocher et al.*’ including the non-consideration of the study of the recent incidence data of the atomic bomb survivors (Grant et al., 2017), and their selection of epidemiological studies used to deduce relevant information (Wakeford et al., 2019).
3. Hoel examined the procedure used by the BEIR VII committee (Hoel, 2015). For example, he demonstrated that using the full LSS data set up to a dose of 4 Gy and allowing for a cell killing term in the dose response model would result in a DDREF value of 2. Instead, BEIR VII chose a dose cut off of 1.5 Gy ignoring cell killing and reported a DDREF value of 1.3. Hoel also argued that breast and thyroid cancer should have been excluded from the BEIR VII analysis, because these cancers show an appreciable influence on the curvature of all solid cancers combined (this includes lymphoma in mice). Additionally, BEIR VII used mice data produced at Oak Ridge and included 11 cancer sites. Instead of comparing acute and chronic data, however, they based their analyses on fitting a linear-quadratic dose-response to the acute effects observed among the animals. Hoel also argued that quite a few of the 11 cancer sites investigated by BEIR VII should have been left out. Analysing the four remaining sites by comparing acute and chronic effects he obtained DDREF values between 1.9 and 6.3. Hoel concluded that ‘*What is the best DDREF estimate from the LSS incidence data is not obvious. What is clear is that the BEIR VII estimate of 1.3 is misleading and the lowest possible value one could obtain with a selective choice of the data to use*’. He recommended making use of all available animal data in addition to those used by BEIR VII from Oak Ridge, and including the numerous data from epidemiological studies in future analyses. This has actually been done (see sections further below).
4. Chadwick highlighted some of the limitations of the application of DDREF (Chadwick, 2017) with a focus on chromosome aberrations and cellular effects. For example, he emphasized that DDREF depends on dose (see also Section 2.1) and, consequently, he questioned the ‘*usefulness of the constant value DDREF concept*’. He acknowledged, however, that DDREF was chosen by ICRP for practical radiological protection purposes. He also stressed that any linear-quadratic fits to epidemiological data will not provide well-defined values for the linear (*α*) coefficient which describes the shape of dose response at low doses, because the overall fit is largely governed by the quadratic (*β*) coefficient at higher doses. He concluded that the risk at low dose rates should be derived ‘*from epidemiological studies of, for example, worker populations, together with information from cellular radiation biological research.*’. This has actually been done by the Task Group (see sections further below).
5. In an effort to refine the NASA risk model for cosmic radiation (Cucinotta et al., 2012), Cucinotta et al. proposed a mean DDREF value of 2 with a log-normal distribution with 90% CI of (1.2 – 3) to be used in the penumbra region of a particle track produced by protons or heavy ions (Cucinotta et al., 2017).

## Conclusions

1. The effects of ionising radiation at low doses and low dose rates have been continuously assessed over a long period by various international organisations including ICRP. Depending on the prevailing scientific knowledge on radiation-induced effects the view of various international organisations interested in radiological protection has changed over time. This development has been briefly described above. More detailed reviews have been published recently (Rühm et al., 2015; Gonzales, 2018).
2. In general, this development was characterized by an increasing scientific knowledge on the effects of ionising radiation at low doses and low dose rates, and the biological processes that govern radiation response to ionising radiation at various levels of biological organisation from sub-cellular and cellular endpoints to more complex organisms such as mammals and humans. Although not conclusive, an overall trend over the years in the application of dose and dose rate factors appears to be towards lower values for these factors from the early values of 10 - 20 towards more recent estimations of 1 - 2 suggesting less difference between high-dose and high-dose-rate effects per unit dose as compared to low-dose and low-dose-rate effects per dose than previously thought. As will be seen from the sections that follow, there is a tendency for numerical evaluations of LDEF and DREF to be higher for endpoints assessed at lower levels of biological organization (cellular and molecular endpoints) than those at higher levels (experimental animals and humans). This observation suggests that there are mechanisms acting during the process of radiation carcinogenesis that modulate the transformation of subcellular effects at the genetic/epigenetic level to cancer.

# CELLULAR RADIOBIOLOGICAL STUDIES

## Identifying mechanisms and cellular endpoints relevant for studying LDEF and DREF

1. In its 2010 summary of low-dose radiation effects on health, (UNSCEAR, 2010) places prime emphasis on the role of DNA damage and subsequent gene mutations and chromosome aberrations in driving both cancer and hereditary effects. A more detailed summary of UNSCEAR’s judgements on the biological mechanisms of radiation actions at low doses is provided in its White Paper (UNSCEAR, 2012). This again notes the important role of DNA damage and mutations in somatic cells with regard to cancers and in germ cells in respect of hereditary effects. In 2006, UNSCEAR evaluated the impact of non-targeted and delayed effects on radiation-associated disease, but no causal relationship between these phenomena and disease was established (UNSCEAR, 2008b). UNSCEAR also considered the role of the immune system in modulating outcomes of radiation exposure. The evidence base was judged to be mixed with no consistent and clear indication whether low-dose exposures served to stimulate or suppress immune responses (UNSCEAR, 2008c). The 2012 White Paper considered key publications since 2006 relating to genomic instability, bystander and abscopal effects, adaptive response, reactive oxygen metabolism and mitochondrial function, DNA sequence analysis, gene and protein expression, cellular interactions and tissue-level phenomena and, finally, systems biology approaches.
2. More recently UNSCEAR has published a comprehensive evaluation of the biological mechanisms relevant for low-dose and low-dose-rate radiation cancer risk inference (UNSCEAR, 2022c). Little robust information was identified that suggested a need to change the current approach taken for low-dose radiation cancer risk inference as used for radiation protection purposes. The potential contributions of phenomena such as transmissible genomic instability, bystander phenomena and adaptive response remained unclear on the basis of the evaluation. UNSCEAR concluded that good justification remained for the use of a non-threshold model for risk inference given the robust knowledge on the role of mutation and chromosomal aberrations in carcinogenesis. However, the evaluation noted that there was evidence that some processes, such as immune reactions, tumour vascularisation and enhanced DNA repair functions may modulate radiation carcinogenesis. The evidence available in relation to these endpoints was not judged to be sufficient to change approaches to risk inference. In a similar fashion, the implications of the studies on the induction of transmissible genomic instability, bystander effects, hyper-radiosensitivity and adaptive responses were judged to be unclear. Some studies suggest thresholds for the induction of transmissible instability and bystander effects at around 100 mGy low-LET radiation; if confirmed, this would indicate the phenomena are not relevant for low-dose cancer risk inference. Adaptive response studies were judged to remain without a confirmed mechanistic basis and to be mixed in outcome (paragraph 242 in UNSCEAR, 2022c).
3. The UNSCEAR conclusions differ somewhat from those reached by a report from the US Electric Power Research Institute {EPRI, 2009 #10764}(EPRI, 2009) ‘*Recent radiobiological studies in the low dose region demonstrate that the mechanisms of action for many biological impacts are different from those seen in the high dose region. When radiation is delivered at a low dose rate (i.e. over a longer time period), it is much less effective in producing biological changes than when the same dose is delivered in a short time period, therefore the risks due to low dose rate effects may be overestimated*’. The EPRI study acknowledges the importance of DNA damage and mutations in radiation carcinogenesis but noted the expanding data on phenomena that are differentially induced by high- and low-dose exposures. These latter have not been firmly associated with radiation carcinogenesis. EPRI states: ‘*There is agreement that induced DNA damage and subsequent response processes are likely to play an important role in radiation-associated cancer risks. In addition, a variety of less well understood non‑targeted and epigenetic effects may also play a role. Until there is a comprehensive biological understanding of carcinogenesis in general, identification and precise quantification of the particular roles of ionizing radiation remain elusive, particularly at low doses. Furthermore, there is no compelling reason to suspect that advances in technology or systems biology-based approaches will necessarily overturn current thinking about low-dose effects. While this report has concentrated on new data that tends to challenge the current paradigm for radiation protection, there continues to be a large amount of research that seems to support and reinforce traditional concepts in radiation biology and radiation protection*’.
4. In a more recent report (SENES, 2017) it is also considered which cellular and molecular endpoints are most relevant to the evaluation of dose- and dose-rate effectiveness. The report provides a summary of available numerical evaluations of LDEF and DREF from cellular endpoints. Ultimately the report places most emphasis on genetic and cytogenetic endpoints while noting the potential for phenomena such as genomic instability and bystander responses to modify dose-response relationships particularly at low doses and dose rates.
5. Therefore, considering the conclusions drawn from the major reviews summarised above in paragraphs 68-71, the most secure data which to consider in terms of relevance to low-dose and low-dose-rate risk inference relate to DNA damage, its repair and the induction of gene mutations and chromosomal aberrations. This conclusion is broadly similar to that apparent in the recent very comprehensive review of cellular and molecular endpoints relating to cancer risk and the specific impact of low-dose-rate exposure (Brooks et al., 2016).
6. Clearly, to be relevant for carcinogenesis, the endpoints and mechanisms considered must lead to lasting change in cells that can be transmitted through cell divisions. In the sections that follow we refer largely to endpoints where there is some direct relevance for cancer induction on the basis of the stability of changes through cell divisions. There are some endpoints however where there is a less direct relationship, though informative on the issue of dose and dose-rate effects. For example, cell survival is not of direct relevance, though is likely to be relevant indirectly as discussed in section 3.2.4. Where considering the induction of chromosomal aberrations, the type of aberration needs to be borne in mind as some are stable (i.e. transmissible though cell division) while others are not. Where exchange-type aberrations are concerned, while some are stable (such as translocations) others (such as dicentrics) are not. The underlying mechanisms of formation may however be shared. Furthermore, the studies considered focus predominantly on those using low-LET radiations for which DDREF is applied.

## Consideration of specific endpoints

### DNA damage induction and repair assayed *in vitro* and *in vivo*

1. Biophysical considerations argue strongly that damage to DNA, and indeed other cellular components, will be induced as a simple linear function of dose. Much emphasis is placed upon the importance of DNA double strand breaks (DSB) and complex damage sites in determining the cellular effects of radiation exposure. As these lesions are rare at doses of a few mGy and below (around 40 per cell per Gy for low LET radiation), DSBs will be present in only a fraction of irradiated cells. The use of immuno-staining and fluorescence tagging of DNA damage response related chromosomal proteins, γH2AX and 53BP1 (see Rothkamm et al., 2015, for a review) in particular, have brought some potentially interesting new information on the quantitative aspects of DSB formation and repair following radiation exposure.
2. In terms of DSB formation as assessed by 53BP1 focus formation using live cell imaging of fluorescently tagged protein, (Neumaier et al., 2012) observed that more but smaller foci formed per unit dose following low dose by comparison with high-dose exposure. Similar observations of supra-linear induction of foci have been made using immunofluorescence methods (Beels et al., 2009, 2010). These observations may relate to the aggregation of breaks into ‘repair complexes’ following higher dose exposures. However, there remain a number of technical issues that might be relevant to these results and impact on their interpretation (Barnard et al., 2013). It remains important to obtain a better understanding of the early stages of formation and processing of DSBs, particularly the quantitative aspects and relocation / movement of breaks to putative repair centres. Taken at face value, however, if low radiation doses do induce more breaks per unit dose, this may be predicted to lead to higher risk from low doses.
3. Following the time-course related repair of DNA DSBs, analysis of numbers of foci also indicate some potential differences between high- and low- dose exposure. Although the number of DSBs induced may be low and less than one per cell, at low doses repair as monitored by loss of foci may be slower or even incomplete, leading to long-term persistence of residual foci over time after irradiation (Rothkamm and Löbrich, 2003; Grudzenski et al., 2010; Ojima et al., 2011). These findings indicating incomplete repair following low-dose exposure are suggestive of an inducible component to DSB repair.
4. Critical to the interpretation of both the break induction and break repair data will be secure knowledge of the subsequent fate of low-dose exposed cells carrying persistent breaks. If as one study suggests (Rothkamm and Löbrich, 2003) they are lost through an apoptotic pathway within a few cell cycles, then risk from low doses may be reduced. However, results of in vitro and in vivo assessment of micronucleus induction at low doses is not fully consistent with a complete lack of repair of double strand breaks in the few mGy range (see Section 3.3.3.).
5. Chadwick (2017) summarised the relationships between DNA DSBs induced by radiation (quantified by neutral filter elution) and cell killing, chromosomal aberrations and mutations. Over a wide dose range up to several tens of Gy DSB induction is best described by a linear-quadratic dose-effect relationship. Direct correlations between DSB and cell killing, chromosomal aberrations and somatic mutations are observed. A series of equations is developed relating cancer induction to mutation frequency per irradiated cell, and these indicate simple linear dose-response relationships for cancer after low-dose-rate exposures but linear quadratic relationships with a peak above which cancer induction declines at high dose rates. This therefore suggests that DREF varies as a function of dose, and no single value can be expected to apply.

### Induction of gene mutations

1. Gene mutation assays at low doses present significant challenges due to the low frequency of induction. In studies using an HLS-A2 gene loss system in human TK6 or p53-/- WI-L2-NS cells a linear dose-response for gene loss was observed in the 50‑500 mGy range (Boei et al., 2012) and p53 status did not affect mutation yields. Using a more traditional thymidine kinase locus mutation assay, (Manesh et al., 2014) observed no dose-rate dependence of mutation induction at 0.5 or 1 Gy doses accumulated at 1.4, 5, 15 mGy min-1 or 24 Gy h-1.These results from TK6 cells and derivatives suggest low dose and low dose rates are broadly similar in effectiveness as higher doses/dose rates; some caution in interpretation is needed as the cell lines employed are derived from malignant cells and so may not be representative of untransformed cell populations. However, the extensive data used in the analyses of Vilenchik and Knudson (2000, 2006) that consider results from transformed and normal cell populations, clearly demonstrate that dose rate affects mutation induction frequency. All of these studies contrast with a publication suggesting that 0.2 Gy x-irradiation reduces the somatic mutation frequency below ‘spontaneous’ levels in *Drosophila* larvae (Koana et al., 2012).
2. Okudaira and co-workers investigated deletions of a *red-gam* bacteriophage lambda transgene in spleen and liver of SWR mice gamma-irradiated at a range of dose rates (Okudaira et al., 2010). Mutation induction was investigated at dose rates of 920 mGy min-1, 1 mGy min-1 and 12.5 μGy min-1 with total accumulated doses of 2-8 Gy. Mutation rates were about 5-fold higher at the high by comparison with low dose rate. Some differences between tissues may have been present at the intermediate dose rate; dose‑response relationships at all dose rates and in all tissues were linear. Larger, multi-locus deletions appeared less frequently in low-dose-rate irradiated tissue. A retrospective analysis of data on specific locus mutations in mouse spermatogonia (i.e. germ line mutation) has been published recently (Russell and Hunsicker, 2012). These studies, while using an in vivo system, are relevant to mutagenesis at the level of the cell as the observed mutations are the result of mutations in single cells. The studies included x- and γ irradiation between 0.0007 and 1000 R min-1 of hundreds of thousands of mice in the 1950s, 60s and 70s. The analysis concluded that protracted exposures (0.0007‑0.8 R min-1) were less effective than high-dose-rate exposures (24‑1000 R min-1) at inducing large multi-locus deletions, but smaller (single gene or intragenic) mutations showed no dose‑rate dependence over the dose range 86-1000 R. In common with the (Okudaira et al., 2010) study this analysis indicates dose-rate sensitivity for larger deletions but not for point and other small mutations. The ratio of high-/low-dose-rate large mutation induction slopes was 3.4. Taken together these studies suggest that dose rate affects preferentially larger mutations that are likely to require interaction between two radiation tracks rather than single track events. Thus, DREF is most relevant for endpoints driven primarily by large scale mutations – as is generally considered to be the case for radiation-induced cancer.
3. A recent study has investigated genetic changes in a sample of 359 papillary thyroid carcinomas in children exposed to 131I as a consequence of the Chornobyl accident (mean dose 250 mGy, range 11-8800 mGy). This analysis revelled a radiation dose-dependent increase in gene fusion driver mutations, mainly in the mitogen-activated protein kinase pathway, and increases in clonal small deletions and simple/balanced structural variants. These mutations carried indications of having been caused by the non-homologous end joining pathway of DNA double strand break repair. The results are interpreted as evidence that radiation-induced DNA double strand breaks are early events that lead to papillary thyroid carcinoma after environmental radiation exposure. (Morton et al., 2021).

### Induction of chromosomal aberrations

1. Early studies of the effect of dose rate on the induction of chromosomal damage, including reciprocal translocations, in spermatogonia in mice and monkeys exposed *in vivo* indicated substantial dose‑rate effects with low dose rates being a factor of 2-10 less effective than higher dose rates (e.g. Searle et al., 1976; Pomerantseva et al., 1984; van Buul et al., 1986; van Buul, 1989). A more recent mouse study has had estimated dose rate effectiveness factors for the induction of chromosomal aberrations (translocations and dicentrics) and *Dlb-1* gene mutations to be 3.8-9.1 and about 6 respectively (Tucker et al., 1998). The observation of aberrations in the lymphocytes of those living in 60Co contaminated buildings (30‑40 mGy year-1) suggest modest low dose rate effectiveness factors (Hsieh et al., 2001, 2002). An extensive low-dose-rate exposure mouse study found a linear induction of dicentrics and rings up to 8 Gy at 20 mGy day-1 and the dose-rate effectiveness estimate for chromosomal changes comparing 20 mGy day-1 to 890 mGy min-1 was 4.5-5.2 at 100 mGy. The dose rate effectiveness factor showed strong dose dependence rising to 24.5 at 1 Gy (Tanaka et al., 2009). Further similar studies report DREF values of 4.5 for translocations and 2.3 for dicentrics comparing 20 mGy day-1 with 890 mGy min-1 (Tanaka et al., 2013). Slopes of aberration induction curves further reduce between 20 mGy day-1 and 1 mGy day-1 (Tanaka et al., 2014). Dose-rate effects on aberration induction, at least in the 10-0.01 Gy min-1 range have been attributed to DNA repair activities (Foray et al., 1996). Studies in TK6 cells found no dose-rate dependence (1.4 – 30 mGy h-1) of stable chromosomal aberration induction (Manesh et al., 2014) while other studies provide evidence for dose-rate effects operating on both mutations and chromosomal aberrations (e.g. Vilenchik and Knudson, 2000, 2006; Ulsh et al., 2001).
2. Using a sensitive *in vitro* system the induction of micronuclei in primary human skin fibroblasts was observed to be linear in the 0-100 mGy range with statistical significance of increase present at 20 mGy (Boei et al., 2012). S-phase cells were observed to be more sensitive than those in other cell cycle phases. Induction of micronuclei in reticulocytes after *in vivo* irradiation of mice is also observed to be linear over the 10-100 mGy x-ray range with no evidence for a threshold (Manning et al., 2014). These studies demonstrating the induction of micronuclei at doses in the mGy region both in vitro and in vivo are not consistent with the finding from γH2AX staining studies of DSB repair that suggest breaks are not repaired in the mGy region and cells may be lost to apoptosis (Rothkamm and Löbrich, 2003). The reticulocyte assay results would seem particularly relevant as they relate to in vivo exposure and the cells in which micronuclei are scored are derived from exposed Haematopoietic stem/progenitor cells. Analysis of micronuclei induction in human blood irradiated in vitro indicates that at approx. 0.3 Gy min-1 induction is linear with dose, while at an approx. 1 Gy min-1 dose rate a linear quadratic relationship applies (Bertucci et al., 2016).
3. Considering *in vitro* induced chromosomal damage in human lymphocytes and fibroblasts, large amounts of data have been accumulated. For chromosomal aberration studies (EPRI, 2009) quote DDREF estimates range between 4 and 6 based on the BEIR VII analysis (NAS, 2006). The report by (SENES, 2017) states that central estimates of DDREF derived from chromosomal aberration studies lie in the range 2 – 6.

### Induction of cell cycle checkpoints and apoptosis

1. Following exposure of actively cycling cells to ionising radiation complex signalling responses are activated. The assumed function of these is to coordinate cellular responses to damage and collectively are referred to as the DNA damage response (DDR). The cellular responses include DNA repair, activation of apoptosis, transcriptional responses and activation of cell cycle checkpoints. Cell cycle checkpoints allow the integrity of genetic material to be monitored before progression through key stages such as replication and mitosis. Checkpoints at G1/S and G2/M as well as intra-S phase stage have been described. Checkpoints are initially activated by ATM in mammalian cells following ionising radiation exposure. The G2/M checkpoint has an activation threshold of 10-20 DSB (Löbrich and Jeggo, 2007). Radiation doses less than 200 mGy (low LET) therefore fail to activate the G2/M checkpoint. Failure of the checkpoint leads to increased chromosomal radiosensitivity, a feature of many cancer prone disorders (Scott, 2000). In this context low doses (less than 200 mGy) may be predicted to be more effective in terms of carcinogenic potential than higher doses where G2/M checkpoints are effectively induced. The low-dose hypersensitivity described in several cell types following exposure to low doses (e.g. Marples and Joiner, 1993; Krueger et al., 2007) is likely attributable at least in part to the lack of G2/M checkpoint induction. The low-dose hypersensitivity is associated with induction of apoptosis when cells in G2 are irradiated (Marples et al., 2003). Thus, low-dose damaged cells may survive and progress through a G2/M phase transition but subsequently enter apoptosis and so are eliminated from the pool of damaged and therefore potentially pre-cancerous cells. Apoptosis is induced by mGy doses of radiation and radiation exposure can increase the apoptosis of transformed pre-cancer cells through an intercellular process (Bauer, 2007).
2. The relevance of apoptosis induced in either normal or pre-cancer cells is not entirely clear. The killing of pre-cancer cells would be expected to reduce risk, and similarly the killing of cells with directly induced damage and/or mutations would be expected to reduce risk. However, the reduction in cell numbers is likely to be compensated by repopulation through stem cell proliferation and differentiation. Recent studies suggest that a majority of mutations observed in human cancers may have their origin in DNA replication errors (Tomasetti and Vogelstein, 2015; Tomasetti et al., 2017), and thus any factor that leads to increased stem cell replication could enhance cancer risk through replication-associated mutation or mis-repair. However, some stem cell populations appear to have properties that serve to reduce the burden of replication-associated mutations (see ICRP (2015) for review (Section 2)). Additionally it should be noted that the views of Tomasetti and Vogelstein have been challenged by (Little et al., 2016) who failed to find a correlation between stem cell proliferation and risk of radiation-associated cancer. Thus, the relationship between stem cell division and cancer risk remains uncertain.
3. Sufficient data on the dose-response for other cell cycle checkpoints are not available.

## Effects of low dose and dose rate – should they be considered together?

1. As has been discussed earlier DDREF is a single value used to adjust for the difference in magnitude of the health impact per unit dose of ionising radiation at high and low doses and dose rates, to be used in radiological protection. The main rationale for considering, and adjusting for, dose and dose-rate effects together has its basis in the biophysics of radiation energy distribution (See Rühm et al., 2015). In the case of sparsely ionising, low LET radiations, as radiation dose reduces so does the number of radiation tracks traversing individual cells, until the point at which each cell in a tissue or population is traversed by one or no tracks. Similarly, as dose rates reduce the number of radiation tracks per unit time reduces to a point such that, at any given time each cell in a tissue or population is traversed by a maximum of one track. The amount of DNA damaged, and to an extent its complexity is determined by the deposited energy (i.e. number of track traversals). When the number of track traversals per cell is one or less, there is no chance of the damage caused by individual tracks interacting within a single cell. It is these track interactions that are taken to be of importance in determining the upward curvature in dose response relationships for cellular phenomena such as chromosomal aberration induction and mutation induction. This has been succinctly summarised in NRCP Report 64 (NCRP, 1980) (pages 172-173):

*‘The apparent equivalence of the dependence of effect on dose magnitude and on dose rate is not surprising, since both must depend on the same basic phenomenon, i.e. the relative rates of build-up and of decay (or repair) of some form of damage or lesions which must interact in combination to eventually produce the observable biological effect of interest. The result (the net amount of persistent lesion interaction and thus of apparent effect) is thus critically dependent not only upon the dose magnitude, but also upon the temporal pattern of dose delivery. The expectation of a dose rate dependence has a firm basis in known biomolecular mechanisms of repair of DNA damage and would be expected from most biophysical models of radiation effects at the cellular level …’.*

1. Thus, it is the density of DNA lesions in the nucleus that is of importance in determining cellular outcomes. Reducing radiation dose leads to a reduced spatial density of DNA lesions. Reducing radiation dose rate reduces the temporal density of DNA lesions.
2. Amongst the most extensive data examining the effects of varying dose and varying dose rate independently remain those using the plant, *Tradescantia,* published in the 1970s. Mutations in the flower stamen hairs are scored; the wild type being blue and mutant, pink. These data are summarised in (NCRP, 1980). In this simple system the initial slope of the linear quadratic dose-response determined with high-dose-rate exposure is similar to the slope of the low-dose-rate response. Thus, these studies provide evidence for the equivalence of low-dose and low-dose-rate effects.
3. While induction of primary DNA damage, for example, DNA double strand breaks is observed to be linear with dose (e.g. Rothkamm and Löbrich, 2003), many if not all of the direct consequences of radiation exposure such as cell killing, chromosomal aberration induction and mutation induction follow linear-quadratic dose-response relationships as in the case of *Tradescantia* mutations noted briefly above and in mammalian systems. However, detailed examination of the induction of chromosomal aberrations in human cells has questioned the validity of LQ relationships. Fluorescence in situ hybridisation (FISH) methods for assessing chromosomal damage have been developed that allow each chromosome pair to be simply and unambiguously identified – the so-called multicolour FISH, mFISH methods. Application of mFISH methods revealed that many of the apparently simple translocations and dicentric aberrations scored by conventional methods were, in fact, complex in origin involving a minimum of three breaks in at least two chromosomes (Griffin et al., 1995; Simpson and Simpson, 1995; Anderson et al., 2000). It has become clear that the actual dose-response for the induction of genuinely simple reciprocal translocations is very near linear with no substantial evidence of upward curvature (Loucas and Cornforth, 2001; Loucas et al., 2004; Cornforth, 2006). These studies indicate an LDEF of 1.2‑1.3. Despite the observed near linearity of induction of simple reciprocal translocations with dose, a substantial dose-rate effect was observed with an estimated DREF of 5.7 for a 0.8 mGy min-1 exposure compared to 1.1 Gy min-1 (Loucas et al., 2004). These observations argue against dose and dose-rate effects being considered the same and together even for direct DNA based endpoints.
4. While it has long been held that chromosomal aberrations provide a mechanistic link between direct radiation outcomes at the cellular level and cancers, which are frequently characterised by chromosomal aberrations, the specific type of aberration(s) induced by radiation and leading to cancer is not generally known. While a range of aberrations, including deletions and insertions have been observed in specific cancers, establishing a causal link is challenging. In a mouse model of radiation‑induced acute myeloid leukaemia there is strong evidence for aberrations directly induced by radiation to be causally linked to disease (Verbiest et al., 2015). Also several human population studies have suggested that chromosomal aberrations in peripheral blood act as an indicator for cancer risk (Bonassi et al., 2008, 2011). So, while there is evidence for an association between chromosome aberrations and cancer, it is likely that a range of aberration types will be involved, some cytogenetically ‘simple’ in origin and some ‘complex’: therefore, it is not clear that the observation of a linear induction of simple reciprocal translocations should be any more closely associated with cancer risk than the more complex forms of aberrations. Transmissibility of aberrations through cell division is, of course, essential and likely to be more common for genuinely simple aberrations.
5. If the induction of gene mutations and chromosome aberrations is a main contributor to radiation carcinogenesis, then modulated expression of DNA repair genes should modify radiation cancer risk. There is evidence that genes involved in the two main DNA double strand break repair pathways, non-homologous end joining and homologous recombination repair, modify radiation cancer risk in mice and there is some tissue specificity (Degg et al., 2003; Haines et al., 2010, 2015). Also, a single nucleotide change or polymorphism (SNP) in a factor that affects repair pathway selection, CtIP, has been demonstrated to lead to increased radiation leukaemogenic sensitivity in mice (Patel et al., 2016).
6. Going back to the LQ model and the limiting dose rate where the slope of a dose‑response should be that of the initial slope of a high-dose-rate response, the limiting dose rate would be that where the rate of impact of damage is less than the repair. For mammalian systems this is generally taken to be 0.1 mGy min-1 where 1/100 cells would be traversal by a track per minute and so no cells would receive more than one track traversal per hour – i.e. no probability of track interaction (Hall and Giaccia, 2011; UNSCEAR, 2022c). Therefore, when looking at dose-rate dependency, one would not expect further reductions in slope below 0.1 mGy min-1. In line with expectation, (Loucas et al., 2004) observed reductions in the linear term of simple translocation dose-response between 1 Gy min-1 and 1 mGy min-1, similarly reduction was observed for male germ cell mutation between 1 Gy min-1 and 10 mGy min-1 (Russell and Kelly, 1982). More surprisingly slopes were observed to reduce further down to 0.01 mGy min-1 in female gene cell mutation assays (Searle, 1974). While it has been argued that the observations by Loucas et al. (2004), and, Russell and Kelly (1982) on reducing slope with reducing dose rate argue against a conventional LQ model operating, it seems likely the dose rates used do not go sufficiently low (Niwa in Rühm et al. (2015)). It is well known that tissue stem cells are under constant competition with each other for their survival to stay on in the stem cell niche. The competitiveness may be modified by any physiological disturbance to the stem cells and single-track traversals could be one such disturbance. Thus, when cells are exposed to very low-dose-rate radiations, a hit stem cell is surrounded by non-hit stem cells and the former can likely be competed out by the latter, leading to further reduction of the slope of the dose response curves at dose rates below 1 mGy min-1 (ICRP, 2015).
7. To summarise there is an extensive body of literature and evidence that supports use of LQ models for early cellular outcomes following radiation exposure. More recent evidence has brought this into question, suggesting that linear responses for specific transmissible aberration types are observed. However, it must be kept in mind that there is no proven relationship between any of the cellular endpoints and cancer, and clearly direct cellular effects will be modulated at the tissue and organism level through the ‘latency’ period between initial exposure and clinical presentation of cancer. Together this suggests that substantial caution is required to use cellular and molecular data in quantitative estimations of LDEF, DREF or DDREF.

## Modulation of responses to radiation

1. There are processes that have been described to operate in mammalian systems that could serve to modulate carcinogenesis and therefore risk differentially at low- as opposed to high-doses and dose rates. These include the ‘non-targeted’ effects, differential modulation of gene expression, and differential modulation of the immune system. In its 2012 White Paper (UNSCEAR, 2012), UNSCEAR concluded, ‘*While mechanistic understanding of non-targeted effects is improving, many studies remain primarily observational. There are also reports of differential gene and protein expression responses at high and low radiation doses and dose rates. As noted, these reports remain mixed in outcome and there is little of the coherence required of robust data that can be used confidently for risk assessment. Similarly there is as yet no indication of a causal association of non-targeted phenomena with radiation-related disease and indeed, some may not operate at low doses in vivo*’. With regard to the immune system, the White Paper concluded, ‘*In the case of radiation-induced perturbation of immune function or induction of inflammatory reactions, there is a clearer association with disease but the impact of radiation is less well understood*’. These conclusions were re-stated in UNSCEAR (2022c). In this section a brief update on these and related issues is provided, with attention to the strength of evidence supporting the operation of the proposed modulating processes, the likely impact of the modulation and thus impact on low-dose and low-dose-rate risk modulation.
2. Several authors have studied gene expression patterns following high and low doses or high- and low-dose-rate radiation exposures in an effort to identify mechanisms that may be different at the different doses and dose rates. While many studies claim to identify differences between dose and/or dose-rate levels, there remain difficulties with these studies when considered as a body of evidence. (Sokolov and Neumann, 2015) reviewed this area and concluded that ‘The studies into LDIR exposures in human cells involving high-throughput genomic techniques such as DNA microarrays demonstrated that even LDIR exposures below 1 cGy could potentially trigger measurable changes in global gene expression. However, these alterations are often not lasting, and may not depend on dose of IR within LD range. DNA microarray datasets suggest that LDIR responses are highly genotype, cell type, and tissue-dependent, with a remarkable degree of variability both between individuals and different cell types…. Apparently, both genetic and epigenetic background affects the response of human cells to LDIR exposures. Unfortunately, many of “consensus” gene expression signatures identified after LDIR were not proven in independent studies, and many LDIR-responsive genes vary among published reports.’ (LDIR – low dose of ionising radiation) Thus, there is no consensus on a specific ‘low-dose’ gene expression signature that is distinct from a ‘high-dose’ signature that would, if present suggest that the basic cellular responses, including potentially risk modifying effects such as the modulation of DNA repair gene expression, to high and low doses differ. UNSCEAR in its 2020/21 report on biological mechanisms relevant for the inference of cancer risks from low doses and low-dose-rate radiation considered the gene and protein expression literature extensively and also concluded that there is no consensus on specific low-dose radiation exposure signatures (UNSCEAR, 2022c) This makes apparent the difficulties faced when interpreting such studies. The fact that many of the observed responses are not long lasting, with many studies including a 24-hour post exposure sample as the longest, the relevance of the reported changes for cancer risk assessment is further questioned.
3. The induction of the non-targeted effects, including transmissible genomic instability, bystander effects and adaptive response are phenomena generally defined at the cellular level that could affect radiation dose-response relationships, and thus the inference of risk at low- by comparison with high- doses and dose rates. Transmissible genomic instability is the phenomenon whereby mutations or chromosomal aberrations arise several cell generations after initial exposure. If this were to contribute to carcinogenesis following radiation exposure, consideration of effects directly following exposure only could be misleading. Several more recent studies of transmissible genomic instability on both cellular and whole animal systems suggest that transmissible instabilities are not induced following low-dose exposures (e.g. Zyuzikov et al., 2011; Rithidech et al., 2012; Cho et al., 2015; Candéias et al., 2018) and thus are not likely to need to be considered with respect to risk inference. It could be argued that this transmissible instability operates only at higher doses and that it could contribute to the generally greater impact of high as opposed to low doses.
4. Bystander effects and their relevance in tumour therapy have been considered in a recent review (Daguenet et al., 2020). Bystander effects are those effects of radiation observed at distance from directly irradiated cells. When the distance is substantial operating at the organ level or inter-organ level, they are referred to as abscopal effects. While having a primary focus on bystander and related phenomena in relation to therapeutic applications the review has relevance to low dose considerations. It is clear that the outcome of bystander effects can be either detrimental or beneficial, and therefore potentially risk-enhancing or risk-reducing. Multiple mediators of bystander effects have been proposed, including microvesicle-mediated intercellular communication, intercellular junctional communication, diffusion of soluble mediators amongst others. With the absence of a specific mechanism and variation in reported study outcomes, including both beneficial and detrimental bystander effects it remains difficult to apply the findings in evaluation of low-dose and low-dose-rate risk inference.
5. The phenomenon of adaptive response where small ‘priming’ exposures of cells or organisms (on the order of a few to around 10 mGy) serve to reduce the subsequent magnitude of response to a higher ‘challenge’ exposure has been proposed to underline some of the protective effects of low-dose radiation exposure observed in human populations (high natural background area) and experimental studies (see UNSCEAR (1994) for an extensive review). There are continuing reports of adaptive responses occurring at the cell and whole animal level (e.g. Saini et al., 2012; Jin et al., 2015; Park et al., 2015; Vieira Dias et al., 2018), with some revealing a differential adaptive response in males and females (López-Nieva et al., 2016). By contrast some studies have reported equivocal findings (e.g. Gridley et al., 2013) and others fail to demonstrate adaptive response at all (e.g. Bannister et al., 2015).
6. With this mixed evidence base and a lack of mechanistic understanding it remains very difficult to use such findings for evaluation of LDEF or DREF. While the phenomenon of adaptive response has been held to underlie the reports of extension of lifespan in low-dose irradiated animal life span studies, and potentially the claims of reduced health impacts on those inhabiting high natural background radiation areas, the variable evidence available does not allow a firm conclusion to be drawn.
7. That the immune system can modify responses to radiation exposure is demonstrated in studies of health risk in populations carrying differing variants of immune-related genes (see Sigurdson et al., 2007; Schonfeld et al., 2010) The immune system is complex and tightly regulated and several studies show that radiation exposures can lead to its long lasting perturbation, for example the studies of the Japanese atomic bombing survivors (e.g. Kusunoki et al., 2010). Radiation exposure appears to reduce inflammation of tissues already in an inflamed state (e.g. Arenas et al., 2006, 2008). It is however less clear what the effects of low doses on non-inflamed tissue are, and if there is a reduction in inflammation that might contribute to a level of protection against inflammation-related conditions. Should a consistent effect be demonstrated then low doses might be viewed as risk reducing while higher pro-inflammatory exposures could be viewed as risk enhancing, again potentially explaining some of the results of studies from high natural background radiation areas and low-dose animal studies. In the absence of a consistent picture however it is premature to take such studies into account in evaluation of LDEF or DREF.
8. Were radiation to affect some of the later stages of carcinogenesis such as metastatic invasion or tumour vascularisation, then a risk modulating effect would be anticipated. Currently there is little evidence available on such topics, but a number of studies have considered the effects of radiation on cell migration, invasiveness, epithelial-mesenchymal transformation (EMT, that is associated with increased invasiveness of epithelial tissue tumours) and tumour vascularisation. While very few studies consider low-dose or low-dose-rate exposures, some studies suggest that low and moderate dose exposures can promote EMT and cell migration (Sofia Vala et al., 2010; Wang et al., 2012a,b; Ghosh et al., 2014) but there is one report where low doses apparently reduce cell migration (Kaushik et al., 2017). So, on balance these studies would tend to suggest that low-dose exposures might promote the later stages of carcinogenesis, however the available data are too scarce to draw firm conclusions currently.

## Conclusion

1. Studies of chromosome aberration (pooled stable and unstable) and large mutation induction *in vivo* and *in vitro* tend to indicate a LDEF and DREF values of around 3-5. Evidence for dose thresholds for the induction of chromosomal endpoints (micronuclei in particular) is weak within evaluated dose ranges suggesting LNT extrapolation of low-dose values is valid. The use of LNT to extrapolate from higher to lower doses implies (but does not actually require) the mechanisms that operate at different dose levels to be similar. There is developing evidence that the induction and persistence of DNA DSBs may differ between low and high doses. To understand the risk implications of this potentially higher induction and longer persistence it is critical that longer term follow-up studies establish the fate of cells carrying such low-dose damage and the fate of the damage itself. Results of low dose in vivo micronucleus induction studies in primitive haematopoietic cells indicate that mGy levels of radiation can give rise to cells that progress to mitosis, potentially with damage subsequently being eliminated. Similarly, evidence that the G2/M cell cycle is activated only after relatively high (> 200 mGy) doses might be suggestive of greater risk at low doses. However, available data would suggest cells carrying DNA damage that progress through the G2/M checkpoint are eliminated by apoptosis, and this underlies the observed higher dose radiosensitivity. It will be important to determine whether the elimination of low-dose damaged cells is complete or partial.
2. There are few data that pose a significant challenge to the central role of DNA damage and mutation in radiation carcinogenesis. Indeed recently reported whole genome sequencing studies provide evidence for a ‘signature’ of radiation exposure (Behjati et al., 2016); while this study relates to relatively high exposures delivered for radiotherapy, similar findings in cancers arising following lower dose exposures may become available in the future. There is however a number of potential risk modulating processes that might serve to increase or decrease risk. The role of such processes in radiation carcinogenesis *in vivo* is presently insufficiently defined to bring them into considerations of health risk assessment.
3. The literature relating to potentially risk modulating effects including adaptive response, transmissible genomic instability, bystander phenomena, differential gene expression, cell migration/EMT and immune system effects is not yet sufficient to allow firm conclusions to be drawn on their impact on the evaluation of DDREF.
4. The developing literature on the effects of radiation exposure at both high- and low-dose levels delivered acutely or chronically on micro-RNA expression (Chaudhry et al. 2012; Luzhna and Kovalchuk, 2014; Wang et al., 2015) may become relevant given the importance of micro RNAs in cancer (see Romano et al., 2017).
5. In general terms cellular and molecular data tend to support the application of a DDREF to estimate risk at low doses and dose rates. A broadly similar conclusion was drawn in the review of (Brooks et al., 2016) that specifically considered dose-rate effects on cellular and molecular endpoints; the authors summarise,‘*…a review of the available molecular, cellular and tissue data indicates that not only is dose rate an important variable in understanding radiation risk but it also supports the selection of a DREF greater than one as currently recommended by ICRP (2007) and BEIR VII (NAS, 2006*)’. The magnitude of the DDREF value is not large with chromosomal studies, which include some of the largest data sets, indicating around 4 and there are sound data indicating that DNA damage responses and mutational processes operate at low doses (down to 20 mGy) and dose rates (down to 20 mGy day-1 and 1 mGy day-1) as they do at higher doses/dose rates. Considering the data overall, the value of 4 above based on chromosomal aberration studies is towards the higher end of values based on a wider range of endpoints. There is of course much time that elapses between induction of gene and chromosomal mutations and clinical presentation of cancer. Many processes are likely to modulate this and while poorly defined could together have a significant influence on the magnitude of DDREF.

# ANIMAL STUDIES

## Introduction

1. Efforts to improve the DDREF estimate and the calculations of LDEF and DREF focus on two areas - development of new computational models and approaches, and collection of additional data. While human radiation exposure databases have been regularly updated to include longer follow-up of exposed cohorts under study, less effort has been made to archive all of the existing data on irradiated animals or extend archival efforts to new animal studies. Nevertheless, detailed data archiving is an important step in arriving at DDREF estimates.
2. The existing archives of irradiated animal studies contain information about historical animal experiments concluded by the 2000’s, and include samples from hundreds of thousands of animals (Tapio et al., 2008; Birschwilks et al., 2011, 2012) exposed to different qualities and doses/dose rates of radiation. High LET radiation does not generally have a DDREF or DREF associated with it (although exceptions have been seen (Tran and Little, 2017)), so studies estimating DDREF and DREF have generally naturally focused on low LET studies. In addition, only a few of these data resources could be and were utilized when DDREF was calculated by BEIR VII (BEIRVII, 2006). This was compounded by absence of accessible digital versions of the available data for some of the older as well as more recent animal studies. Animal studies with mixed field exposures were not included because they did not evaluate DDREF, DREF or LDEF; this type of work could be important in the future.
3. Despite the volume of historic data and recent efforts to use animals to study the effects of low-dose radiation, and despite of the fact that the majority of these studies included high-dose or high-dose-rate work for comparison, little of these data on experimental animals were used for DDREF re-evaluation. However, efforts to use experimental animal data for DDREF estimates were a subject of renewed interest in recent years (Haley et al., 2015; Hoel, 2015) and some of this work shows the promise of possible advantages of animal data. Other studies have focused on use of more standard statistical models, specifically Cox proportional hazards models (Cox, 1972) adjusting simultaneously for effects of dose and dose rate, age at exposure and time since exposure and sex and interactions between these (e.g. Tran and Little, 2017). Thus, approaches to animal data used in these studies are varied – from intra-experiment comparisons (Haley et al., 2015; Hoel, 2015) to evaluations of data pulled from different experiments and even for different species (Tran and Little, 2017).
4. This however, is not the only merit of animal data. For example, some of the most interesting recent low-dose radiation data were obtained with transgenic animals with genetic susceptibilities for accumulation of mutations or other endpoint(s) under consideration (e.g. Mancuso et al., 2015; Bakshi et al., 2016; Hofig et al., 2016). Considering that even relatively minor strain-to-strain differences have been used effectively in molecular low-dose radiobiology studies (Snijders et al., 2012) it is obvious that DDREF, LDEF and DREF estimates based on animal experiments could incorporate genetic, epigenetic, metabolic and other planned experimental variations into modeling, as well as capitalize on finer details of radiation delivery (e.g. fractionated vs. acute vs. chronic radiation etc.). Future studies may range from detailed, experiment-specific investigations, and meta-analyses focusing on parameters of dosimetry and specific animal and strain characteristics. In this possible new approach of comprehensively modeling animal radiation studies, data from this source could be used to supplement and support information from the epidemiology. Comparisons of these mouse and rat studies have shown that there are strain-specific differences and age-specific differences (with the young being more radiosensitive) for dose- and dose-rate-responses that need to be considered.

## Summary of Data on Low-Dose and/or Low-Dose-Rate Irradiated Animals

### Historic Studies on Irradiated Animals Suitable for DDREF, DREF and LDEF Evaluation

1. The ERA database has been established as a clearing house of general information on all animal studies conducted world-wide (Tapio et al., 2008; Birschwilks et al., 2011, 2012). This database remains the most extensive archive on irradiated animals and is best connected with its counterparts such as the Janus archive (Grahn et al., 1995) that is partially recombined with the National Radiobiology Archives (Gerber et al., 1996; Watson et al., 1997), especially with regard to data obtained prior to 2000’s. Studies encompassed in ERA include rodents of different families, species and strains as well as dogs and a few other species. Despite the fact that both in Europe and the US these materials led to numerous publications prior to 2000’s (as listed in BEIR VII report (BEIRVII, 2006) and primary literature e.g. Ullrich and Storer (1979); Maisin et al. (1983); Covelli et al. (1988); Grahn and Carnes (1988); Maisin et al. (1996); Carnes et al.(1998)), this material was not considered as a source for DDREF re-evaluations until recently (Haley et al., 2015; Tran and Little, 2017).
2. A recent publication using Janus archive (Zander et al., 2020) is focused on cancer as a cause of death for different protracted and acute radiation exposures. For example, cumulative incidence model used to extrapolate effects of total dose and radiation protraction on incidence of tumours-other-than-lung predicts that acute exposures to total doses of 0.1 or 1 Gy cause tumours more effectively than fractionated exposures to same total doses, with the total dose of 0.1 Gy associated with a higher disease incidence. However, the comparison between fractionated exposures for the same two doses finds almost no difference in incidence of tumours other than lung. This however is no longer the case for 0.1 vs 10 Gy comparison where acute 10 Gy exposure has by far the lowest tumour incidence, naturally, because animals exposed to such a high dose die much sooner than a tumour takes to develop. Therefore, application of innovative approaches and models to the archival data may still allow the examination of animal radiation data from new perspectives.
3. Most of the studies in the Northwestern Janus Archive are aimed to understand the effects of external beam neutron and Cobalt-60 gamma-ray irradiation on lifespan and tumourigenesis across a wide range of dose and dose-rate patterns. In addition, beagle dogs were also used for inhalation and injection experiments in the US; the radionuclides used included 241Am, 144Ce, 249, 252Cf, 253Es, 237Np, 237, 238, 239Pu, 226, 228Ra, 90Sr, 228Th, and 90, 91Y; these were delivered via inhalation or injection, in different chemical forms modulating bioavailability and biokinetics (Puukila et al., 2017, 2018). Regardless of the question of whether it is appropriate to study DDREF, LDEF or DREF in animals exposed to internal emitters (a concern raised by Brooks, e.g. Brooks et al.(2009); Puukila et al. (2017)) these data could be reanalysed if digitized and made publicly available.
4. A large historic body of work from the same period of radiobiological research could become available if Russian data from the Southern Urals Biophysics Institute (SUBI, Ozyorsk), Biophysics Institute (Moscow), and Urals Center of Radiation Medicine (Chelyabinsk) could be digitized and made public. More than 23,000 animals involving mice, rats, rabbits, dogs, pigs and monkeys were included in this work. In addition to external exposures, exposures from internal emitters were also studied. Alpha-emitters such as 234,235U, 237Np, 238, 239Pu, and 241Am, and beta-emitters such as 3H, 90Sr, 137Cs, and 144Ce emitters were delivered by different pathways, often simulating accident scenarios at different dose ranges. While research on human cohorts from Russia is conducted internationally (e.g. many Mayak workers studies), very few animal studies (for an exception see e.g. Paunesku et al., (2012)) follow that path. Thus, for example, the ERA database does not contain more than general information about most of the Russian studies (Abbott, 2012; Abbott et al., 2016). For six of these studies, more detailed information on the experiments and on available biomaterial is given in the STORE database (https://storedb.org; Schofield et al., 2019), but data on individual animals are not included (http://dx.doi.org/doi:10.20348/STOREDB/1056).
5. Currently datasets (but not archives tissues) are the gene experiments from NASA work done in the US at the NASA GeneLab (https://genelab.nasa.gov/). New efforts to develop datasets and tissue archives from animals exposed to radiation that would be available to the public are being developed by the Canadian Nuclear Laboratory (https://www.cnl.ca/). The entire community would benefit from the establishment of an international consortium for irradiated animal tissues and datasets to allow for better communication among the data and therefore improved analyses.
6. A further large body of work using laboratory animals will be made publicly available from Japanese projects evaluating the effects of radiation, within the National Institutes of Quantum and Radiological Science and Technology (QST), National Institute of Radiological Sciences (NIRS) and the Institute for Environment Sciences (IES), which have focused on risk analyses for life shortening and cancer prevalence using laboratory animals. It should be noted that life shortening is a problematic endpoint statistically, and measures based on it (which have often skew distributions) have non-standard statistical properties. This work aims at constructing an archive called the Japan-Storehouse of Animal Radiobiology Experiments (J-SHARE) (Morioka et al., 2019).
7. Table 1 lists studies on irradiated animals where information that is relevant about DDREF can be noted. This information is included here to provide a compendium of animal studies that considered low dose and low dose rate as important variables in their experimental conditions and therefore can inform DDREF.

Table 1**.** Studies on Irradiated Animals after 2000’s Suitable for DREF and LDEF Evaluation

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Dynamics of radiation exposure** | **Source** | **Animals, strain, age etc.** | **Number of animals** | **Doses and/or Dose Rates** | **Study Endpoint** | **Reference** |
| Environmental contamination exposures | Fukushima | Domestic and ‘wild’ | 302 cattle, 57 pigs, 200 macaque, 8 wild pigs, 5 horses | NA | NA | Takahashi et al., 2015 |
| Environmental contamination exposures | Fukushima |  | 9 | NA | NA | Takino et al., 2017 |
| Experimental internal exposure | 137Cs injection | Mice | NA |  | Spermatogenesis process alterations caused by radiation | Nakajima et al., 2015 |
| Experimental chronic external beam | 137Cs-gamma ray | Mice, C3H/HeN 56 days and older | NA | 1, 20, 400 or 890 mGy per day | chromosomal aberrations in splenic lymphocytes noticeable above 400 mGy per day | Tanaka et al., 2013 |
| Experimental chronic external beam | 137Cs-gamma ray | Mice, C3H/HeN 56 days and older | 215 (Tanaka et al., 2008) / 468 (Tanaka et al., 2009) | 1, 20, 400 or 890 mGy per day | Linear increase of aberrations below 3 Gy for dose rate 400 mGy per day and below 8 Gy for exposures of 20mGy day-1 | Tanaka et al., 2008,  Tanaka et al., 2009 |
| Experimental chronic external beam | 137Cs-gamma ray | Mice B6C3F1 | 1129 | 20 mGy day-1 for 400 days | Obesity and fatty degeneration of the liver and different degenerative changes in adrenal glands and ovaries | Tanaka et al., 2017 |
| Experimental chronic external beam | 137Cs-gamma ray | Mice, males only B6C3F1/Jcl | 250 | 20 mGy day-1 for 400 days | A calorie restriction diet extends lifespan of irradiated mice and controls | Yamauchi et al., 2019 |
| Experimental chronic external beam | 137Cs-gamma ray | Mice: B6C3F1, C3H, C57Bl/6, (gpt delta × SWR) F1 mice | 4000 | Total doses 20–21, 400–420 or 8,000–8,050 mGy delivered over 400-485 days | Review of IES findings focused on lifespan, neoplasm incidence, body weight, tumour cell transplantability, changes in chromosome structure, gene mutations, changes in mRNA and protein levels, and transgenerational effects on lifespan and neoplasm incidence | Braga-Tanaka et al., 2018 |

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Table 1**.** *(continued)*

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| --- | --- | --- | --- | --- | --- | --- |
| **Dynamics of radiation exposure** | **Source** | **Animals, strain, age etc.** | **Number of animals** | **Doses and/or Dose Rates** | **Study Endpoint** | **Reference** |
| Experimental external beam | Variety:  fast neutrons gamma ray | Rodents: Mice and Rats | NA (review) | Variety of conditions | Review paper listing 9 mGy of fast neutrons or 100 mGy of gamma rays are required for detectable changes in comet assay or micronuclei frequency | Shimura and Kojima, 2018 |
| Experimental external beam | 137Cs-gamma ray | B6C3F1 mice, 35 to 365 days of age at the beginning of irradiation | 4000 | Acute vs. chronic exposures | The age of exposure influenced sensitivity to cancer with a weight ratio greater than five. Chronic exposure to 21 mGy day-1 had 0.33 fold risk of malignant cancer development compared to acute exposure. | Doi et al., 2020 |
| Experimental fractionated, external beam | X-ray and gamma ray | Mice, C57BL/6 | 72 | 7.2 Gy in 1.8 Gy fractions, w or w/o low-dose treatment | Incidence of lymphoma reduced with 75 mGy X-ray pre-treatment 6h before fractions or continuous exposure to gamma rays at 1.2 mGy h-1 | Ina et al., 2005 |
| Experimental external beam | Gamma ray | Mice | 615 | 1.4 mGy h-1 for 45 days | DNA damage | Graupner et al., 2016 |
| Experimental fractionated, external beam | X-ray | Mice C57BL/6 ‘resistant’ and BALB/c ‘sensitive’ | 54 | four weekly doses of 75 mGy or 1.8 Gy per week | Breast cancer development and gene expression; gene expression profiles strain and dose specific | Snijders et al., 2012 |
| Experimental external beam | X-ray | Mice | NA | 1 Gy and 100 mGy exposures | Evaluation of T cell receptor spectra: 100 mGy exposure (but not 1Gy) caused accelerated aging as shown by loss of receptor diversity | Candeias et al., 2017 |

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Table 1**.** *(continued)*

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| --- | --- | --- | --- | --- | --- | --- |
| **Dynamics of radiation exposure** | **Source** | **Animals, strain, age etc.** | **Number of animals** | **Doses and/or Dose Rates** | **Study Endpoint** | **Reference** |
| Experimental external beam | Gamma ray | Wild-type C57BL/6 mice and their p53+/- counterparts | 1824 | 5 days a week exposures to 48, 97 or 146 mGy total at dose rate 0.7 mGy h-1 | Life shortening and increased cancer incidence in wild type mice exposed for 30 or 60 weeks, but not 90 weeks. No differences in heterozygotes | Mitchel et al., 2008 |
| Experimental external beam | X-ray | Wild-type C57BL/6 mice and their p53+/- counterparts | 474 | 10 mGy | A single 10 mGy x-ray exposure significantly delayed onset of cancer in irradiated compared to unirradiated p53 +/- animals | Lemon et al., 2017 |
| Experimental external beam | X-ray | Mice, inducible expression of the Ki-rasG12C gene in lungs | NA | 80 -160 mGy | Irradiation increases cancer incidence, especially in female mice | Munley et al., 2011 |
| Experimental external beam |  | Mice, Ptch1+/- | NA | 50 mGy | DNA damage, death of sebaceous gland cells but reprogramming of bulge epidermal stem cells and increase in skin cancer over baseline | Revenco et al., 2017 |
| Experimental external beam | Gamma ray | Mice, Ptch1+/- | NA | 100-500 mGy total delivered at 25 - 125 mGy day-1 | 100 mGy dose mutation pattern and spontaneous mutation patters identical while 500 mGy caused LOH that was different; studies included radiation-induce medulloblastoma | Tsuruoka et al., 2016 |
| Experimental external beam | Gamma ray | PU.1 inactivated mouse | 50 | 3 Gy given at 20 mGy day-1, 200 mGy day-1, or 1000 mGy day-1 | Development of AML in mice is dose-rate dependent in hematopoietic stem cells | Ojima et al., 2019 |

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Table 1**.** *(continued)*

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| --- | --- | --- | --- | --- | --- | --- |
| **Dynamics of radiation exposure** | **Source** | **Animals, strain, age etc.** | **Number of animals** | **Doses and/or Dose Rates** | **Study Endpoint** | **Reference** |
| External beam | Gamma ray | Mice | NA | 4 or 8 Gy at 20 mGy day-1 | Different protein expression at low-dose-rate and high-dose-rate exposures | Nakajima et al., 2017 |
| External beam | Gamma-ray | Rat | 531 | 0.5-8 Gy total dose delivered at 3-30 Gy h-1 | Induction of mammary carcinoma with continuous exposure was age dependent | Imaoka et al., 2019 |
| External beam | Gamma-rays and X-rays | Mice, rats | 11,528 | Range of doses under 4 Gy | Life shortening of 11,528 rodents of mixed gender comparing doses under 4Gy; DREF of 2 was reported; comparing doses under 3Gy gave DREF of 2.6 with larger error bars. | Haley et al., 2022 |

1. Japan is currently collecting an archive of tissues from animals living in proximity of the Fukushima power plant after 2011 (Takahashi et al., 2015); samples include both domestic and wild animals. Most informative studies with these samples have been those conducted on animals with limited roaming range such as small rodents (e.g. Takino et al., 2017). Importantly, companion studies with animals exposed internally to radiation from 137Cs were also carried out (Nakajima et al., 2015). Unfortunately, it appears that archiving of data about these animals was either not done or that it is not designated for open access sharing in larger archives. Many similar ‘medium size studies’ world wide with few hundreds of mice are also often not considered for open access data sharing (e.g. Howell et al., 2013; Graupner et al., 2016).
2. Numerous studies involving external radiation exposure with large numbers of chronically irradiated rodents were also done in Japan; in most of these studies data are recorded although not publicly available. Such examples include a study that used female SPF mice (C3H/HeN) mice and that were exposed from day 56 onward, to 137Cs-gamma rays at different dose rates (i.e. at 1, 20, 400 or 890 mGy per day) and for different total doses (Tanaka et al., 2013). Screening of chromosomal aberrations in splenic lymphocytes found that the ratios of dicentrics and translocations in 890 mGy min-1 mice vs. 20 mGy day-1 mice were much higher at higher total cumulative doses (e.g. 5 or 10 Gy) than at total cumulative dose of 1 Gy. At the same time, minimal differences were found between non-exposed controls and animals given 1 mGy per day for total doses of up to 6 Gy. Nevertheless, some dose-dependent increase in number of aberrations was detected in this and other studies done by the same team (Tanaka et al., 2009). It is worth noting that this dependence was linear (not linear-quadratic) for all dose rates (from 1 mGy day-1 to 400 mGy day-1) for low total doses. For the dose rate of 400 mGy day-1, linear dependence was lost after total dose of 3-4 Gy was reached, while for mice that received 20mGy day-1 linear dependence persisted until total dose of 8 Gy. This work is an interesting example of how dose rate factor exploration can be done with DNA damage as endpoint (see also Section 3).
3. Another animal study (Ina et al., 2005) focused on incidence of lymphoma in low-dose-rate exposed wild-type mice. In C57BL/6 strain, the induction of lymphoma was noted when animals received 7.2 Gy of X rays in 1.8 Gy fractions, but protection against development of lymphoma was afforded by pre-irradiation with 75 mGy X rays 6 h before each fraction, or by continuous exposure to gamma rays at 1.2 mGy h-1. Moreover, low-dose-rate gamma irradiation alone (daily exposure to 1.2 mGy h-1) did not result in any lymphomas even when the total dose reached 12.6 Gy.
4. Experiments conducted over long periods of time allow that lasting effects of low-dose radiation be made obvious even when they are minor, especially if a study endpoint is carefully chosen. For example, mice exposed to radiation *in utero* showed significant differences at six months and two years with respect to proteomics profiles in response to X-ray exposures to doses of 100 mGy and 1 Gy. Not surprisingly, the number of protein differences between controls and mice exposed to 1 Gy was two times higher than for mice exposed to100 mGy (Bakshi et al., 2016). Of all possible broad cellular functions, mitochondrial protein differences were found to be most substantial.
5. In a different example, long-term exposures of mice to low-dose-rate gamma rays were coupled with allowing the animals to live out their full life spans. For example, when female B6C3F1 mice were exposed to 20 mGy day-1 for 400 days, they started to develop, beginning with day 200 post irradiation, obesity and fatty degeneration of the liver and different degenerative changes in adrenal glands and ovaries. On the other hand, the most significant life span shortening in these mice was caused by malignant lymphomas (Tanaka et al., 2017).
6. It should be noted that life shortening is a potentially somewhat misleading measure. The years of life lost associated with specific cancer type *c* following a radiation dose *D* assuming a relative risk  at attained age *a* and time since exposure *t* in a group is given by

(4)

where and are the probabilities of an individual surviving to age given that they have survived to age (), without or with radiation dose *D* (Little et al., 2000). This is substantially non-linear as a function of dose *D*, even if the relative risk function is linear in *D*.

1. A more recent study using the same irradiation conditions and B6C3F1/Jcl male mice (Yamauchi et al., 2019), found that animals on a calorie restricted diet lived the longest regardless of their radiation status. When the comparison was focused on irradiated vs. non-irradiated animals however, the extent of life shortening caused by radiation in calorie restricted animals was much more pronounced than in their high calorie counterparts.
2. Combining rodents from European and US databases Haley et al. (2022) examined 11,528 rodents of both sexes exposed to X-rays and gamma-rays comparing single dose exposures with fractionated exposures for differences in life-shortening. These results demonstrated that fractionated exposures have two-fold less risk per Gray than acute exposures in the dose ranges of 0.25-4Gy.
3. Focusing on DNA damage as an endpoint, Graupner et al. (2016) found an increased frequency of single strand breaks and alkali labile sites in reticulocytes of mice exposed to low dose rates of gamma radiation (1.4 mGy h-1 for 45 days) at the end of exposure, but a two times decreased frequency of these DNA lesions 45 days after cessation of radiation. This work however, was performed with relatively few animals, and this trend of using few animals seems to be prevalent in other low-dose radiation studies world-wide. When the endpoints under investigation are sufficiently sensitive that they can be ascertained after low-dose exposures, then comparisons of a few dozen mice may be all that is necessary for such a study to have adequate statistical power.
4. For example, an in vivo study on two mouse strains with different susceptibility for development of breast cancer including six weeks old C57BL/6 (breast cancer ‘resistant’) and BALB/c (breast cancer ‘sensitive’), mice were exposed to low-dose x-ray radiation (four weekly doses of 75 mGy) and their breast tissues collected at four hours or one month after the final exposure (Snijders et al., 2012). mRNA array data demonstrated strain and time-point differences in gene expression. Initial differences between the two strains prior to irradiation were notable, and they became even more pronounced at one month post irradiation. Interestingly, in the breast cancer resistant strain expression of certain cancer-associated genes (e.g. EZH2) was decreased, while the same gene was increased in cancer prone BALB/c mice. While these data are of interest, it is difficult to decide whether these radiation-induced gene differences depend primarily on pre-existing strain differences (baseline difference in stress response and RNA processing genes) and/or additional genetic differences. It should also be mentioned here that very high doses (1.8 Gy per week) were performed and gene expression profiles compared with those obtained at low doses (75 mGy weekly for 4 weeks). No overlap in gene expression was found between low- and high-dose exposures in either mouse strain.
5. A further study with a different endpoint was an investigation of T cell receptor spectra in mice exposed to low dose (100 mGy) and medium dose (1 Gy) X radiation. The effects of these two doses were found to be very different (Candeias et al., 2017). While exposure to 1 Gy had no irreversible effect on T cells, 100 mGy exposure resulted in accelerated aging as shown by loss of receptor diversity. While all of these studies and their fine-tuned endpoints are informative about low doses, they do not provide sufficient information on dose and dose rate to be used for LDEF estimates on their own, without comparison with other similar studies. Some type of comprehensive data archiving initiative will be necessary in order to provide basis for use of these data for LDEF estimates.
6. Many of the recent studies focusing on low-dose radiation effects used genetically modified animals or additional treatments to ‘draw out’ effects of low doses of radiation. This includes studies on cancer prone p53 heterozygous and knock-out mice which were used for low (and medium) dose radiation research (Kemp et al., 1994). In some respects, it may be said that the existence of the Muta mouse (e.g. Uehara et al., 2008) and p53+/- mice allowed the initial growth of the low-dose radiation research field. Interestingly, irradiation of p53+/- mice sometimes leads to apparently unexpected findings. For example, there was an apparently counterintuitive finding in comparison of heterozygote and wild type mice, in a study mice exposed for 5 days a week to 0.33 mGy daily of gamma ray radiation at a low dose rate (0.7 mGy h-1), totalling 48, 97 or 146 mGy (Mitchel et al., 2008). Wild-type C57BL/6 mice and their p53+/- counterparts were included in this study. Surprisingly, life shortening and increased cancer incidences were found in wild type mice exposed for 30 or 60 weeks, but not the animals exposed for 90 weeks. The above caveats on use of life shortening as an endpoint should be noted. At the same time, no differences in cancer incidence were found between non-irradiated or any of the long-term-irradiated heterozygote animals. In addition, a more recent study using p53 heterozygotes found that a single 10 mGy X-ray exposure significantly delayed onset of cancer in irradiated compared to unirradiated p53 +/- animals (Lemon et al., 2017). These studies are considered as proofs of the concept of an ‘adaptive response’ as described by Mitchel and others (Mitchel et al., 2008).
7. While other types of mutations are numerous in p53 heterozygote or knock out animals because of a diminished capacity to respond to radiation exposure by a decrease in p53 protein quantity (di Masi et al., 2006), loss of the second copy of p53 gene is still the most important step in the development of cancer. For that reason, cross breeding of p53+/- mice with animals of different genetic backgrounds was also done, in many different permutations and with different results in studies that involved medium and high doses. It should be emphasized that different versions of p53 transgenics were used in so many low-dose radiation studies that it would be feasible to develop a data repository with data on sufficient numbers of animals to enable ‘genotype specific’ DDREF investigation.
8. Another transgenic model is bi-transgenic CCSP-rtTA/Ki-ras mice (FVB/N background with doxycycline inducible expression of the Ki-rasG12C gene in lungs). These animals were developed as a model to study promotion of lung cancer, with multiple cancer foci in lungs developing after doxycycline exposure (Floyd et al., 2005). When these animals were exposed to low doses of X radiation (80 -160 mGy) this further increased lung cancer frequency, with statistically significant gender differences. It was found that after irradiation higher numbers of cancer foci were recorded in female mice (Munley et al., 2011).
9. Another frequently used transgenic mouse model is based on the Patched gene (Ptch) (Revenco et al., 2017). Patched encodes a protein that is a transcription regulator involved in the hedgehog pathway and also functions as a tumour suppressor. In a recent study these mice were used to study skin cancer induction by low-dose radiation (50 mGy) (Revenco et al., 2017). The endpoints studied were death of sebaceous gland (SG) and bulge epidermal stem cells (SCs). DNA damage induced by 50 mGy led to cell death of SG cells, while SCs survived the exposure and underwent a metabolic switch with activation of Hif1α and overexpression of many cellular pathways (with endocytosis as the only pathway that was decreased). In Ptch1 heterozygous mice, low-dose irradiation led to the development of skin cancer similar to human basal cell carcinoma (Revenco et al., 2017). The same transgenic animals, Ptch1+/- mice were used to investigate the types of mutations induced by low-dose radiation that results in the loss of heterozygosity (LOH) and the development of medulloblastomas (with the Ptch-/- genotype). Exposure to 500 mGy of gamma rays delivered at 125 mGy day-1 caused interstitial deletions, beginning downstream of the wild-type Ptch1gene and extending towards the centromere. Exposure to 100 mGy (25 mGy day-1) on the other hand led to the same deletion pattern as LOH mutations in unirradiated mice – loss of a portion of chromosome arm from telomere to beyond the Ptch1 gene resulting from a faulty recombination (Tsuruoka et al., 2016).
10. Numerous publications were also focused on strain to strain differences between wild type mice in response to radiation and many have been presented in two recent literature reviews. Summary of work done at the Japan’s Institute for Environmental Sciences (IES) (Braga-Tanaka et al., 2018) discussed mouse strains B6C3F1, C3H, C57Bl/6 and transgenic (gpt delta × SWR) F1 mice that were exposed to gamma rays for 22 hours a day over a range of dose rates between 0.04–0.06 mGy day-1, 0.8–1.1 mGy day-1 and 16–21 mGy day-1. Exposures lasted 400 to 485 days and the total doses delivered were either 20–21, 400–420 or 8,000–8,050 mGy. Ten different endpoints – lifespan, neoplasm incidence, body weight, tumour cell transplantability, changes in chromosome structure, gene mutations, changes in mRNA and protein levels, and transgenerational effects on lifespan and neoplasm incidence - were studied in both genders. In brief, C57BL/6J and B6C3F1male mice exposed to 20 mGy day-1 demonstrated life shortening; in B6C3F1females life shortening also occurred at 1 mGy day-1. Males exposed to the total accumulated dose 0f 20 or 400 mGy did not show life shortening. A different type of comprehensive review of irradiation literature including animal and human exposures both, was done by Shimura and Kojima (2018). This review extracted from the literature those studies where a low dose of radiation was associated with either cancer or life shortening. This included the finding that at least 9 mGy of fast neutrons or 100 mGy of gamma rays are required for detectable changes in comet assay or micronuclei frequency in mice or rats, respectively.
11. Recent studies on DREF for mortality from malignant tumours examining the mouse data from Japan noted that after inclusion of age, risk for development of cancer in chronic vs. acutely irradiated mice was threefold lower for mice that received 21 mGy per day chronic exposure (Doi et al., 2020). This work was done by combining two published studies – from the Institute for Environmental Sciences (IES) where animal studies only included low-dose-rate exposures (0.05, 1.1, 21 mGy day-1 for 400 days) and the National Institute of Radiological Sciences (NIRS) where only animals receiving acute exposures were studied. Comparison of the dose-rate parameter for 21 mGy day-1 from a linear-quadratic dose response model that included consideration of age at exposure, with that from chronic exposure provided a DDREF value of 3.0 (95% CI: 1.8, 5.1). In contrast, the model without considering age at exposure effects provided a DDREF value of 5.7 (95% CI: 4.0, 8.0).

## Task Group Attempts to Develop LDEF and DREF Models

1. As mentioned before, the ERA database is the most comprehensive source of irradiated animal data. While much of it was acquired at medium and high dose rates with medium and high total dose exposures, low dose rate as well as low total dose exposures were also included in many of the ERA accumulated studies. For example, a recent effort to consolidate the data from Janus and ERA databases (Haley et al., 2015) and cross-validate it with the literature has shown that there are 34,000 digitized records from 26 mouse studies using low LET external radiation and exposures to doses between 40 mGy and 1.5 Gy delivered at dose rates from 1 mGy min-1 to 4 Gy min-1. These data were used to re-evaluate appropriateness of approach used by BEIR VII to evaluate DDREF using animal data (Haley et al., 2015). The primary motivation of this study was to re-develop the mathematical approach developed by the BEIR VII and apply it both to the datasets used for BEIR VII report and a much larger set of additional datasets over the same dose range. One of the central points of the BEIR VII report was that DDREF can be evaluated from acute irradiations alone, using a linear-quadratic model fitted to LSS data in combination with summary data (taken from a technical memorandum of Edwards (1992)) from a small number of older animal studies, in the absence of direct comparisons to low-dose-rate exposures based on the shape of the curve and based on examining low-dose comparisons (which is actually an LDEF value). Haley and others showed that this is not the case and that DDREF estimated from acute dose exposures only vs. both acute and protracted exposures gave a very different value for DDREF. The Haley paper concluded that the mathematical approach used by BEIR VII led to DDREF estimates that were impracticably imprecise. This conclusion was in full agreement with other papers commenting on BEIR VII approach to animal data (Hoel, 2015).
2. The Haley studies were limited to a subset of mouse data that would have matched BEIR VII inclusion criteria, but it used an order of magnitude more animals than the BEIR VII study itself. Using as an endpoint the decrease of life expectancy, processed in the same manner as in the BEIR VII work, this study showed that DDREF evaluation based on the BEIR VII approach lacks robustness when applied to the direct comparisons between mice exposed to acute and protracted radiation. Thus, paradoxically, the addition of new animal data made that DDREF estimate less clear (Haley et al., 2015). Another study by Hoel (2015) used, again, the BEIR VII approach for data cutoffs and several competing models (based on linear-quadratic and linear-linear dose response). This work suggested that DDREF estimates depend on choice of data, especially the total dose cutoffs. For example, Hoel noted that DDREF estimate decreases and approaches a value of 1 as the total dose cutoffs for data collection are increased.
3. A recent study by Tran and Little (2017) attempted to re-evaluate DREF and LDEF using only the Janus archive data and pulling together two different species of rodents and all doses and qualities of radiation available. The primary purpose of this work was to compare a number of different models adjusting for both dose and dose rate, to facilitate evaluation of both DREF and LDEF for different endpoints and radiation types (neutron, gamma).
4. A Cox proportional hazards model (Cox, 1972) with loglinear link was used, with age as timescale, and stratifying on sex and experiment (Tran and Little, 2017). For both neutron and gamma radiation exposure the optimal model was one with linear and quadratic terms in cumulative lagged dose, with adjustments to both linear and quadratic dose terms for low-dose-rate irradiation (<5 mGy h-1) and with adjustments to the dose for age at exposure and sex. After gamma ray exposure there was significant non-linearity (generally with upward curvature) for all tumours, lymphoreticular, respiratory, connective tissue and gastrointestinal tumours (*p*<0.001). Tran and Little (2017) estimated the overestimation in low-dose risk resulting from linear extrapolation (i.e. LDEF) for lymphoreticular tumours as 1.16 (95% CI 1.06, 1.31) (Tran and Little, 2017). For all tumours the LDEF was estimated as 1.06 (95% CI 0.99, 1.14). However, for a rather larger group of malignant endpoints the LDEF was significantly less than 1 (implying downward curvature), with central estimates generally ranging from 0.2 to 0.8, in particular for tumours of the respiratory system, vasculature, ovary, kidney/urinary bladder and testis. In contrast to the situation at higher dose rates, there were statistically nonsignificant decreases of risk per unit dose at gamma dose rates of less than or equal to 5 mGy h-1 for most malignant endpoints. Associated with this, the dose rate extrapolation factor (DREF), the ratio of high-dose-rate to low-dose-rate (≤5 mGy h-1) gamma dose response slopes, for many tumour sites was in the range 1.2–2.3, albeit not statistically significantly elevated from 1 (Tran and Little, 2017). The log-linear nature of the Cox model fitted should be noted, so that the implied curvature on a linear scale is possibly underestimated.
5. Interestingly, analyses in which *Peromyscus leucopus* were excluded yielded very similar results, doubtless a consequence of the much larger numbers of *Mus musculus* in the dataset (Tran and Little 2017). However, it is known that *Mus musculus* and *Peromyscus leucopus* have significant differences in the frequencies of cancer incidence at death, with the ratio of lethal cancer to lethal non-cancer diseases of about 85:15 in laboratory mice and 60:40 in white footed deer mice. Exposures to 0.9 or 1.43 Gy gamma rays did not hasten animal death, nor changed breakdown of lethal pathologies in either species (Thomson et al., 1986; Liu et al., 2013). As the doses increased, animals died earlier and the incidence of non-cancer lethalities in *Mus musculus* increased while it decreased in *Peromyscus leucopus*. This example points out the opportunities inherent in work with animal data – it is often possible to use different animal models to conduct direct comparisons of doses, dose rates or other factors, allowing the scientific question asked to be nuanced – e.g. the possible influence of genomic differences on cancer incidence and how ionising radiation exposure may alter it. At the same time, this example also points out the possible pitfalls inherent in work with animal data – one may easily assume that the responses to radiation will have the same relative distribution for cancer and non-cancer causes as they do in human population. That, however, is not necessarily the case and reiterates the importance of the endpoint chosen for a study.
6. Studies by Haley et al. (2022) compared DREF for life-shortening for 11,528 mice and rats of both sexes exposed to gamma-rays and X-rays from combined studies of the US and Europe. Acute exposures were compared with protracted (often fractionated) exposure. When a dose of less than 4 Gy was used, a DREF of 2.1 was determined. When the data were analysed for doses under 3 Gy (with far fewer animals than the <4 Gy analyses), the value increased to 2.6, but the confidence intervals were much wider. When mice and rats were singled out for the studies, no differences were noted (but again there were substantial uncertainties). When males (mostly mice) and females (rats) were compared, the DREF in each case was close to 2.0. Animal life-shortening data therefore suggest that fractionated radiation exposures have about a two-fold less risk per Gy than acute exposures for a range 0.25-4 Gy of total dose.

## Conclusion

1. The animal studies discussed in this section had two different endpoints: (1) life shortening as a whole and (2) death from cancer. Cancer deaths were included because this is considered a relevant endpoint for DREF and LDEF. Life-shortening was also included, because historically this has been used for determination of DDREF in animal systems in BEIR VII and some of the earlier BEIR reports. In addition, deaths from low-dose exposures in mice are predominantly from tumours and not from other causes (Zander et al., 2020).
2. The reanalysis of some large animal datasets done under the auspices of the Commission suggests that after gamma ray exposure there is some evidence of dose and dose rates effects that deserve further study. Haley et al. (2015) used the data from the European Radiobiology Archives (ERA) and the Janus reactor data to critique the BEIR VII linear-quadratic model, a tool that produces contradictory DDREFLSS values – a range between 2.9 and infinity for the data directly comparing protracted and acute exposures and a range between 0.9 and 3 for the data on animals with acute exposures only. Another reanalysis using a more sophisticated linear-quadratic model (with adjustment for age at exposure, sex) of the Janus data for gamma-ray doses up to 30 Gy found evidence of significant non-linearity (generally with upward curvature) for all tumours, lymphoreticular, respiratory, connective tissue and gastrointestinal tumours with an associated LDEF for all tumours of 1.06 (95% CI 0.99, 1.14) and for lymphoreticular tumours of 1.16 (95% CI 1.06, 1.31) (Tran and Little, 2017), although for a rather larger group of malignant endpoints the LDEF is less than 1, in some cases significantly so. The DREF for many tumour sites after gamma exposure is in the range 1.2–2.3, albeit not statistically significantly elevated from 1 (Tran and Little, 2017). In contrast, in B6C3F1 mice irradiated at lower dose rates, 21mGy day-1 or lower, the DREF for lethal tumours is higher than 2 (Doi et al., 2020).
3. Table 2 summarizes the major findings on DREF and LDEF found in this review from animal data sets. None of the papers in Table 2 gave DDREF estimates for both doses and endpoints in the sense used by BEIR VII. Studies evaluating life shortening only used doses up to 1.5 Gy, while studies focused on cancer incidence used doses up to 49 Gy.

Table 2: Major findings on DREF and LDEF found in this review from animal data sets.

|  |  |  |  |
| --- | --- | --- | --- |
| Study | Endpoint | DDREF or DREF or LDEF or EER | Comments |
| Tran and Little, 2017  (gamma ray data only) | All tumours (lethal, coincident, non-lethal) | DREF = 1.190 (95% CI 0.861 to 1.723)  LDEF = 1.056 (95% CI 0.992 to 1.139) | All doses (up to 49 Gy for fractionated exposures) projected to 1.5 Gy mathematically |
| Doi et al., 2020 | All lethal tumours | DREF=3.0 (95% CI: 1.8, 5.1);  If no age at exposure effects are considered, DREF=5.7 (95% CI: 4.0, 8.0) | Chronically (up to 8 Gy) vs acutely (up to 5.7 Gy) irradiated B6C3F1 mice |
| BEIR VII  (Table 10-2) | Life shortening | ‘LSS’ DDREF  0.1-3.2 | Radiobiology animal experiments (total dose up to 1.5 Gy) |
| Hoel, 2015 | Life shortening | DDREF at 1 Gy  2.3 RFM mice  2.4 BALB/c mice | Acute vs. chronic animal IR datasets from Storer et al 1997  (total dose up to 1 Gy) |
| Haley et al., 2015 | Life shortening | ‘LSS’ DDREF based on BEIR VII approach  2.9-infinity | All mice from ERA database (total dose up to 1.5 Gy) |
| ‘LSS’ DDREF based on BEIR VII approach  0.9-3 | Only acute exposures from ERA database (total dose up to 1.5 Gy) |
| ‘LSS’ DDREF based on BEIR VII approach  4.8-infinity | Comparison acute vs. chronic ERA datasets on B6CF1, C57BL/Cnb, BALBc/Cnb (total dose up to 1.5 Gy) |
| Haley et al., 2022 | Life shortening | DREF=2.0 for exposures of 0.25-4 Gy, 2.6 for exposures of 0.25-3 Gy | Acute and protracted exposures were compared for a variety of mouse and rat strains; no sex differences were observed. |

1. The value of combining studies of animals to acquire large datasets is especially important when examining low-dose and low-dose-rate effects where the number of animals affected by radiation may be small. Based on studies using large animal datasets (compared to BEIR VII where smaller datasets were used), it is obvious that DREF values are best determined by direct comparison of acute to protracted exposures. Variations in low-dose and low-dose-rate responses to cancer induction in rodent systems suggest that calculations of LDEF and DREF may vary with each different cancer type. Animal studies have also suggested that many factors may influence low-dose radiation responses including genetic background, diet, overall health of the animal, and others.
2. Additional animal models are needed for low-dose radiation research, although doses may be significantly different from one species to another. For example, the zebrafish is a versatile model for assessment of epigenetic effects, although its use to assess effects of ionising radiation was initiated only recently (Kong et al., 2016a,b). While ionising radiation has been studied longer in *C. elegans* (Sakashita et al., 2010) low-dose radiation has not been very much studied in this model system. Finally, addition of new rodent transgenic models should also be considered
3. It is noted that animal radiation data provide information that is qualitatively different than that coming from either epidemiological or *in vitro* studies. Many efforts were made to collect and preserve these data. However, what is still necessary is creation of an open and additive dataset led by an international consortium (Abbott, 2012). A successful compilation of animal radiation materials would have to include both the existing archival data and the materials coming from new studies from NASA, Japanese chronic animal exposure studies, and others (Woloschak, 2016). Radiation work with animals is still, despite its decreased volume (in comparison to the period before 2000’s), in progress. As noted above, new computational approaches provide opportunities for meta-analyses of large and small-scale animal studies, which will greatly expand our understanding of dose-rate effects. Moreover, DDREF, LDEF and DREF evaluations suggest that calculation for specific cancers (rather than for all cancers) may provide qualitatively new data.

# EPIDEMIOLOGICAL STUDIES – LOW-DOSE-RATE EFFECTS

## Introduction

1. In this section, evidence regarding the numerical value of DREF is reviewed from an assessment of the available human data. Additionally, a comprehensive evaluation is conducted, of the risk estimates of epidemiological studies of cohorts with exposures to low doses and/or low dose rates (LDR) of radiation in comparison to risk estimates from the Life Span Study (LSS) of one-time exposure at a high dose rate and a wide dose range including low, medium and high doses (see Section 1).
2. Epidemiologic studies frequently examine the association between radiation exposure all solid cancers because this outcome provides an overall assessment of risk from radiation that is delivered to approximately the whole body, and hence is useful for radiation protection assessments. The larger number of observed total solid cancers tends to increase statistical power and relative precision compared to assessments of cancers of individual organs, and solid cancers would be assumed to be developed based on common substantial mechanisms in radiation carcinogenesis, but it masks the heterogeneity among organs as to variations in background rates, magnitudes of risk, dose-response shapes, contributions of other etiologic factors, and degrees of confounding by lifestyle factors or other environmental exposures (Cologne et al., 2019; Boice et al., 2022a). Cancer incidence data, when available, have advantages over cancer mortality data because the accuracy of incident diagnoses is often higher, incident cancers are more numerous than only lethal ones, and incidence data are not skewed by variations in lethality across cancer types. However, mortality data have been almost uniformly available for the full years of interest, whereas systematic cancer incidence data of high quality are often available only in more recent years. Often cancer registries, particularly at national level have only comparatively recently been set up, so for example in the UK only since 1971. Some developed countries (e.g. USA, Germany, France) still lack a national cancer registry. National level mortality data by contrast has been collected over a very long period in most developed countries, often going back to the turn of the 20th century. Nonoccupational radiation exposures vary among radiation cohort members, especially medical radiation exposures, but individual exposures to nonoccupational radiation have rarely been available (Little et al., 2014, 2018a), so it is assumed, but not verifiable, that such exposures are uncorrelated with occupational radiation dose overall (Boice et al., 2023).
3. The individual studies of worker or environmental cohorts have a variety of sources of uncertainty, including limited statistical precision and power and sometimes potential biases. Many of the studies have wide confidence intervals (CI) on risk estimates due to limited sample sizes and lengths of follow-up, and small-to-moderate numbers of solid cancer deaths or cancer cases. A few studies have unavoidable limitations in the ascertainment of cancer deaths or incident cancer cases and limited diagnostic information. Most occupational studies have relatively small numbers of females. There were also photon dose uncertainties, especially for workers in the 1940s and 1950s, or from retrospective dose reconstructions in environmental exposure studies. Typically, quantitative information on neutron and internal exposures was inadequate or missing. There is also the potential for biases when lacking lifestyle risk factor information, especially smoking, or lacking exposure to other potential carcinogens, such as asbestos. Nevertheless, a review of the available evidence and a combined estimate of risk in the LDR studies is useful for examining DREF because a combined estimate provides a broad assessment or LDR risk, may have increased statistical precision, and will tend to compensate for disparate potential biases in individual studies.
4. Numerous publications have informally compared risk estimates from epidemiological studies of persons with LDR exposures to the risk estimates in comparable subsets of the LSS (Cardis et al., 2007; Schubauer-Berigan et al., 2015; Leuraud et al., 2021). However, several studies have broadly and systematically examined radiation risk among LDR cohorts (Jacob et al., 2009; Shore et al., 2017; NCRP, 2018b; Hauptmann et al., 2020).
5. The 15-Country Study was a pooled analysis of 407,000 workers at 154 nuclear facilities in 15 different countries (Cardis et al., 2005, 2007). The results proved to be problematic because of inaccurate dosimetry in an influential cohort within the study (Ashmore et al., 2010; Zablotska et al., 2013). The second, more recent INWORKS study (Richardson et al., 2015), examined solid cancer mortality among 308,000 nuclear workers in three countries, the UK, US and France (see description below). The INWORKS study has been formally compared with the LSS risk estimates (Leuraud et al., 2021), though the data for the component cohorts have since been updated substantially with further follow-up (Haylock et al., 2018; Kelly-Reif et al., 2023a; Laurent et al., 2023 and a new combined analysis has been published; Richardson et al., 2023a).
6. The third study was a meta-analysis of nearly all the worker cohorts with dose-response results available at that time (Jacob et al., 2009). The study used methods essentially identical to the ones being used by this Task Group, as described below. They concluded that radiation risk in LDR cohorts was equivalent to that seen in the LSS, in proportion to dose, i.e. that the DREF was about 1. However, the study did not include Mayak workers, an influential study group but one excluded because it contained relatively high cumulative doses. Moreover, a number of the studies have been updated since that time plus several new ones have been published. Furthermore, the study was limited to worker studies and did not include the several studies of cohorts with elevated environmental exposures.
7. The Task Group has therefore sought, in addition to reviewing the current literature on the topic, to provide an up-to-date and comprehensive comparison of available quantitative LDR studies to LSS risk estimates for studies of either occupational or environmental radiation exposures. The aim was to collect the risk estimates of all the studies that have both (1) low-dose and/or low-dose-rate (LDR) exposures to radiation, (2) individual doses, and (3) dose-response based estimates of risk. For each study, their solid cancer risk estimates were compared with matching estimates from the atomic bomb survivor LSS, and a meta-analysis of the LDR study to LSS study ratios of risk (LDR/LSS) was performed. This was done for total solid cancer (or all cancer except leukemia). Most of the studies considered were very largely of adult-onset cancer. In certain sections (e.g. Section 6) we shall consider risks associated with all age exposure. Recent LSS analyses have confirmed a linear dose-response form for all solid cancer with no evidence of upward curvature after exposure in adulthood (Brenner et al., 2022).

## Summary of LDR Studies with Dose-Response Analyses for Solid Cancer

### Radiation Workers

1. INWORKS, an international collaborative study to examine the health of workers occupationally exposed to ionising radiation (Leuraud et al., 2015; Richardson et al., 2015; Thierry-Chef et al., 2015; Hamra et al., 2016; Gillies et al., 2017), combined three cohorts of 309,932 workers (13% females) from 13 facilities/companies in the UK, USA and France who were monitored for exposure to external sources of ionising radiation. Recent accounts of the three individual cohorts are reported in (Haylock et al., 2018; Kelly-Reif et al., 2023a; Laurent et al., 2023; Richardson et al., 2023a, 2024). Follow-up was from 1944 to 2016 for the various countries (mean follow-up of 34.6 years), with personal dosimetry available over essentially all of that time period. The changes in dosimetry associated with variations in technology and recording policies over calendar year period, were evaluated and harmonized by the study dosimetry team (Thierry-Chef et al., 2007), although there were missing neutron and internal doses in the early years. The mean cumulative colon dose to the entire cohort was 17.7 mGy, while that to all who had an estimated dose greater than zero was 20.9 mGy. The study had high completeness rates for mortality follow-up and ascertainment of causes of death. The analyses were adjusted by stratification on country, attained age, sex, birth cohort, socioeconomic status, and duration of employment or radiation work. A total of 28,089 solid cancer deaths in 10.72 million person-years was observed. The linear ERR Gy-1 was 0.52 (90 % CI 0.27, 0.77) for all solid cancer, with a weak indication of quadratic curvature (p = 0.11) (Richardson et al., 2023a). When the adjustment factors were limited to country, attained age, sex and birth cohort the ERR Gy-1 was 0.49 (90% CI 0.30, 0.69). When recorded cumulative dose rather than adjusted colon dose was applied, the ERR Sv-1 was 0.37 (90% CI 0.19, 0.55). There was little indication of confounding by smoking, as the estimate was nearly the same when lung cancer was excluded (ERR Gy-1 0.46, 90% CI 0.18, 0.76), and the association between radiation dose and chronic obstructive lung disease, an indicator for smoking, was null (ERR Gy-1 0.12, 90% CI -0.43, 0.68). There was a weak suggestion of confounding by asbestos: an analysis excluding lung and pleural cancers yielded an ERR Gy-1 of 0.43 (90% CI 0.15, 0.73). Indications of monitoring for neutron exposures had little impact on risk estimates; those with no monitoring had an ERR Gy-1 of 0.55 (90% CI 0.23, 0.90). There was evidence of a difference in external photon dose risk by radionuclide internal monitoring status: an ERR Gy-1 of 0.21 (90% CI -0.11, 0.56) for those with internal monitoring and 0.82 (90% CI 0.46, 1.22) for those without, suggesting some potential for confounding but limited to a small proportion of the cohort. To focus on lower doses, analyses were conducted for restricted cumulative dose ranges. The risk estimates (ERR Gy-1) were 0.63 (90% CI 0.34, 0.92) for 0-400 mGy, 0.97 (90% CI 0.55, 1.39) for 0-200 mGy, 1.12 (90% CI 0.45, 1.80) for 0-100 mGy, 1.38 (90% CI 0.20, 2.60) for 0-50 mGy. These provided no indication of a dose threshold for radiation risk. Further analyses of the sub-cohorts of workers hired before 1958, 1958 or after, and 1964 or after yielded ERR Gy-1 risk estimates of 0.20 (90% CI -0.07, 0.49) 1.22 (90% CI 0.74, 1.72) and 1.44 (90% CI 0.65, 2.32), respectively. Some downward curvature was observed in the dose-response, particularly in the cohort first employed in 1965 or after (exponential term, *p* = 0.02) and suggested this was principally attributable to curvature for lung cancer risk. The greater risk estimates in more recent cohorts was potentially partly attributable to increased accuracy of radiation dose measurements after the earliest years of operations, though different temporal sub-cohorts may have had different distributions of follow-up duration and ages, and of other modifying factors. This high-quality study was among the most statistically powerful of the radiation worker studies conducted to date, with a thorough dosimetric assessment, excellent mortality ascertainment and a long-term follow-up. However, study results would be strengthened by a detailed evaluation of attributable causes for the differences in risk estimates by early vs. later workers and by internal monitoring status for radionuclides, as well as by a close inspection of dose-related nonlinearities in lung cancer risk and of temporal patterns of solid cancer risk (by time since exposure and attained age; see Daniels et al., 2017; Richardson et al., 2023b; Wakeford, 2023a).
2. The UK National Registry for Radiation Workers (NRRW), the largest component of the INWORKS study, has updated its follow-up an additional ten years (Haylock et al., 2018) beyond the prior publication (Muirhead et al., 2009) which increased the number of solid cancer deaths by about 40%. The cohort consisted of 167,003 workers (10% females) with an average follow-up of 32 years and a mean recorded cumulative external dose of 25.3 mSv; about 25% of the cohort had been monitored for internal exposure as well, including for plutonium, uranium or tritium, but quantitative information on internal exposures was often not available. Those monitored for internal exposures tended to have higher cumulative external doses (mean of 62.1 mSv among the monitored and 13.3 mSv among others). About 6 % of the workers had received a cumulative dose of 100 mSv or more (Muirhead et al., 2009; Hunter et al., 2022). Based on 10,779, deaths from solid cancers, the ERR Sv-1 was 0.238 (95% CI -0.03, 0.53) (Haylock et al., 2018). Including all cancers except lung, pleural cancers (associated with smoking or asbestos exposure) and leukemia raised the mortality ERR estimate slightly to 0.37 (90% CI 0.11, 0.65). Hunter et al. (2022) studied solid cancer incidence in the NRRW, including 18,310 cases. They found an ERR Sv-1 of 0.20 (95% CI -0.001, 0.43). They found evidence that a linear-exponential model fit better over the entire dose range than a linear model (p=0.01 for improvement in fit), although the evidence for non-linearity disappeared when the data were restricted to 0-400 mSv. A recent NRRW publication (Hunter and Haylock, 2024) examined radiation risk of cancer incidence by time of first employment for comparison with the full INWORKS study (Richardson et al., 2023a) and its US component (Kelly-Reif et al., 2023a), both of which had reported much larger risks of solid cancer per unit dose among more recent workers than among early workers. Hunter and Haylock found that the solid cancer risk was slightly nominally larger for those first exposed in 1960 or after: ERR Sv-1 of 0.14 (95% CI -0.08, 0.38) for those hired before 1960 and 0.39 (95% CI 0.04, 0.76)) for first hire in 1960 or after. However, this difference was mainly attributable to lung cancer, with ERR Sv-1 risks of -0.006 (95% CI -0.39, 0.52) and 0.915 (95% CI -0.006, 2.00), respectively. The ERR Sv-1 risks for solid cancers excluding lung were 0.20 (95 % CI -0.05, 0.48) and 0.33 (95% CI -0.04,0.74), respectively. When the comparison was made for those first hired before or after Jan. 1, 1965, for solid cancers excluding lung the ERR Sv-1 were 0.32 (95% CI 0.065, 0.61) and -0.09 (95% CI -0.51, 0.39), respectively. The NRRW study thus did not support the large temporal disparities in risk reported in the full INWORKS cohort (Richardson et al., 2023a) or the US subcohort (Kelly-Reif et al., 2023a). The NRRW study was large and had an extended and high-quality follow-up for mortality and cancer incidence. A limitation was that quantitative neutron and internal doses were not available to include in the dose estimates, nor were individual smoking histories available.
3. Kelly-Reif et al. (2023a) recently updated the study of the pooled cohort of US nuclear workers (19% females) previously reported by Schubauer-Berigan et al. (2015) from nuclear facilities, including Hanford, Idaho National Laboratory, Oak Ridge National Laboratory, Savannah River and the Portsmouth Naval Shipyard. Follow-up of the 101,363 workers was from the start of radiation work at the sites (between 1944 and 1952) through 2016. Average follow-up was for 39.3 years. Annual badged dose information was generally available from start of work and was cross-checked with other sources. Exposures were mainly to gamma radiation but doses from neutrons (0.6% of workers) and tritium (0.2% of workers) were also included. Individuals monitored for other internal exposures (1.9% of workers) were flagged in the database, but quantitative information was not generally available. The dose metric used for individuals was total equivalent external and tritium dose. The mean cumulative recorded dose was 26.5 mSv among ever-exposed workers. By the end of follow-up 51% of the cohort were deceased. Analyses were adjusted for attained age, sex, facility at first hire, neutron monitoring, occupational status, and duration of radiation monitoring. For solid cancer deaths the ERR Sv­-1 was 0.19 (95% CI -0.10, 0.52, n= 12,069). When the analysis was restricted to those whose cumulative dose was less than 200 mSv, the ERR Sv-1 was similar: 0.15 (95% CI -0.41, 0.74). For solid cancer deaths excluding lung the ERR Sv-1 was -0.01 (95% CI -0.34, 0.36), while for lung cancer it was 0.65 (95% CI 0.09, 1.30). For the subset of solid cancer deaths considered unrelated to smoking the ERR Sv-1 was 0.11 (95% CI -0.37, 0.67, n= 3,819). Mesothelioma and pleural cancer were elevated about 2.7-fold (n= 178 deaths) in the cohort compared to the general population, suggesting an asbestos exposure effect. A subsidiary analysis of the 56% of workers first employed after 1959 was conducted because of improved dosimetry in the more recent period (Kelly-Reif et al., 2023a). This sub-cohort had a mean photon dose of 14.5 mSv and 3,712 solid cancer deaths, 31% of the solid cancer deaths in the total cohort. The solid cancer ERR Sv-1 for the post-1959 workers was an order of magnitude higher than the overall risk estimate: 2.23 (95% CI 1.13, 3,49). A critique of this finding maintained it was unlikely that recorded doses before 1960 would have been sufficiently inaccurate to account for such a large difference and that possible departures from linearity would be worth investigating further (Wakeford, 2023b; 2025). In response, Kelly-Reif et al., (2023b) suggested there may also be ‘important but undefined differences in the groups themselves’. Strengths of the study include reasonably complete external dosimetry, along with neutron and tritium doses, and a long follow-up of a large pooled cohort, while weaknesses include lack of information on internal depositions, potential exposure to other carcinogens, lack of individual information on smoking, and open questions about the large difference in risk estimates between early and later hires.
4. The combined French cohort of nuclear workers, which includes 80,348 workers (13.5% females) employed by the Commissariat à l’énergie atomique et aux énergies alternatives (CEA), Orano (formerly AREVA or Cogema), or Électricité de France (EDF), was evaluated for their mortality experience between 1968 and 2014 (Laurent et al., 2023). The average cumulative photon dose (Hp(10)) was 15.7 mSv for all workers (17.7 mSv for males and 3.1 mSv for females) and 23.1 mSv among exposed workers, including prior exposures back to 1950. Flags were used to identify workers potentially exposed to neutrons (1.8% of person-years) or to internal radionuclides (3.4% of person-years). The analyses, which were adjusted for sex, calendar year period, attained age, social economic status (SES), company and duration of employment, showed an ERR Gy-1 colon dose for solid cancer of 0.69 (95% CI -0.28, 1.77, n= 5691) for both sexes combined. Further analyses were for males only, for whom the ERR Gy-1 was 0.71 (95% CI -0.28, 1.80, n=5,130), while the ERR Gy-1 excluding lung cancer was 0.45 (95% CI -0.65, 1.69, n=3778). Including modifiers for age at exposure or attained age did not improve the model fit. Because dosimetry methods improved after about 1956, an analysis conducted for workers hired after 1956 was conducted; the risk coefficient was similar to the overall one: ERR Gy-1 of 0.65 (95% CI -0.40, 1.83). Including terms in the model for potential neutron or radionuclide exposures had little impact on the risk estimate. When the dose range was restricted to 0-100 mGy the ERR Gy-1 was 0.57 (95% CI -1.14, 2.41) which was statistically compatible with the risk coefficient for the unrestricted range. Strengths included the good photon dosimetry data, a long duration of follow-up and high follow-up success, a substantial number of solid cancer deaths and ability to adjust for socioeconomic status. Limitations were that only about 20% of the cohort has died yet, and individual lifestyle data were not available.
5. The Mayak Production Association, the first and largest plutonium (239Pu) production plant in the former Soviet Union, included facilities for plutonium production, radiochemical work and nuclear reactors as well as auxiliary plants. The full cohort consisted of 25,757 Mayak workers (25% were females) who were first employed during 1948 to 1982. Follow-up was until 2004 for cancer incidence (Hunter et al., 2013) and 2008 for cancer mortality (Sokolnikov et al., 2015, 2017). Annual external doses were available for each cohort member. About 80 % of the external doses were based on personal dosimeter data and 20 % on reconstructed doses (Sokolnikov et al., 2015). Dose uncertainties in the early years were likely fairly high: unshielded film badge readings were affected by the range of energies, geometries, and high-energy betas that were present (Vasilenko et al., 2007). The mean cumulative external gamma Hp(10) dose was 0.51 Sv (Hunter et al., 2013). Over 3,800 workers had cumulative doses > 1 Sv. About 15 % of workers had indications of exposure to neutrons, but that may be an underestimate because before 1970 neutron doses were not recorded or poorly measured. Internal doses from plutonium (239Pu) exposure were calculated from urine and autopsy samples, but systematic plutonium urine monitoring was not performed until the early 1970s, so plutonium dose estimates are available for only 38% of potentially exposed workers. Hunter et al. (2013) investigated the incidence of solid cancers excluding lung, liver and bone, the primary plutonium deposition sites (called non-LLB) through 2004 among 22,366 Mayak workers. They identified 1,447 incident non-LLB solid cancer cases. After adjusting for age, sex, smoking, alcohol consumption and internal doses, the ERR Gy-1 was 0.06 (95% CI –0.01, 0.14). Sokolnikov et al. (2015, 2017) examined 1,825 deaths from non-LLB solid cancers among 25,757 Mayak workers up to the end of 2008. The dose response for mortality from non-LLB solid cancers yielded an ERR Gy-1 of 0.16 (95% CI 0.07, 0.26) when adjusted for sex, attained age and internal exposure (Sokolnikov et al., 2015). A parallel analysis of a sub-cohort that excluded the plutonium-production and radiochemical facility workers, many of whom had high external doses (mean cumulative doses of about 415 mGy) and substantial plutonium exposures, gave an ERR Gy-1 of 0.19 (95% CI 0.02, 0.39) (Sokolnikov et al., 2017). Strengths of the Mayak Production Association worker study included a long follow-up period (over 60 years), a large cohort size and a wide range of individual measured doses of radiation exposure, as well as complete clinical information of high quality and individual smoking information on many workers, while weaknesses included uncertainties in the individual external dose measurements, uncertain or no plutonium measurements in the early years of the plant, and possible outcome biases due to dose-dependent autopsies and occasional reliance on reports of family members for cause of death (NCRP, 2018b).
6. Zablotska et al. (2014) published a re-analysis of cancer mortality (1956-1994) in a cohort of 45,316 Canadian nuclear industry employees (16.8 % females). An earlier analysis of this cohort (Zablotska et al., 2004) had reported an unexpectedly high ERR Gy-1 of 2.80 (95 % CI -0.038, 7.13) and these data were included in the 15-country study of nuclear workers (Cardis et al., 2007). In the re-analysis (Zablotska et al., 2014) the individual doses for the full cohort ranged from 0 to 679 mSv with a mean of 21.6 mSv plus a mean of 3.0 mSv from tritium exposure, and the risk analyses were based on the total recorded dose. They found an ERR Sv-1 of 1.77 (95% CI –0.42, 5.30) for all solid cancer for the full cohort, but this was heavily influenced by the 3,066 persons employed from 1956 to 1965 at Atomic Energy of Canada Limited (AECL). Exclusion of this AECL group from the risk analysis resulted in a negative non-statistically significant ERR Sv-1 of -1.20 (95 % CI –1.47, 2.39) based on 324 solid cancer deaths among the remaining 42,228 employees. These results, plus the further finding that no increased leukemia risk was found for the 3,066 employees with increased risk for all solid cancer, led to the conclusion that the data were inaccurate for the early AECL workers, most likely due to incomplete transfer of dose records to the National Dose Registry (Zablotska et al., 2014). The study strengths included a large cohort size and reasonably accurate and precise dose information for the 93% of the workers included in the analysis. Limitations included inability to include early AECL workers who likely had some of the largest exposures but for whom accurate dose information was not available.
7. Furuta et al. (2022) reported on a cohort of 204,103 Japanese nuclear workers (mostly at nuclear power plants) with follow-up from 1991 to 2010. Individual doses for the nuclear workers were based on personal dosimetry going back to the first exposures in 1957. Changes over time in dose measurement methods and circumstances were accounted for. Few had neutron or internal exposures. The average individual cumulative colon dose was 11.0 mGy. Mortality follow-up through the Japanese *koseki* system was essentially complete. Information from 35% of the 71,733 workers was available on smoking, alcohol consumption, obesity, education and other lifestyle and occupational factors (Murata et al. 2002; Kudo et al., 2022). The analysis of all cancer except leukaemia yielded an ERR Gy–1 of 1.22 (90% CI 0.24, 2.26, n = 7929). However, excluding both lung cancer and leukemia yielded an ERR Gy-1 of only 0.50 (90% CI -0.56, 1.56) (Furuta et al., 2022), and an analysis of solid-cancer radiation risk based on a subset with lifestyle data further confirmed that smoking was a confounder in this cohort (Kudo et al., 2022). Study strengths included the large cohort of workers with good-quality individual exposure monitoring and high rates of follow-up and death ascertainment. For a fraction of workers, information was available on lifestyle factors. Weaknesses included inability to adjust for smoking in the entire cohort, and that cohort follow-up was short and began years after the inception of radiation exposures for some workers which introduces a potential for survival bias (Richardson et al., 2004).
8. Solid cancer mortality was studied among 135,193 workers (3.3% females) at U.S. commercial nuclear power plants who were first employed between 1957 and 1984, with follow-up through 2011 (Boice et al., 2022a). The cohort included all workers with cumulative doses of 10 mSv or more and a 10% random sample of those with <10 mSv. Most recorded doses were external exposures from 58Co, 60Co and 137Cs. The mean duration of follow-up was 30.2 y and the mean age at follow-up was 62.2 y. The mean career colon dose was 43.7 mGy, with 11.5% receiving >100 mGy. The dose-response analyses were adjusted for sex, year of birth, age and socioeconomic status, with a 10-year dose lag. Employment at multiple nuclear power plants and duration of employment were also examined as covariates but did not affect risk estimates. For all solid cancer (3,445 deaths) the ERR per 100 mGy was 0.01 (95% CI -0.03, 0.05); corresponding to 0.1 Gy-1(95% CI -0.3, 0.5). The strengths of the study were the large cohort and high quality dosimetric assessment, mortality follow-up and cause of death ascertainment. A limitation was that the cohort is still relatively young—22% had died.
9. Boice et al. (2011) reported solid cancer mortality risks in a cohort of 46,970 workers employed at Rocketdyne (Atomics International) during the period 1948 to 1999, of whom 5,801 were involved in radiation activities. Occupational x-ray or gamma doses from all places of employment were obtained and radiation doses from intakes of 14 different radionuclides were calculated for 16 organs or tissues using ICRP biokinetic models. The dose from external radiation ranged up to 1 Sv with a mean of 13.5 mSv. In the follow-up period (1948-2008) there were 684 cancer deaths. They found an RR at 100 mSv of 0.98 (95 % CI 0.82, 1.17; ≈ ERR Sv-1 of -0.2, CI -1.8, 1.7) for all cancer mortality excluding leukemia. Strengths included the detailed dosimetry and high rates of follow-up and cause of death ascertainment, but the study had low-statistical power because of the small number of cancers observed in the population and the distribution of radiation exposure levels.
10. Kashcheev et al. (2015) reported solid cancer incidence and mortality risks in a cohort of 67,568 Russian emergency workers who worked in the Chornobyl exclusion zone in 1986–1987. In the follow-up period (1992-2009) there were 4,002 incident solid cancers identified through annual compulsory health examinations and 2,442 solid cancer deaths. External radiation whole-body absorbed doses from gamma radiation were determined using either individual dosimeters, group dosimeters, or dose-rate measurements at the work place with a range of 0.1-1,240 mGy and with a mean of 132 mGy. They found an ERR Gy-1 of 0.58 (95 % CI 0.002, 1.25) for all solid cancer mortality and an ERR Gy-1 of 0.47 (95 % CI 0.03, 0.96) for all solid cancer incidence. The study strengths included the large cohort size with relatively high cumulative doses. The weaknesses included substantial dose uncertainties, and uncertainties in cancer incidence ascertainment.
11. A total of 27,011 medical x-ray workers and 25,872 non-radiologist Chinese physicians who worked sometime between 1950 and 1980 were followed up through 1995 for the incidence of all cancers excluding leukemia (Sun et al., 2016). Since personal dose monitoring began only in 1985, earlier worker doses were modelled for 3,805 workers based on a simulation of multiple x-ray machines, workplaces, working conditions, protective measures used and calendar year periods (Zhang et al., 1998). The average modelled dose for each calendar year was then applied as the estimated dose for all who worked that year. The mean cumulative Hp(10) dose was 250 mSv; because low energy x-rays were employed the corresponding mean colon dose was 86 mGy (but ranged to >500 mGy for those who began work before 1950). Investigators found 795 cancer cases in the exposed cohort and 848 in the unexposed cohort. Histologic information was available for about 70 % of cancers. Investigators calculated an ERR of 0.87 Gy–1 (95 % CI 0.48, 1.45) based on estimated colon dose. Study strengths included the lengthy follow-up and the matched hospitals of the exposed and unexposed groups. Weaknesses of the study included substantial dosimetric uncertainties due to lack of personal dose information, limited cancer diagnostic information, and potential dose-related differences in socioeconomic status.
12. A mortality study was conducted on 109,019 U.S. medical workers (49.4% females) through 2016 who were first monitored between 1965 and 1994 based on Hp(10) dose records (Boice et al., 2023). The study included a wide variety of types of workers in medical settings with external radiation exposure. Members were included if they had radiation monitoring for at least two years and had cumulative Hp(10) doses of at least 10 mSv. A comprehensive dose reconstruction was conducted, for example, to account for orientations to sources and to the use of lead aprons. The mean estimated dose to the heart (mean dose to the colon was not reported) was 14.6 mGy, with 1.48% receiving over 100 mGy. Workers were followed up for a mean of 25.5 years. Analyses were adjusted for sex, year of birth, age and occupational category (general radiology, interventional radiology, nuclear medicine and radiation oncology, other). For mortality from all solid cancers the ERR at a colon dose of 100 mGy was 0.07 (95% CI -0.01, 0.15); corresponding to 0.7 Gy-1(95% CI -0.1, 1.5; n=3,191 solid cancer deaths). The excellent mortality follow-up and ascertainment of causes of death were strengths of the study, while a weakness was the uncertainties associated with the dosimetry because of limited information on the positioning of radiation badges vis a vis lead aprons, or location/orientation with respect to the radiation beam for interventional radiologic procedures.
13. A study of cancer incidence was conducted among South Korean diagnostic medical radiation workers (Lee et al., 2021). It included 93,920 workers (43% females) enrolled between 1996 and 2004, with follow-up through 2017. Badged radiation doses (including doses received before 1996) were converted to colon doses assuming dominant energies of 30-40 keV, an anteroposterior irradiation geometry, and adjusting for the probability of protective apron use and badge placement. The estimated mean cumulative colon dose was only 7.4 mGy. The dose-response analysis took account of sex, ages at exposure, attained age, employment duration and type of medical facility. The outcome was solid cancer, including nonmelanoma skin cancers because of good national records for that outcome, but excluding thyroid cancer because of variable numbers of thyroid ultrasound screenings due to the extensive thyroid screening programs conducted in South Korea during that time period. The ERR Gy-1 colon dose was 2.4 (95% CI -1.5, 6.4) for solid cancer (except thyroid cancer). The estimates with and without lung cancer were statistically compatible (ERR Gy-1 of 1.7, 95% CI -2.4, 5.7 excluding lung). This was a high-quality study, but the main limitations were the low-dose distribution and relatively short duration of follow-up which constrained its statistical power. An earlier report of cancer mortality in this cohort lacked dose-response analyses (Lee et al., 2018).
14. The solid cancer mortality experience of 26,846 German aircrew personnel (Dreger et al., 2020) was studied between 1960 and 2014. Dose estimates were available for the cockpit crew for 1960-2014 and from the federal dose register for 2004-2014 for the cabin crew. A job exposure matrix was used to model exposures for 1960-2003 for the cabin crew as a function of individual age, sex, employment history, solar activity and corresponding pilots’ doses. The median cumulative dose equivalents were 44, 25 and 50 mSv for male cockpit, female cabin and male cabin personnel, respectively. The mean follow-up duration was 28.0 years and mean age at follow-up was 53.2 years. Analyses of solid cancer mortality were conducted adjusting for age, calendar year and employment status, and using a 10-year dose lag. The Cox hazard ratios (HR) per 10 mSv were 0.93 (95% CI 0.83, 1.04; ≈ ERR Sv-1 of -7 (95% CI -17, 4); n=195 solid cancer deaths), 1.04 (95% CI 0.94, 1.14; ≈ ERR Sv-1 of 4 (95% CI -6, 14); n=213) and 1.04 (95% CI 0.93, 1.16; ≈ ERR Sv-1 of 4 (95% CI -7, 16); n=72) for male cockpit, female cabin and male cabin crew, respectively. The study strengths included adequate mortality and cause of death ascertainment and relatively high estimated cumulative doses, but the limitations included imprecise risk estimates because of the fairly small number of deaths and dose uncertainties with the job exposure matrix.
15. Several additional studies, described in succeeding paragraphs, made smaller contributions to risk assessment than those described in previous paragraphs, because of some combination of relatively low doses and small numbers of deaths.
16. The cohort studied by Merzenich et al. (2014) included 8,746 German males who were employed as radiation workers at any of 17 nuclear power plants (NPP) sometime during 1991-2008, though their radiation work may have begun as early as 1966. At the end of the follow-up, the mean cumulative effective dose among male workers (including doses prior to 1991) was 29.5 mSv. About 48% had cumulative doses < 5 mSv and only 8.5% received > 100 mSv. Neutron exposures were negligible. There were 119 deaths from cancer excluding leukaemia. The risk estimate, via a Cox model was a hazard ratio (HR) of 0.999 (95% CI 0.996, 1.001) per mSv (corresponding to an ERR Sv-1 ≈ –1 (95% CI –4, 1)). Study strengths included good dosimetry and a high rate of follow-up, but the major limitation of the study was low statistical power because of the small size of the cohort and limited follow-up period.
17. A cohort of 85,033 U.S. male nuclear submariners between 1969 and 1982 had a mean dose of 5.7 mSv and 21.2 years of follow-up on average (Friedman-Jimenez et al., 2022). The cumulative radiation doses were based on radiation badges, including doses that were received before 1969 by a small fraction of the cohort. The ERR Sv-1 was 5.2 (95% CI -3, 18, n= 492) for solid cancer. Study strengths included good dosimetry and a high rate of follow-up, but the major limitation of the study was low statistical power because of low doses and the young ages at follow-up (only 3.8% deceased).
18. Jeong et al. (2010) followed up a cohort of 8,429 male nuclear power workers in South Korea between during 1978–2005, plus a comparison group of 7,807 male non-radiation workers at nuclear power facilities. The majority of recorded doses came from external exposure with high-energy photons (100 keV), the mean dose was 19.86 mSv, and ~5% received >100 mSv. About a quarter of the radiation workers had records of internal doses greater than zero, and 7.8% had neutron doses of > 10% of their total dose (mean neutron dose: 0.44 mSv). Follow-up for cancer incidence was for 1992-2005 and information was available on smoking (54% were current smokers). For all incident cancers except leukaemia the ERR Sv-1 was 2.06 (95% CI –1.91, 9.0, n=96). The study was limited with insufficient statistical power mainly due to the small size of the cohort, short period of follow-up and young ages of the cohort members.
19. Kreuzer et al. (2015) reported on all solid cancer mortality risks based on 4,054 male employees at the Wismut uranium mining company who had worked at some time between 1946 and 1989 in processing uranium ore, but were never employed in the underground mines. The yearly external gamma doses for each worker were calculated using a Job Exposure Matrix to account for estimated or measured exposure variations specific to work-place and type of occupation, to derive mean yearly doses. From 1963, the gamma effective dose was calculated from measurements of the 226Ra-concentration in the rocks, using estimated conversion factors. The cumulative effective gamma dose in this cohort ranged up to 667 mSv, with a mean of 26 mSv, and 169 persons were recorded with over 100 mSv. The mortality follow-up period for this group (1946 to 2008) included 434 deaths from all solid cancers. The risk from external effective dose was an ERR Sv-1 of 1.86 (90 % CI –0.08, 3.80). One study strength was that this was one of the largest cohort studies of uranium millers exposed to radium progeny, gammas, long-lived radionuclides and silica dust with essentially complete vital status and cause of death ascertainment. However, there was low statistical power to determine the effects of gamma exposure partly due to the low photon exposure levels.
20. Zablotska et al. (2013) reported on all solid cancer mortality (1950-1999) and incidence (1969-1999) risks in a cohort of 3,000 persons (11.8 % females) employed in refining and processing of radium and uranium at the Port Hope company. The cohort data included radiation exposures from external gamma radiation, and internal exposure due to the incorporation of radium and uranium and inhalation of radon and radon decay products. The mean effective dose from external gamma radiation was 134.4 mSv with a range of 0.4-5099 mSv. Based on 225 deaths from solid cancer there was an ERR Sv-1 of 0.12 (95 % CI: < 0, 0.98) for external gamma exposure. This risk estimate was not adjusted for concomitant exposures to radon decay products. A study strength was the characterization of γ-ray doses associated with refining and processing work with concomitant estimation of exposures to radon decay products. However, there was low statistical power, partly because of the relatively small number of cancer deaths.
21. A pooled analysis of the Wismut and Port Hope uranium processing workers included 7,431 workers (1946-2008; 3.6% female) and an average follow-up time of 36 years (Zablotska et al., 2018). Measurements of radon and external radiation began in 1955 and missing dose information was supplemented by a job exposure matrix defined by calendar time, facility, work place and job type. The mean cumulative gamma ray dose was 61.5 mSv. A regression model for lung cancer showed it was primarily related to exposure to radon decay products, so an analysis of gamma dose with solid cancer excluding lung cancer was conducted which provided an ERR Sv-1 of 0.20 (95% CI <-0.46, 1.26). No individual types of cancer or cardiovascular disease were significantly related to gamma dose.
22. The mortality experience of 6,638 male workers at the Rocky Flats nuclear weapons plant was reported for 1951 through 1979 (Gilbert et al., 1993; Cardis et al., 1995). The majority of doses were to 100 keV to 1 Mev photons, and workers were excluded if > 10 % of dose was from low-energy photons, neutrons or intake of radionuclides. The mean cumulative dose was 36.4 mSv. Analyses were stratified by attained age, calendar period and educational level. For all cancer except leukaemia the ERR Sv-1 was –1.63 (90% CI < 0, 0.5) (Cardis et al., 1995)
23. The mortality of an Australian cohort of 4,717 workers at the Lucas Heights Science and Technology Centre who were employed between 1972 and 1998 was documented through 1998 in the Australian national mortality registry (Habib et al., 2005). A fraction of these, totalling 877, of whom 27.7% were female, were included in the 15-Country study as radiation workers with an average follow-up of 13.8 y (Cardis et al., 2007; Vrijheid et al., 2007). Their estimated mean colon dose was 6.1 mSv. Based on 17 cancers, excluding leukaemia, the ERR Sv-1 was 13.4 (90% CI -6.0, 119) (Cardis et al., 2007).
24. The Belgian study followed up the vital status of workers from five nuclear facilities for 1953-1994 through the National Population Registry and other sources (Engels et al., 2005). From each facility they obtained the annual effective dose for each worker, with indications for neutron and internal exposures. The 15-Country study included 5,037 Belgian workers (4.8 % females), and a mean follow-up of 15.3 y (Cardis et al., 2007; Vrijheid et al., 2007). They had an estimated mean colon dose of 26.6 mSv. Based on 87 cancers excluding leukaemia, the ERR Sv-1 was -0.59 (90% CI -7.42, 6.24) (Cardis et al., 2007).
25. The Finnish study consists of 15,629 workers (4.6% females) from two nuclear power plants followed up during 1971 through 1998 (average follow-up of 13.3 y) (Auvinen et al., 2002). Their estimated mean colon dose was 7.9 mSv among the 6 ,782 included in the 15-Country study (Cardis et al., 2007; Vrijheid et al., 2007). Based on 33 cancers excluding leukaemia, the ERR Sv-1 was 174 (90% CI -722, 1070) (Cardis et al., 2007).
26. The Slovak Republic cohort consisted of 2,776 employees (8.1% females) with follow-up from 1973 through 1993 (Gulis, 2003), for 10.4 y on average. The estimated mean Hp(10) dose was 1.91 mSv. Based on 13 cancers (none of them leukaemia), the estimated risk, ERR Gy-1 was 9.5 (95% CI -60.4, 35.7) (Cardis et al., 2007).
27. The Spanish cohort, which was reported in the 15-Country study (Cardis et al., 2007; Vrijheid et al., 2007), included 3,633 workers at two nuclear fuel cycle facilities and eight nuclear power plants. The study period was 1970-1996 with a mean worker follow-up of 12.8 y, during which there were 25 cancers excluding leukaemia. The mean colon dose was 25.5 mSv. The ERR Sv-1 was 1.02 (90% CI -11.9, 13.9) (Cardis et al., 2007).
28. The Swedish cohort, which was reported in the 15-Country study (Cardis et al., 2007; Vrijheid et al., 2007), included 16,347 workers at a nuclear research facility and four nuclear power plants. The study period was 1954-1996 with a mean worker follow-up time of 13.5 y, during which there were 190 cancers excluding leukaemia. The mean colon dose was 6.1 mSv. The ERR Sv-1 was -0.58 (90% CI -7.65, 6.49) (Cardis et al., 2007).
29. Mortality was evaluated in a French cohort of 4,688 uranium enrichment workers potentially exposed to soluble uranium compounds at three gaseous diffusion plants (Zhivin et al., 2016). The cohort members were 9% females and had a median follow-up time of 30.2 years and a median external dose of 0.75 mGy (range, 0.3 – 230 mGy). A total of 406 deaths from solid cancers were recorded. The ERR Gy-1 was 1.6 (95% CI < 0, 7.5) for external γ-radiation. The association with internal exposure likewise was nonsignificant.

### Studies of Risks after Environmental Exposure

1. Between 1949 and 1956 the Mayak plant released radioactive waste into the Techa River while producing plutonium for the Soviet nuclear weapons program. Approximately 30,000 residents (60 % females) of 41 villages along the river were potentially exposed to radiation from these releases – external gamma rays and internal exposures from ingesting 137Cs, 90Sr, 89Sr and other uranium fission products (Degteva et al., 2007; Napier, 2014). External exposures were estimated using exposure rate measurements available at various locations along the river bank, with further modelling based on river proximity, residence history, and gender- and age-dependent behavioural factors. Among 29,730 residents 2,303 solid cancer deaths occurred between 1950 and 2007. The ERR Gy-1 was 0.61 (95 % CI 0.04, 1.27) (Schonfeld et al., 2013). An incidence study of 17 435 individuals with stomach doses ranging up to 960 mGy (mean of 60 mGy) yielded an ERR Gy-1 of 0.77 (95 % CI 0.13, 1.5; n= 1,933 solid cancer cases) (Davis et al., 2015). Strengths of the Techa River cohort were that it is an unselected general population of all ages and both sexes for whom an extensive effort was made to reconstruct individual doses, and the incidence analysis was able to adjust for smoking. However, uncertainties stemmed from limitations in the completeness of cancer mortality ascertainment and the wide range of assumptions required in dose reconstruction. It should also be noted that 40% of the cohort were under age 20 at exposure.
2. The Kerala study of cancer incidence in a high background radiation area (HBRA) compared with a low-radiation background area was recently updated based on an enlarged cohort of 149,585 Kerala residents (54% females), ages 30 to 84 years at entry to the cohort with follow-up extended from 1990 through 2017, and a mean follow-up of 19.1 years (Jayalekshmi et al., 2021). The earlier reports with shorter follow-up included 70,000 persons (Nair et al., 2009; Akiba, 2013). The elevated gamma radiation exposure was primarily from thorium in the monazite sands. The investigators measured ambient exposure rates for ~94% of the dwellings of initial cohort members (Nair et al., 2009; Akiba, 2013), measuring indoor and outdoor dose rates. They then estimated age/sex averages of house occupancy from interviews with 11% of the initial cohort. In this HBRA study members had a fairly high cumulative dose (from birth) with a mean of 96.6 mSv (maximum over 500 mGy). Personal dose measurements were not available except for a small sample. The cancer incidence registry was based on information from several sources of varying quality and completeness, with histopathologic or cytologic confirmation available for 78%, death certificate information only for 6% of cases, and other sources for 16% of cases. The analysis included 6,804 cases of all cancer except leukaemia, which was stratified on sex, attained age, follow-up period and original/newly added subcohort, and yielded an ERR Gy-1 of 0.12 (95% CI -0.19, 0.48) based on the estimated colon dose. When the analysis was further stratified on education, bidi smoking, tobacco chewing and alcohol consumption, the ERR Gy-1 was -0.05 (95% CI -0.33, 0.29). In summary, the study examined very protracted exposures spread out over the attained lifetime. The investigators made a considerable effort to reconstruct ambient exposures to the study members, and the cumulative exposure levels were relatively large. Nevertheless, there were considerable uncertainties in individual dose estimates from the dose reconstruction, especially regarding the historical house occupancy factors, and the investigators had mentioned potential limitations in the completeness and quality of the cancer ascertainment (Nair et al., 2002, Nair et al., 2009). There may have been differences other than levels of radiation exposure between the high background and control areas, such as variations in lifestyle, medical care availability and quality, and retrospective disease ascertainment in the additional sub-cohort, which complicate interpretation of risk estimates derived from the study.
3. Tao et al. (2012) reported on residents of an HBRA in the Yangjiang region of China for the period of 1979 to 1998 compared to residents of a nearby low background area for a total of about 31,000 individuals 30 to 74 years of age. They divided the region into three dose groups (high, medium, low) on the basis of environmental dose rates per year. Sun et al. (2000) estimated individual annual doses and cumulative doses based on indoor and outdoor exposure data for each hamlet, plus estimated sex- and age-specific indoor occupancy factors from a survey of ~5,300 individuals. Morishima et al. (2000) reported a good correlation across hamlets between average estimated doses and average personal dose measurements. For the HBRA areas and the control areas the estimated mean cumulative colon doses lagged 10 years were 84.8 mGy and 21.6 mGy, respectively, a difference of 63.2 mGy. Using several sources of mortality data of varying quality, they found 941 deaths from cancer excluding leukemia (Tao et al., 2012). However, diagnoses were based on pathological determination for only 26 % of cancer deaths, radiographic or ultrasound information for 62 % and other sources for 12 %. Because of a high prevalence of liver cancer mortality that differed by region and that was probably associated with variation in hepatitis B virus prevalence, they estimated the radiation risk excluding liver cancer as well as leukaemia. The resulting ERR Gy-1 was 0.19 (95 % CI –1.87, 3.04). Though the high- and low-background regions were comparable on socioeconomic and lifestyle factors, there were some indications of differences in quality of medical care and infectious disease prevalence, plus uncertainties in cancer diagnosis and dose reconstruction modelling. As with the Kerala study, there may have been differences other than levels of radiation exposure between the HBRA and control areas which complicate interpretation of risk estimates derived from this study.
4. Between 1982 and 1984 radioactive 60Co was inadvertently incorporated into rebar reinforcing rods used in ~180 buildings, including over 1,670 dwelling units in Taiwan which exposed about 10,000 individuals. A detailed dosimetric survey was conducted within the dwellings (Chen, 2002), along with interviews and records of the daily living activities of the residents. However, faulty or nonspecific recall of information regarding daily activities 10 to 20 y in the past produced substantial uncertainties in individual dose reconstructions. The mean cumulative dose was estimated to be 47.8 mGy (Hwang et al., 2006). Cancer incidence was ascertained from the national cancer registry (Hsieh et al., 2017). The mean age at first exposure was 17 years and the mean length of follow-up for cancer incidence was 30 years (Hsieh et al., 2017). There was a marginally significant increase in risk for all solid cancers (hazard ratio at 100 mSv of 1.04 (90% CI 1.01, 1.08; ERR Gy–1 ≈ 0.4, 90 % CI 0.1, 0.8). In summary, the dosimetry effort to reconstruct exposures was thorough, albeit the estimated doses were based on ambient exposure measurements and imputed occupancy factors. The ascertainment of cancer incidence was of good quality. The small sample size and young age of the study subjects limited the statistical power, and there were residual questions about statistical methods and possible variations in disease surveillance.

### Prior Systematic Reviews of Epidemiologic LDR Studies

1. A detailed comparison has been made between risk coefficients for parallel subsets of the LSS (Japanese atomic bombing study) and INWORKS (pooled occupational studies) cohorts (Leuraud et al. 2021). The cohorts were ages 20-59 years at first exposure and included 7982 LSS and 16,279 INWORKS solid cancer deaths. Across the full dose range the solid cancer ERR Gy-1 were very similar for the two cohorts: LSS 0.28 (90% CI 0.18, 0.38) and INWORKS 0.29 (90% CI 0.07, 0.53). There was minimal evidence of curvature or of a modifying effect by sex, age at initial exposure or attained age for either cohort. For the restricted dose range of 0-100 mGy the estimates were 0.38 (90% CI -0.27, 1.07) for the LSS and 0.49 (90% CI -0.21, 1.23) for INWORKS. Corresponding estimates for 0-200 mGy were 0.50 (90% CI 0.17, 0.86) and 0.63 (90% CI 0.21, 1.07), respectively. When lung cancer was excluded, the ERR Gy-1 was 0.25 for both cohorts. This was an exemplary comparison of two major cohorts, one with a single brief exposure and the other with protracted exposures at low dose rates. The evidence indicated the excess risks per unit dose were similar, suggesting a DREF of about 1.
2. NCRP recently reviewed the quality of individual studies with low doses or low dose rates and the degree to which they provided support for a linear no-threshold dose response (NCRP, 2018b; Shore et al., 2019). The quality assessment included a descriptive characterization of the strengths and weaknesses of the major occupational and environmental studies and evaluations of three study components: dosimetry, epidemiology and statistical modelling. The review included 29 studies or study groups. Fifteen studies were of solid cancer after primarily adult occupational or environmental radiation exposure. Evaluations of the dosimetry, epidemiology and statistical quality, indicated that about a third were considered to be of moderately good quality, and most of the remainder were considered weak-to-moderate because of component weaknesses that detracted from their quality but were not fatal flaws. The studies broadly provided modest-to-strong support for the presence of risk at relatively low doses and low dose rates, albeit most individual studies had inadequate statistical power.
3. A recent systematic review by Hauptmann et al. (2020) assessed studies of solid cancer risk after adult exposure to low doses (with mean exposure <100 mGy) that had appeared since the BEIR VII report (BEIRVII, 2006). They derived a meta-analysis ERR at 100 mGy of 0.029 (95%CI: 0.011; 0.047), based on a mixture of 13 mortality or incidence studies. The authors pointed out that the adult solid cancer risk estimate of 0.29 Gy-1 was similar to the estimate for males in the LSS (derived from the incidence study of Grant et al. (2017)) of 0.27 Gy-1 but lower than the LSS estimate for females of 0.64 Gy-1. Although the eligible studies had a mean cumulative dose of less than 100 mGy, the risk estimates in many studies were derived partially from doses much higher than this level. In particular, in four studies that contributed ~95% of the total weighting, those of the Techa River cohort (Davis et al., 2015), Taiwanese 60Co-exposed residents (Hsieh et al., 2017), the UK NRRW (Muirhead et al., 2009) and the US nuclear workers (Schubauer-Berigan et al., 2015), 5-11% of cumulative doses exceeded 100 mGy and a small fraction exceeded 400 mGy. Additional publications dealt with the strengths and weaknesses of the dosimetry (Daniels et al., 2020), possible confounding and selection bias (Schubauer-Berigan et al., 2020), possible outcome misclassification (Linet et al., 2020), and certain statistical issues in interpretation including statistical power (Gilbert et al., 2020).

## Meta-analysis

### Rationale

1. The primary question with regard to the DREF is whether the risk coefficients for low-dose or low-dose-rate (LDR) studies are as great (indicating a DREF of 1) or smaller (DREF >1) than corresponding risk coefficients in the LSS, where the LSS data provide the best measure of risk after a single brief exposure ranging up to 4 Gy. A ‘weight of evidence’ approach was used to minimize the potential for bias in the estimation of a DREF value in various epidemiological LDR studies. This implies being as comprehensive as possible to avoid biased selection of studies. At the same time, a DREF analysis has to use studies that have appropriate quantitative data, accounting for potential confounders when possible. This requirement means that studies should have individual doses and outcomes and should have a dose-response analysis. Simple exposed versus unexposed group comparisons of health outcomes may be biased (i.e. results may differ appreciably from those that would be obtained if a dose-response analysis could be done (UNSCEAR, 2008a)). In addition, it is well documented in the literature that comparisons of worker groups with the general population for health outcomes (i.e. Standardized Mortality (Incidence) Ratios – SMRs/SIRs) are nearly always biased due to ‘healthy worker’ selection effects and survival effects (Richardson et al., 2004), so SMR/SIR data should not be used to estimate the association of radiation dose with cancer risk.
2. A concern in trying to avoid bias in the results of a joint analysis of studies pertains to publication bias. This can occur when editors decline to publish studies with null results, although probably most reasonably large cohort studies of radiation effects do get published in some radiation journal or elsewhere. Most recent studies with individual doses tend to report dose-response results for total solid cancers or all cancers except leukaemia, though with a few exceptions (Boice et al., 2020, 2022b; Golden et al., 2022), so publication bias for solid cancers or its close proxies may be minimal. However, there may also be the possibility of ‘file drawer’ bias – investigators decide not to write a paper if the results are null/negative; again, for large cohort studies that consume substantial resources, this is thought not to be common. However, for individual solid cancer sites there may be more potential for a form of publication bias than there is for the total solid cancers outcome. As part of the analyses, statistical tests for publication bias were performed (Sterne and Egger, 2001; Duval and Karlsson, 2002; Sterne et al., 2011), although those tests tend to have low statistical power so null results should be taken as suggestive, not conclusive.
3. Another source of bias in an epidemiological study of radiation health effects may be other exposures or medical risk factors (Hauptmann et al., 2020; Linet et al., 2020). Lifestyle factors are usually the exposures of most concern because of their high prevalence; these were recently reviewed by Schubauer-Berigan et al. (2020). Smoking is the paramount lifestyle factor because of the large risk it confers for lung cancer and, to a lesser extent, a number of other cancers. Unfortunately, many of the studies have no smoking information for individuals. Several methods have been employed to examine whether smoking confounds the radiation-solid cancer relationship. In particular, some studies with individual smoking information have statistically adjusted for smoking (Auvinen et al., 2002; Nair et al., 2009; Jeong et al., 2010; Hunter et al., 2013; Davis et al., 2015; Sokolnikov et al., 2015; Kudo et al., 2018; Furuta et al., 2022). Others have adjusted for individuals’ educational or occupational status as a lifestyle surrogate (Cardis et al., 1995; Nair et al., 2009; Zablotska et al., 2014; Leuraud et al., 2017), have compared the ERR Sv-1 for all solid cancer with solid cancer excluding lung cancer (Tao et al., 2012; Zablotska et al., 2014; Sun et al., 2016; Haylock et al., 2018; Zablotska et al., 2018; Furuta et al., 2022; Kelly-Reif et al., 2023a; Laurent et al., 2023; Richardson et al., 2023a), have compared the ERRs for subsets of smoking-related and smoking-unrelated cancers (Merzenich et al., 2014; Schubauer-Berigan et al., 2015; Friedman-Jimenez et al., 2022; Kelly-Reif et al., 2023a), have compared the ERRs for total solid cancer and lung cancer (Howe et al., 2004; Boice et al., 2011; Kashcheev et al., 2015; Kelly-Reif et al., 2023a). Many studies (e.g. Leuraud et al., 2017; Haylock et al., 2018; Kelly-Reif et al., 2023a; Laurent et al., 2023; Richardson et al., 2023a; exception Kashcheev et al., 2015) have evaluated whether there is a null association between radiation dose and chronic obstructive pulmonary disease, a disease which is largely attributable to smoking. Most studies, but not all (Furuta et al., 2022), have found that lung cancer and smoking make little discernible difference in the risk estimates, suggesting that smoking usually tends to be fairly independent of radiation dose level. These various indirect methods to evaluate confounding (Richardson et al., 2014) by smoking appear to be useful surrogates in lieu of smoking information, and can at least detect substantial confounding by smoking. In addition, a meta-analysis may be helpful, as any bias from smoking confounding for a given study may be mitigated when averaged with other studies.
4. Exposure measurement error is also a potential source of uncertainties in assessing the magnitude of dose-response relationships. When doses are based on individual exposure measurements, random measurement errors (called classical measurement error) will tend to attenuate the dose-response relationship. Badge measurements among early workers were especially prone to measurement error due to the characteristics of the badges available. Reported radiation measurements for medical workers tend to have uncertainties in how often the badges were worn beneath protective body shielding. Individual dose estimates based on retrospective dose reconstructions or environmental measurements have shared uncertainties (potential uncertainties and inaccuracies that apply to groups within the cohort) as well as random individual uncertainties. Exposure measurement uncertainties were noted in a number of the LDR study summaries in Section 5.2, and more information on dose uncertainties in various epidemiologic radiation studies is given elsewhere (NCRP, 2018b; UNSCEAR, 2018; Daniels et al., 2020).

### Methods

1. *Literature searches*. The aim of the literature search was to compile a comprehensive list of LDR studies since 1980 of primarily low-LET radiation that reported risk estimates for total solid cancer that were based on dose-response analyses via internal comparisons of individual dose data and provided estimates of ERR per unit dose (i.e. Sv-1 or Gy-1). If a study contained results only for similar cancer outcomes, but not solid cancer per se, then the outcome closest to solid cancer was chosen as a proxy (but hereafter referred to generically as ‘solid cancer’). Inclusion of leukemia was avoided because the slope and shape of the leukemia dose response tend to differ from that for solid cancers (Hsu et al., 2013). A comprehensive search was intended in order to minimize study selection biases and publication bias. The latest available update for each study cohort was used so as to maximize the information the study provides and avoid redundancy among study reports. Several approaches were used to find relevant published articles. PubMed and Google Scholar were searched, most recently in November 2023. Focus was on articles published in English, with the following search criteria: (‘ionising radiation’ OR ‘radiation exposure’ OR (radiation AND exposure)) AND risk AND (epidemiology OR ‘cancer incidence’ OR ‘cancer mortality’) AND (occupational OR worker OR environmental OR ‘low dose’).The PubMed search was fairly sensitive (detecting relevant papers) but not specific (many irrelevant papers found), and Google Scholar provided an additional relevant reference. In addition, references in the identified publications and in the tables of the UNSCEAR (UNSCEAR, 2008) and BEIR (NAS, 2006) reports plus the 15-country study (Cardis et al., 2007; Vrijheid et al., 2007) were scanned to identify additional relevant papers, augmented by expert knowledge of the literature. Abstracts and articles were reviewed to determine their applicability. Because the objective was quantitative, studies lacking dose-response information or those with a large potential for dosimetry bias were eliminated.
2. The most common LDR studies of solid cancer mortality were those of occupationally exposed cohorts; 22 studies and about 94% of the total study subjects and person-years fell into this broad category, which included cohorts of workers in nuclear weapons and processing facilities, commercial nuclear power plants, clean-up and restoration work, or a combination of these, and medical x-ray workers. Two other mortality studies were based on elevated environmental exposures from high natural radiation background in Yangjiang, China (Tao et al., 2000, 2012) or from significant manmade sources: Techa River residents exposed to Mayak effluents (Eidemüller et al., 2010; Schonfeld et al., 2013; Preston et al., 2017).
3. Meta-analyses of LDR studies with solid cancer incidence data also were conducted. The rationale is that cancer incidence data tend to have greater diagnostic accuracy than cancer mortality data, and incidence data are not skewed toward the more lethal cancer sites and types as cancer mortality data are. Five LDR studies had only incidence data but not mortality data: Kerala, India HBRA (Nair et al., 2009; Akiba, 2013), Taiwan residents of radio-contaminated dwellings (Hwang et al., 2006, 2008), China medical diagnostic x-ray workers (Zhang et al., 1998; Wang et al., 2002; Sun et al., 2016), South Korean medical diagnostic radiation workers (Lee et al., 2021), and South Korean nuclear power plant workers (Jeong et al., 2010). Four additional studies reported on solid cancer incidence data which overlapped with the mortality data reports: Russian Mayak nuclear workers (Hunter et al., 2013), Techa River nearby residents (Davis et al., 2015), Chornobyl clean-up workers (Kashcheev et al., 2015), and the UK NRRW study (Haylock et al. 2018, Hunter et al., 2022).
4. *Dose Metric Conversions*. The solid cancer mortality risk estimates for the LSS cohort have been reported based on weighted absorbed colon doses (Ozasa et al., 2012), while most of the LDR studies reported risk estimates based on personal dose equivalent Hp(10) or other dose bases. Usually radiation dosimeters used in occupational radiation protection are calibrated in terms of Hp(10). When the risk estimate of a given LDR study was compared to that of the matched LSS risk estimates, comparison was made based on the same or the closest organ dose to that in the LDR study. For an LDR study with either Hp(10), skin dose or whole-body dose, the corresponding LSS total solid cancer used breast dose with an appropriate dose conversion factor to estimate solid cancer risk. For an LDR study that reported an estimate based on effective dose, conversion was made to estimated colon dose for comparison with the LSS. For an LDR study reporting colon or stomach doses the corresponding organ was used for the LSS risk comparison.
5. For dose conversions, the coefficients were based on those published in (Zankl, 1999) and *Publication 116* (ICRP, 2010).For example, for Hp(10) doses, conversion coefficients (Hp(10) per air kerma in Sv Gy-1) were taken from Zankl (1999) who had calculated coefficients for various positions on the human chest. Coefficients calculated for a typical dosimeter position were used in this study, with rotational geometry. These coefficients were divided by the corresponding *Publication* *116* (ICRP, 2010) male and female conversion coefficients for the breast (absorbed breast dose per air kerma in Sv or Gy) for the same energy range and geometry. An average ratio was calculated separately for males and females, and the sex-averaged ratio of 0.99 was obtained. Then the LDR/LSS ratio corresponding to any study that reported Hp(10) doses was based on an analysis using breast doses multiplied by 0.99 in the tabulated LSS data. For studies that reported effective dose estimates, the similarly-calculated conversion factor to absorbed colon dose was 1.02.
6. *Comparison of LDR and LSS risk estimates*. Each LDR study’s outcome was matched to the comparable LSS outcome. In particular for the outcome of non-leukemia, the LSS rates for solid cancers plus lymphoma and myeloma were used. For a few studies, certain diagnoses were not included as part of the solid cancer outcome because analyses had shown concerns that those diagnoses may introduce biases because their risk was partly attributable to other correlated exposures. Namely, biases were suggested for liver cancer in the Yangjiang, China HBRA study (Tao et al., 2012), for lung cancer in the German and Canadian study of uranium processing workers (Zablotska et al., 2018), for thyroid cancer in the South Korean diagnostic medical radiation study of cancer incidence (Lee et al., 2021), and for liver, lung and bone cancers due to plutonium exposures in the Mayak worker study (Sokolnikov et al., 2015, 2017). In these cases, the LSS sex/age-specific rates of the corresponding diagnoses were subtracted from the LSS total solid cancer rates (except detailed rates for bone cancer were not available in the LSS mortality data to subtract out for the Mayak study comparison, but bone and connective tissue cancers constitute only about 0.7% of cancers in the LSS, so their impact is very small). It should be noted that the LSS estimates used for comparisons with risk in the specific LDR studies will tend to be highly positively correlated. No account will be taken of this in the meta-analysis.
7. For each included LDR study the starting point of the comparison of LDR to LSS risk estimates was the published point estimate of the ERR Gy-1 (or Sv-1) of solid cancer and its confidence interval (CI) given by the study authors, based on the assumption of a linear dose response. To derive a ratio of the risk in LDR cohorts to that in the atomic bomb LSS cohort, the risk estimate per unit dose for each individual LDR dose-response study was compared with the appropriate organ risk estimate per unit dose of the LSS models matched on age and sex (Jacob et al., 2009). The models for solid cancer risk in the LSS atomic bomb cohort vary by sex, age at exposure, attained age and the corresponding categories of cancer, so the LSS risk coefficients that correspond to various LDR cohorts were matched to the characteristics of each LDR cohort study.
8. It was not possible to derive the full matrix of person-years by outcome, sex, age at exposure and attained age, from the LDR publications, so the approximations of mean ages at study entry and at the end of follow-up (‘attained age’), and the proportion of females were used to generate a matched LSS risk estimate corresponding to that for each individual study. For example, for the Mayak mortality study, 25% were females and the mean entry age and attained age were 24.8 and 61.7 years, respectively. The cancer outcome in this case was solid cancer except for lung, liver and bone. The central risk estimate and confidence interval for the LSS, matched to the Mayak cohort, were calculated as solid cancer, excluding lung and liver, with the LSS risk model effect modifiers for age at exposure and attained age centred to match the Mayak mean entry age and attained age respectively(24.8 to 61.7 years) – rather than the corresponding values of 30 years and 70 years usually applied in LSS publications. The matching also included weighted indicator variable for sex, to obtain the risk centred for 75% male and 25% female. The ratio of the LDR ERR Gy-1 coefficient to the matching LSS coefficient (LDRi/LSSi) and the standard error of the ratio (Bevington and Robinson, 2003) were calculated for each LDRi study. The standard error was then used to estimate the confidence interval on the LDRi/LSSi coefficient. The results of this procedure for each study are shown in Table 3.
9. *Meta-analysis of the LDR/LSS ratios of risk*. The LDRi/LSSi ratios of the respective ERR Gy-1 for the LDR studies with the corresponding values derived from the LSS cohort of atomic bomb survivors were then combined to form a best estimate with a statistical meta-analysis. Study-specific parallel outcomes were analysed in the LSS using the models in Ozasa et al. (2012) for mortality studies and Preston et al. (2007) for incidence studies. (Insufficient detailed information for single-organ risks by age and sex was available to be able to make comparisons with most recent LSS incidence data of Grant et al. (2017).) The basic methodologies for the comparisons and meta-analysis are described in Jacob et al. (2009). For solid cancer mortality outcomes the model employed was an ERR model linear in dose with a stratified baseline (strata: city, sex, age at exposure category and age attained category) as used in the study by Ozasa et al. (2012). For solid cancer incidence the model was a linear in dose ERR model with a parametric baseline as used in the study by Preston et al. (2007). Specifically, calculations of the LSS ERR per unit dose applied a conventional linear ERR model of the hazard for sex *s*, age at first exposure or study entry *e*, attained age *a* and dose *d* with a weighting factor of 10 for neutrons, where the organ dose used for the LSS analysis was as defined above for each LDR study, *h*(*e*, *a*, *s*, *d*) = *h*0(*e*, *a*, *s*) (1 + ERR(*e*, *a*, *s*, *d*)), with baseline risk models, *h*0(*s*, *e*, *a*), and ERR per unit dose models, ERR(*e*, *a*, *s*, *d*).
10. The array of study ERR slope ratios (LDRi/LSSi) and their CIi were subjected to a conventional meta-analysis using the inverse variances of the LDRi/LSSi ratio of each study as its statistical weighting factor in the meta-analysis, which was conducted with and without the assumption of heterogeneity of risk ratios. The methods are described in more detail in Jacob et al. (2009). Heterogeneity and any potential effects of applying different methods for Meta-analysis were evaluated by applying several different methods as described in (DerSimonian and Kacker, 2007). However, there were no indications of statistical heterogeneity with the mortality data or combined mortality and incidence data, and all methods gave consistent results, so the fixed-effects meta-analyses are reported. For the incidence data alone, there was evidence of statistical heterogeneity, so random effects (that is, additionally accounting for inter-study variability in risk estimates) meta-analysis results were reported.
11. A methodological caveat has been noted pertaining to estimating confidence intervals for the LDRi/LSSi ratios, having to do with the inverse variance weightings that were used in the meta-analysis, and the Fieller method (Fieller, 1954) was recommended (Little et al., 2021a,b). However, in practical terms, accounting or not accounting for such theoretical considerations caused only very slight changes in the quantitative meta-analysis results (Walsh et al., 2021a) and had no bearing on the conclusions of the meta-analyses (Walsh et al., 2021b).
12. *Sensitivity analyses*. To evaluate the degree to which individual studies influenced the meta-analysis results, risk estimates were calculated when each individual study was excluded from the analysis (leave-one-out analysis). In addition, meta-analyses to address questions pertaining to specific issues were conducted. For example, analyses have been conducted both including and excluding the Mayak worker mortality study because of its high-dose range and the consequent disproportionate influence on the meta-analysis results. Analyses were conducted to detect publication bias (Egger et al., 1997; Duval and Tweedy, 2000). Another sub-analysis examined only the studies with mean doses less than 100 mGy to evaluate whether there was statistically significant risk over the low-dose range.

### Results for Total Solid Cancer

1. *Individual Study Results.* Table 3 provides descriptive information on the most recent reports of individual or pooled LDR cohorts identified that have dose-response based risk estimates for solid cancer mortality. The 24 studies included in the mortality meta-analysis are marked with asterisks in the first column of Table 3. The Dreger et al. (2020) study of three independent airline flight crew cohorts is treated as three separate studies in the analysis. Redundant data were excluded from the mortality meta-analyses, that is, studies that were pooled for analysis were not also included as separate studies (e.g. Haylock et al. (2018), Kelly-Reif et al. (2023a) and Laurent et al. (2023) were pooled into Richardson et al. (2023a)), and only the most recent report of a cohort was included. The mortality studies included about 1.06 million individuals (10% females), 27.6 million person-years of observation, nearly 54,000 solid cancer deaths and a collective dose of over 30,700 person-Sv. Additional reports of the nine studies with solid cancer incidence risk data were also included in a separate meta-analysis. The solid cancer incidence studies included about 590,800 individuals and 13.0 million person-years of observation, 36,700 cancers and 26,000 person-Sv.
2. Table 3 shows the 24 solid cancer mortality studies used in the meta-analysis. The estimated mean cumulative occupational doses ranged from about 1 to 61 mGy, except for the Chornobyl clean-up workers with a mean of 132 mGy, and the Mayak workers with a mean cumulative colon dose of 354 mGy, or 235 mGy in the Mayak sub-cohort that excluded the Mayak plutonium-production and radiochemical facility workers. This compares to a mean weighted absorbed colon dose of about 230 mGy in the LSS subset with >5 mGy, but some in the LSS had doses >3 Gy. Of the 24 LDR cohorts, 22 were considered to be low-dose studies, with estimated mean doses under 100 mGy. In fact, all but two (uranium processing workers (Zablotska et al., 2018) and Yangjiang, China HBRA (Tao et al., 2012)) had mean cumulative doses of 50 mGy or under. Exposure distributions were highly right-skewed in the occupational studies, with most individuals at quite low doses but small percentages who had received up to several hundred mGy.
3. Four studies with elevated environmental exposures were included in the meta-analyses. Two studies had solid cancer mortality data: residents who lived along the Techa River which had been contaminated with the Mayak plant radioactive effluents, and those residing in the high background radiation area (HBRA) of Yangjiang, China (Table 3). Two other environmental studies, of the HBRA in Kerala, India, and residents of radio-contaminated dwellings in Taiwan, had only solid cancer incidence data. Three other studies with only cancer incidence data among radiation workers are shown in Table 3 as well. Lastly, both solid cancer mortality and incidence data were available for four cohorts, as shown in Table 3.
4. *Overall Meta-Analyses*. Using all 24 of the solid cancer mortality cohorts shown in Table 3 with asterisks, the overall meta-analysis estimate of the ratio of mortality risk in the LDR studies to the corresponding risk in the LSS cohort (LDR/LSS) was 0.50 (95% CI 0.27, 0.73; DREF of 1.99, 95% CI 1.36, 3.71), if all the Mayak workers were included. A summary of all the DREF estimates is shown in Table 4. Since the test for heterogeneity of the risk ratios was not close to statistical significance (*p*= 0.69), a random-effects estimate was not considered. However, in this meta-analysis the Mayak worker cohort, with a low point estimate of the ERR Gy-1 (0.16, 95% CI 0.07, 0.26), had a very high influence: it accounted for 85% of the total weighting (defined as the percentage of the total inverse-variance accounted for) in the analysis because of its narrow CI (Table 3). The narrow CI in the Mayak study probably occurred because of the much higher mean and range of the dose distribution than in any other LDR study. (A similarly narrow CI is seen in the LSS study because of its large dose range.) Only the INWORKS study also accounted for as much as 5% of the total meta-analysis weighting, so the low risk estimate in the Mayak cohort heavily influenced the results.
5. Therefore, a further meta-analysis was conducted including all the mortality studies except the Mayak study. It showed an LDR/LSS ratio of 1.21 (95% CI 0.61, 1.81; DREF of 0.82, 95% CI 0.55, 1.63), with no evidence of statistical heterogeneity (p= 0.94). Thus, the full exclusion of the Mayak study essentially changed the estimated value of DREF from 2 to about 1. Without the Mayak study, the only studies accounting for at least 5% of the meta-analysis weighting were INWORKS (32%), Techa River (26%), US nuclear power plant study (20%) and US medical workers (12%).
6. Although the full Mayak cohort was dominant in the mortality meta-analysis, a fraction of the Mayak workers had appreciable plutonium exposures and high cumulative external doses (Sokolnikov et al., 2015). Therefore, meta-analyses were conducted that included only the Mayak workers who did not work at the two main facilities with plutonium exposure (the plutonium-production and radiochemical facilities) (Sokolnikov et al., 2017). Reasons to consider the sub-cohort without the plutonium-radiochemical workers are that the mean cumulative dose of the remaining sub-cohort is about 235 mGy, closer to the low-dose range that is of more interest than the dose for the excluded workers (who had a mean dose of about 415 mGy), and few in this sub-cohort (only 4%) had any indication of plutonium exposure. Furthermore, plutonium exposure data were not available or not well estimated for many individual workers in the two plutonium facilities before about 1970. As a result, the sub-cohort meta-analysis is not as highly dominated by the Mayak data as when the full Mayak cohort is used. For this Mayak sub-cohort the LDR/LSS ratio was 0.73 (95% CI 0.37, 1.10; DREF of 1.37 (95% CI 0.91, 2.73), a DREF value somewhat intermediate between 1 and 2. Again there was no statistical evidence of between-study heterogeneity of the risk ratio (*p*=0.81). The studies that accounted for at least 5% of the meta-analysis weighting were Mayak sub-cohort (63%), INWORKS (12%), Techa River (9%), US nuclear power plant workers (7%) and US medical workers (5%).
7. Meta-analyses were also conducted of the nine available studies with solid cancer incidence data. Five of these were of cohorts that had no corresponding mortality data and four overlapped with the mortality data (see Table 3). Including all nine incidence studies yielded an LDR/LSS ratio of 0.58 (95% CI 0.20, 0.96); DREF of 1.73 (95% CI 1.04, 5.06), while excluding the Mayak study yielded an LDR/LSS ratio of 0.71 (95% CI 0.34, 1.09), a DREF of 1.40 (95% CI 0.92, 2.95) (Table 4). Unlike the mortality analyses, the results showed statistically significant heterogeneity among studies, so the values reported are for random-effects models that account for inter-study variation (DerSimonian and Laird, 1986). Studies that accounted for at least 10% of the meta-analysis weighting were Mayak workers (27%), Taiwan radio-contaminated dwellings (19%), UK NRRW (16%), China medical x-ray workers (13%) and Techa River (10%). When the Mayak worker study was excluded, the influential weightings were Taiwan radio-contaminated dwellings (30%), UK NRRW (24%), China medical x-ray workers (18%) and Techa River (12%).
8. To obtain the broadest possible assessment of LDR radiation risk, further analyses were conducted of the 29 cohorts that included all the LDR mortality cohorts and the five incidence cohorts that were not redundant with the mortality study cohorts (Table 3). This meta-analysis yielded an LDR/LSS risk ratio of 0.53 (95% CI 0.33, 0.73); a DREF of 1.89 (95% CI 1.37, 3.04) (Table 4). The results of this meta-analysis were similar to those for mortality studies only, but in this case the Mayak cohort had a lesser weighting of 63%. If the Mayak study was excluded, the LDR/LSS ratio was 0.79 (95% CI 0.46, 1.13), a DREF of 1.26 (95% CI 0.89, 2.16). Again, when the Mayak study sub-cohort that excluded the plutonium-production and radiochemical workers was employed, the results were intermediate: LDR/LSS ratio of 0.67 (95% CI 0.41, 0.94) and a DREF of 1.48 (95% CI 1.06, 2.47) (Table 4). There were no indications of risk heterogeneity in these three meta-analyses (heterogeneity p-values all greater than 0.50).
9. To concentrate on solid cancer mortality risk for studies that were at both low doses and low dose rates, a meta-analysis was performed of the 22 cohorts with mean cumulative doses of under 100 mGy (all but two of which had mean doses of 50 mGy or under). The LDR/LSS ratio was 1.16 (95% CI 0.54, 1.77), and a DREF of 0.86 (95% CI 0.56, 1.84). The INWORKS study had the greatest weighting (33%) in this meta-analysis, followed by the Techa River (27%) and US nuclear power plant (20%) studies.
10. *Sensitivity analyses*. Leave-one-study-out analyses were conducted to examine the influence of each of the 29 individual cohorts on the risk estimates for the combined mortality and incidence studies. When the Mayak study was left out the DREF was 1.26 but was 1.89 when Mayak was included, as noted above. The DREF values were altered somewhat when the China medical x-ray workers study (DREF of 2.12) or the INWORKS study (DREF of 2.05) was left out, whereas leaving out any of the remaining studies produced only small changes in the DREF values, ranging from 1.81 to 1.94. In all cases, the confidence intervals on the DREF values were wide. Leave-one-out analyses were also conducted using the Mayak sub-cohort (which excluded the Mayak plutonium-production and radiochemical workers); compared to the DREF for all studies (1.48), DREF values leaving out various single studies were: Mayak workers (1.26), Taiwan radio-contaminated dwellings (1.30), INWORKS workers (1.64), China medical x-ray workers (1.70), while the DREF values leaving out any other study ranged from 1.45 to 1.51. Again, all estimates had wide confidence intervals. The inclusion of the full Mayak cohort appears to make the most notable difference in the estimate of DREF; differences caused by leaving out any other single study were mostly small.
11. The published point estimates of the ERR Gy-1 (or Sv-1) and CIs for solid cancer given by the study authors could also be combined to provide a meta-analysis summary risk over the unrestricted and restricted (mean doses under 100 mGy) dose ranges. However, for this type of ERR meta-analysis, no attempt was made to match the exact outcome, reference dose-type, age-attained, age at exposure and sex characteristics of the cohorts, as was carefully done for the summary LDR/LSS ratio estimates. For the unrestricted dose range in the present analysis, the ERR Gy-1 estimates for the 29 combined mortality and incidence studies, including the full Mayak cohort and then excluding the Mayak plutonium and radiochemical facilities sub-cohorts, were 0.22 (95% CI 0.14, 0.30) and 0.29 (95% CI 0.18, 0.41), respectively. The corresponding earlier result from Shore et al. (2017) including the full Mayak cohort and then excluding the Mayak plutonium and radiochemical facilities sub-cohorts, were slightly lower at 0.15 (95% CI 0.06, 0.23) and 0.26 (95% CI 0.10, 0.42), respectively, based on 22 mortality and incidence studies. For the unrestricted dose range in the present analysis, the ERR Gy-1 estimates for the 24 combined mortality studies, including the full Mayak cohort and then excluding the Mayak plutonium and radiochemical facilities sub-cohorts, were 0.21 (95% CI 0.13, 0.30) and 0.30 (95% CI 0.17, 0.43) respectively. The corresponding earlier result from Shore et al. (2017) including the full Mayak cohort was 0.15 (95% CI 0.07, 0.24) based on 19 mortality studies, but here the Makay cohort had a very high weighting of 91% and essentially defined this result.  The latest INWORKS study publication (Richardson et al., 2023a) reported an ERR Gy-1 of 0.54 (90% CI 0.27, 0.77) over the full dose range, which is higher by approximately a factor of two than the summary results reported here, excluding the Mayak plutonium and radiochemical facilities sub-cohorts but including the INWORKS risk.
12. The magnitude of risk (ERR Gy-1) in the meta-analysis of only studies with estimated mean doses under 100 mGy (a restriction which excludes the full Mayak cohort and the Chornobyl emergency worker cohort (Kashcheev et al., 2015)) can be compared in a limited fashion with results reported in the few individual studies that obtained risk estimates restricted to the dose range of 0 to 100 mGy and these results are reported here. In the present analysis, the ERR Gy-1 estimates for 27 combined mortality and incidence studies and 22 mortality studies were 0.35 (95% CI 0.19, 0.50), 0.40 (95% CI 0.20, 0.61), respectively. An earlier meta-analysis with 16 mortality studies with cumulative mean doses under 100 mGy agreed with this latter value but with larger CIs: 0.41 (95% CI 0.12, 0.71) (Shore et al., 2017). For comparison, a few individual studies reported risk estimates over the restricted dose range of 0 to 100 mGy, and an earlier meta-analysis of 13 mortality and incidence studies by Hauptmann et al. (2020) reported an ERR Gy-1 of 0.29 (95% CI 0.11, 0.47). The latest INWORKS study publication (Richardson et al., 2023a) reported a much larger ERR Gy-1 over the 0-100 mGy range of 1.12 (90% CI 0.45, 1.80); although a prior analysis of the INWORKS cohort reported an ERR Gy-1 of 0.49 (90% CI -0.21, 1.23) for the 0-100 mGy dose range (Leuraud et al., 2021). Haylock et al. (2018) reported an ERR Sv-1 of 1.42 (90% CI 0.51, 2.38) for mortality from all cancer except leukemia over the 0-100 mSv range in the UK NRRW study; they also indicated that if lung and pleural cancers were excluded, the risk estimate over the 0-100 mSv range was not statistically significant (numerical estimate not given), which suggests the primary driver of the high risk estimate was lung cancer. In analysing the UK NRRW solid cancer incidence data, Hunter et al. (2022) reported an ERR Sv-1 of 0.98 (95% CI 0.14, 1.86) over the 0-100 mSv cumulative dose range. Finally, in the France SELTINE study Laurent et al. (2023) found an ERR Gy-1 of 0.57 (95% CI -1.14, 2.41) over the 0-100 mSv cumulative dose range. Most of the individuals in the UK and France studies were also in the INWORKS study, so the results are not independent of each other. In summary, both the present meta-analysis of studies with mean cumulative doses under 100 mGy and the results of analyses over the 0-100 mSv dose range in individual studies support the hypothesis that radiation-associated cancer risk is present at doses under 100 mSv, so an inference of no risk at relatively low doses is not currently warranted by the available data and the incomplete information available on explanatory factors such as smoking and asbestos exposures in the current data.
13. *Publication bias*. Neither of the two methods to statistically evaluate publication bias (Egger et al., 1997; Duval and Tweedy 2000) gave a statistically significant indication of such bias for either the mortality or the mortality plus incidence analyses. Because cohort studies of photon radiation generally provide risk estimates for total solid cancer or some close proxy for it, publication bias was not expected.
14. *Interpretation*. The Task Group meta-analysis of solid cancers after primarily adult exposures, with several new studies added or updated (compared to Shore et al. (2017), or Hauptmann et al. (2020)), was based on 24 mortality cohorts of low-dose or low-dose-rate exposures and five additional incidence cohorts. The meta-analyses indicated a combined ERR Gy-1 of 0.21 (95% CI 0.13, 0.30) for the mortality studies only, or 0.22 (95% CI 0.14, 0.30) when both mortality and incidence studies were included, somewhat lower than the risks reported in the Hauptmann et al. (2020) meta-analysis of 0.29 (95% CI 0.11, 0.47) based on 13 studies. When the plutonium-production and radiochemical facilities at Mayak were excluded from the analysis, however, the ERR Gy-1 for mortality studies was 0.30 (95% CI 0.17, 0.43) and for the combined mortality and incidence studies was 0.29 (95% CI 0.18, 0.41), almost identical to the Hauptmann results.
15. There are some inherent problems in the approach adopted here in deriving DREF by comparing relative risks in the Japanese atomic bomb survivors and some western occupational cohorts. Excess relative risk may be affected by variation in underlying cancer rates in different populations and for different tumour sites, for example between Japan and western populations, as well as by differences in dose rate. It is known for some cancer sites (e.g. breast, lung) that absolute risk (EAR) may be more nearly invariant across populations than relative risk (NAS, 2006; UNSCEAR, 2008a; Little and Wakeford, 2013). However, EAR study results may vary substantially by the range of ages covered; additionally, many of the studies with ERR results did not report EAR results, so a meaningful meta-analysis of EAR results could not be performed.
16. A central concern with the meta-analysis results for total solid cancer was that the major studies differed appreciably in their estimated central values of the DREF. For example, the INWORKS, Techa River and US medical radiation workers studies had central estimates of DREF under 1, whereas the Mayak worker, Kerala HBRA, Taiwan radio-contaminated dwellings and US nuclear power plant worker studies had DREFs over 2. It is unclear how much the discrepancies might be associated with uncertainties/biases in study dosimetry or cancer ascertainment, or may reflect variations among population background rates, lengths of follow-up, ages at follow-up, or simply random statistical variation. For those cohorts with both mortality and incidence data available, there were also moderate differences between the corresponding mortality and incidence DREF values; the mortality DREFs were nominally somewhat greater than the incidence DREFs, perhaps associated with differences in lethality for various types and sites of cancers.
17. The studies also were diverse in study quality, which can be affected by a variety of factors having to do with populations, availability and quality of key types of data, and analysis and reporting. An NCRP Commentary (NCRP, 2018b) provided a detailed description and ratings of the quality of a number of dose-response studies. It is notable that none of the most weighty mortality studies in this meta-analysis were considered weak by those assessors. Of the mortality studies with meta-analysis weights of 10% or more, the INWORKS study (Richardson et al., 2023a) was rated as of strong quality, and the Mayak (Sokolnikov et al., 2015, 2017) and Techa River (Schonfeld et al., 2013) studies were considered to have moderate quality. The two additional studies in this group were too recent to have been included in NCRP (2018b), but the US nuclear power worker study (Boice et al., 2022a) would likely be considered of strong or strong-to-moderate quality and the US medical worker study (Boice et al., 2023) of moderate quality (strong except for dose uncertainties).
18. Another source of uncertainty may come from the fact that the Japanese atomic bomb survivors had been exposed to gamma radiation in the energy range of 2 – 5 MeV (Young and Kerr, 2005), while the studies included in the above meta-analyses were associated with photon exposures with unreported but probably lower photon energies. For example, a somewhat smaller induction of dicentric chromosome aberrations in blood lymphocytes from atomic bomb survivors was reported than in blood samples exposed to 60Co gamma radiation (Straume et al., 1995). Whether this translates into a smaller relative biological effectiveness for cancer induction, which is the outcome studied here, remains, however, unclear. Furthermore, 60Co gamma rays may in turn be biologically less effective than lower-energy photons of several tens of hundreds of keV implying differences of up to a factor 2, depending on photon energy (NCRP, 2017). Thus, it cannot be ruled out or it may well be that underlying higher ERR Gy-1 values from the high-dose-rate LSS exposures were at least partly blurred/masked by a lower relative biological effectiveness of those exposures, as compared to environmental and occupational exposures included in the meta-analyses.

## Conclusion

1. This overview and analysis showed that many epidemiological studies exist that provide quantitative information on low-dose-rate risk from exposure to ionising radiation in adults. These studies mainly include occupational exposures (largely to nuclear and medical workers), and environmental exposures.
2. Using all 29 of the independent mortality and incidence studies identified, the overall meta-analysis estimate of the ratio of mortality risk in the LDR studies to the corresponding risk in the LSS cohort (LDR/LSS) translated into a DREF of about 1.9 (95% CI 1.4, 3.0), or a DREF of about 1.5 (95% CI 1.1, 2.5) when the Mayak sub-cohort, that excluded the two facilities with high doses and substantial plutonium exposures, was used. The results of this analysis were similar to those for the 24 mortality studies only (DREF’s of about 2.0, 95% CI 1.4, 3.7 and 1.4, 95% CI 0.9, 2.7 for the full Mayak cohort and sub-cohort, respectively). A concern about the meta-analysis results, however, was that one single study (i.e. the Mayak worker study) dominated the overall results, as it accounted for 63% of the total weighting for the mortality plus incidence meta-analysis and 85% of the total weighting for the mortality studies only, though this concern was lessened for analyses using the Mayak sub-cohort (34% of the total weighting for the mortality plus incidence studies, 63% for mortality only). A DREF of about 1.3 (95% CI 0.9, 2.2) resulted when the Mayak study was entirely left out from the combined mortality and incidence analysis, or a DREF of about 0.8 (95% CI 0.6, 1.6) for mortality studies only.
3. As noted above, there are inherent problems in the approach adopted in comparing relative risks across different populations, as excess relative risk may be affected by variation in underlying cancer rates in different populations, for example between Japan and western populations, as well as by differences in dose rate. There were also variations among cohort studies in the uncertainties in the dosimetry, adequacy of cancer ascertainment, impact of variations among studies in attained ages, potentially confounding lifestyle factors, and probably relative biological effectiveness depending on photon energies involved in the studied exposures.
4. The overall conclusion of this meta-analysis of most recent epidemiological studies is that the current epidemiologic results do not provide precise bounds on the value of the DREF, though most of the central estimates of DREF from the meta-analyses are between 1 and 2. In general they imply that – given the uncertainties involved – high values of the DREF (e.g. of 3 or above) are unlikely as are values below 1. These values of DREF, however, may not be appropriate for transporting Excess Absolute (additive) Risks (EAR) rather than ERRs because EAR and ERR risk variations may not be parallel by age and sex. Likewise, although these DREF values have been derived from studies based on a variety of populations with differing background rates of cancer, attention should be given to how appropriate the transport of a DREF value is to the population of interest.

Table 3. Low-Dose and/or Low-Dose-Rate (LDR) Studies of Total Solid Cancer (or its Proxies): LDR Risk Estimates and LDR to LSS Risk Ratios.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study Identifiers a | Mean reported external dose (mGy) | No. of cancers | LDR Study Risk:  ERR Gy-1 (90% or 95% CI) a | Corresponding LSS Risk: ERR Gy-1 (90% or 95% CI) a | LDR/LSS: Risk ratio of this study to the LSS (90% or 95% CI) a |
| **Occupational Radiation Exposures and Mortality** | | | | | |
| INWORKS (Richardson et al., 2023a) \* | 20.9b1, b6 | 28,089c1 | 0.52 (0.27, 0.77) | 0.32 (0.24, 0.4) | 1.64 (0.82, 2.68) |
| US, nuclear workers (Kelly-Reif et al., 2023a) | 26.5b3, b6, g | 12,069c1 | 0.19 (-0.10, 0.52) d | 0.27 (0.20, 0.35) | 0.69 (-0.44, 1.93) |
| UK, NRRW (Haylock et al., 2018) a | 25.3b3 | 10,779c1 | 0.24 (0.01, 0.48) | 0.25 (0.18, 0.33) | 0.94 (0.02, 2.06) |
| US, NPP workers  (Boice et al., 2022a) e, \* | 43.7 b1 | 8,445c1 | 0.1 (-0.3, 0.5) d | 0.30(0.19, 0.40) | 0.34 (-1.07, 1.84) |
| Japan, nuclear workers (Furuta et al., 2022) \* | 11.0b1 | 7,929c3 | 1.22 (0.24, 2.26) f | 0.24 (0.14, 0.34) | 5.03 (0.85, 11.26) |
| France, nuclear workers (Laurent et al., 2023) | 23.1b3, b6 | 5,691c1 | 0.69 (-0.28, 1.77) d | 0.25 (0.17, 0.32) | 2.8 (-1.38, 7.54) |
| US, medical radiologic workers (Boice et al., 2023)\* | 14.6b7 | 3,191c1 | 0.7 (-0.1, 1.5) d | 0.48(0.38, 0.58) | 1.47 (-0.21, 3.29) |
| Chornobyl clean-up workers, Russia (Kashcheev et al., 2015)\* | 132b2 | 2,442c1 | 0.58 (0.002, 1.25) d | 0.23 (0.12, 0.34) | 2.54 (-0.19, 6.82) |
| Mayak workers, Russia (Sokolnikov et al., 2015, 2017)\* | 354b1  235b1 | 1,825c4  593c4 | 0.16 (0.07, 0.26) d, g  0.19 (-0.022, 0.39) d | 0.42 (0.30, 0.55)  0.42 (0.29, 0.56) | 0.38 (0.15, 0.68)  0.45 (0.34, 0.66) a |
| US, Rocketdyne workers (Boice et al., 2011)\* | 13.5b3 | 651c2 | -0.2 (-1.8, 1.7) d | 0.23 (0.16, 0.30) | -0.87 (-9.00, 7.07) |
| US, Navy nuclear submariners (Friedman-Jimenez et al., 2022) \* | 5.7b3 | 492c1 | 5.2 (-3, 18) d | 0.42 (0.23, 0.60) | 12.51 (-13.43, 44.39) |

*(continued on next page)*

Table 3. *(continued)*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study Identifiers a | Mean reported external dose (mGy) | No. of cancers | LDR Study Risk:  ERR Gy-1 (90% or 95% CI) a | Corresponding LSS Risk: ERR Gy-1 (90% or 95% CI) a | LDR/LSS: Risk ratio of this study to the LSS (90% or 95% CI) a |
| Germany, airline flight crews \* (Dreger et al., 2020) \*  \* | 44b3, h  25  50 | 195c1  213c1  72c1 | -7 (-17, 4) d, i  4 (-6, 14)  4 (-7, 16) | 0.25 (0.16, 0.34)  0.70 (0.52, 0.88)  0.31 (0.19, 0.42) | -28.31 (-79.37, 14.47)  5.71 (-8.73, 20.93)  13.10 (-25.73, 56.00) |
| Germany, WISMUT Uranium process workers, Germany (Kreuzer et al., 2015) | 26b3 | 434 c1 | 0.26 (-2.47, 2.99) d | 0.35 (0.23, 0.46) | 0.75 (-7.46, 9.14) |
| France, Uranium process workers (Zhivin et al., 2016) \* | 0.8b3 | 406c1 | 1.6 (-4.3, 7.5) d | 0.22 (0.15, 0.30) | 7.18 (-20.14, 36.30) |
| Germany & Canada combined, Uranium processing workers, (Zablotska et al., 2018) \* | 61.5b3 | 371c6 | 0.20 (-0.86, 1.26) d | 0.2 (0.12, 0.27) | 1.01 (-4.63, 7.00) |
| Canada, nuclear workers (Zablotska et al., 2014) \* | 21.6b3, j | 324c1 | -1.2 (-4.79, 2.39) d, i | 0.36 (0.20, 0.52) | -3.38 (-15.69, 7.23) |
| Canada, Port Hope uranium process workers (Zablotska et al., 2013) | 134b3 | 225c1 | 0.12 (-0.74, 0.98) d, k | 0.36 (0.20, 0.52) | 0.33 (-2.27, 3.11) |
| Sweden, nuclear workers (Cardis et al., 2007) \* | 6.1b3 | 190c2 | -0.58 (-7.65, 6.49) k | 0.46 (0.30, 0.63) | -1.26 (-17.89, 15.00) |
| Germany, NPP workers (Merzenich et al., 2014) \* | 29.5b4 | 115c1 | -1 (-4, 1) d, l | 0.31 (0.19, 0.43) | -3.14 (-12.55, 5.12) |
| US, Rocky Flats workers (Cardis et al., 1995) \* | 36.4b5 | 104c2 | -1.63 (-3.76, 0.5) | 0.28 (0.17, 0.40) | -5.73 (-15.27, 1.79) |
| Belgium, nuclear workers (Engels et al., 2005; Cardis et al., 2007) \* | 26.6b3 | 87c2 | -0.59 (-7.42, 6.24) k | 0.48 (0.30, 0.65) | -1.24 (-16.84, 13.98) |

*(continued on next page)*

Table 3. *(continued)*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study Identifiers a | Mean reported external dose (mGy) | No. of cancers | LDR Study Risk:  ERR Gy-1 (90% or 95% CI) a | Corresponding LSS Risk: ERR Gy-1 (90% or 95% CI) a | LDR/LSS: Risk ratio of this study to the LSS (90% or 95% CI) a |
| Finland, nuclear workers (Auvinen et al., 2002; Cardis et al., 2007) \* | 7.9b3 | 33c2 | 174 (-722, 1070) k | 0.43 (0.27, 0.60) | 400.9 (-1773.0, 2713.6) |
| Spain, nuclear workers (Cardis et al., 2007) \* | 25.5b3 | 25c2 | 1.02 (-11.9, 13.9) k | 0.46 (0.29, 0.63) | 2.21 (-27.54, 32.68) |
| Australia, nuclear workers (Habib et al., 2005; Cardis et al., 2007) \* | 6.1b3 | 17c2 | 13.4 (-6.0, 119) | 0.52 (0.35, 0.69) | 25.93 (-99.29, 157.36) |
| Slovakia, Jaslovske Bohunice NPP (Gulis, 2003) \* | 1.91b3 | 10c2 | 9.5 (-60, 36) d | 0.4 (0.21, 0.60) | 23.47 (-106.28, 168.31) |
| **Environmental Radiation Exposures and Mortality** | | | | | |
| Techa River, Russia (Schonfeld et al., 2013) \* | 35b5 | 2,303c1 | 0.61 (0.04, 1.27) d | 0.53 (0.42, 0.64) | 1.15 (-0.01, 2.42) |
| Yangjiang China, HBRA d, e (Tao et al., 2012) \* | 63.2b1 | 941c5 | 0.19 (-1.87, 3.04) d | 0.49 (0.35, 0.63) | 0.39 (-4.80, 5.64) |
| **Radiation Studies with Incidence Data Only** | | | | | |
| Kerala India, HBRAf (Jayalekshmi et al., 2021) | 96.6b3 | 6,804c2 | -0.05 (-0.33, 0.29) d, m | 0.27 (0.18, 0.35) | -0.19 (-1.42, 1.01) |
| S Korea, diagnostic medical radiation workers (Lee et al., 2021) | 7.2b1 | 2,234c7 | 2.4 (-1.5, 6.4) | 0.79 (0.53, 1.05) | 3.04 (-2.01, 8.84) |
| China diagnostic x-ray workers (Sun et al., 2016) | 40.6b1 | 1,643c1 | 0.87 (0.48, 1.45) d | 0.67 (0.54, 0.80) | 1.29 (0.56, 2.12) |
| Taiwan, radiocontaminated dwellings (Hsieh et al., 2017) | 47.7b3 | 236c1 | 0.4 (0, 0.8) k | 0.94 (0.79, 1.10) | 0.42 (0.00, 0.87) |
| S Korea, NPP workers (Jeong et al., 2010) | 19.7b3 | 96c2 | 2.06 (-1.91, 9) d | 0.56 (0.34, 0.79) | 3.66 (-6.35, 15.02) |

*(continued on next page)*

Table 3. *(continued)*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study Identifiers a | Mean reported external dose (mGy) | No. of cancers | LDR Study Risk:  ERR Gy-1 (90% or 95% CI) a | Corresponding LSS Risk: ERR Gy-1 (90% or 95% CI) a | LDR/LSS: Risk ratio of this study to the LSS (90% or 95% CI) a |
| **Radiation Studies: Incidence Data Analyses (along with Mortality Data)** | | | | | |
| UK, NRRW nuclear workers (Hunter et al., 2022) | 25.3b3 | 18,310c1 | 0.2 (-0.001, 0.43) d | 0.36 (0.28, 0.44) | 0.56 (-0.04, 1.22) |
| Russia, Chornobyl clean-up workers (Kashcheev et al., 2015) | 132b2 | 4,002c1 | 0.47 (0.03, 0.96) | 0.32 (0.21, 0.43) | 1.45 (0.02, 3.26) |
| Russia, Techa River residents (Davis et al., 2015) | 52b5 | 1,933c1 | 0.77 (0.13, 1.5) d | 0.71 (0.60, 0.82) | 1.08 (0.12, 2.10) |
| Russia, Mayak nuclear workers (Hunter et al., 2013) | 510b1 | 1,447c4 | 0.07 (0.01, 0.15) | 0.45 (0.36, 0.54) | 0.16 (0, 0.33) |

\*Indicates studies included in the mortality meta-analyses. Certain reports in the table were not included in the meta-analyses to avoid including redundant data. All the incidence studies listed were included in the incidence meta-analyses. The three cohorts in the Dreger et al. (2020) report were treated as separate studies in the meta-analyses.

a The LDR study risks are quoted with the confidence interval given in the original publication (90% or 95% CI), and this level of confidence has been applied to the matching LSS risks and LDR/LSS risk ratios, where the latter were calculated with Fieller’s method (Fieller, 1954).

b Reported dose: b1Colon dose, b2Skin dose, b3Described as whole-body, dose equivalents or Hp(10) dose (mSv), b4‘Effective dose’, b5Stomach dose, b6Mean dose among only those with ‘positive recorded dose’, b7Heart dose (Colon dose was used for risk analysis, but mean was not reported).

c Reported cancer outcome: c1All solid cancers, c2All cancers except leukaemia, c3Excluding leukaemia and alcohol-related cancers (oropharynx, oesophagus and liver), c4Solid cancers except liver, lung, bone, c5All solid cancers except liver, c6Solid cancers except lung, c7Solid cancers except thyroid.

d 95% CI, as given in the original publication, otherwise 90% CI are reported.

e NPP, nuclear power plant; HBRA, high background radiation area

f However, after accounting for duration of exposure, the 35% with available smoking data yielded ERR Gy-1 estimates of 0.76 (90% CI -0.86, 2.71) and 1.78 (90% CI -0.04, 3.96) with and without adjustment for smoking, respectively.

g The first line gives the risk estimate for all Mayak workers; second line is for workers at Mayak plants with little potential for plutonium exposure (excluding workers at the plutonium-production and radiochemical plants).

h First value is for male cockpit crew, 2nd is for female cabin crew, and 3rd is for male cabin crew.

i The report provided relative risks (RRs) at 10 mSv; linearly extrapolated ERR (RR – 1) estimates at 1 Sv are given.

j Reported dose included tritium exposures also.

k Lower confidence bound not estimated in original paper. Estimated here by assuming arithmetic symmetry of the upper and lower bounds around the point estimate.

l When only a Cox regression hazard ratio was given the linearized results at 1 Gy (or Sv) are presented. For example, because hazard ratio estimates are centred at 1.0, a HR of 1.02 at 10 mGy (HR-1 excess = 0.02) would correspond to an ERR of 2.0 at 1 Gy by linear extrapolation.

m The included analysis adjusted for (a) education, bidi smoking, tobacco chewing and alcohol drinking, as well as (b) sex, attained age and follow-up period; when only the (b) variables were included in the model the ERR Gy-1 was 0.12 (95% CI -0.19, 0.48).

Table 4. Estimates of the Dose Rate Effectiveness Factor (DREF) with 95% CIs for All Solid Cancer from Meta-analyses of Low-Dose and Low-Dose-rate Studies a

|  |  |  |  |
| --- | --- | --- | --- |
| **Mortality Studies Only** | |  |  |
|  | All Mayak (N=24) b | Non-Pu Mayak c (N=24) | Mayak Excluded (N=23) |
| DREF | 1.99 (1.36, 3.71) | 1.37 (0.91, 2.73) | 0.82 (0.55, 1.63) |
| **Incidence Studies Only** | | |  |
|  | (N=9) |  | (N=8) |
| DREF | 1.73 (1.04, 5.06) d | -- | 1.40 (0.92, 2.95) e |
| **Combined Mortality and Nonredundant Incidence Studies** | | |  |
|  | (N=29) | (N=29) | (N=28) |
| DREF | 1.89 (1.37, 3.04) | 1.48 (1.06, 2.46) | 1.26 (0.89, 2.16) |
| **Studies with Mean Dose Under 100 mGy (excludes Mayak and Chornobyl cleanup worker studies)** | | | |
|  | Combined Mortality and Nonredundant Incidence Studies (N=27) | | Mortality Studies Only (N=22) |
| DREF | 1.30 (0.90, 2.28) | | 0.86 (0.56, 1.84) |

a Where the DREF is the inverse of the meta-analysis estimate of the LDR/LSS ratio.

b N is the number of studies included.

c ‘Non-Pu’ indicates the exclusion of the plutonium-processing and radiochemical facilities at Mayak in which workers had extensive plutonium exposures and high cumulative doses (Sokolnikov et al., 2017).

d Based on a random effects meta-analysis model because of statistically significant heterogeneity in the estimates of the LDRi/LSSi risk estimates.

# EPIDEMIOLOGICAL STUDIES – LOW-DOSE EFFECTS

## Introduction

1. The previous section discusses the use of epidemiological studies to deduce information on low-dose-rate effects to be used for DREF estimates. As an alternative, as discussed in Section 2, analysis of the shape of a dose response relationship might provide useful information as well. More specifically, comparison of the slope of the dose response at low doses with that over the entire dose range might be used for LDEF estimates.
2. In this section, evidence regarding the numerical value of LDEF is reviewed from an assessment of the available human data. Additionally, the most recent mortality data from the LSS available (Ozasa et al., 2012) were re-analysed with the aim to obtain updated information on curvature in dose response for a number of individual cancer sites. Finally, a similar approach as that used by UNSCEAR is applied, where radiation-related cancer risk at low doses was inferred from use of an LQ-model rather than from the use of a linear extrapolation from higher to lower doses plus application of a DDREF factor. It should be noted that dose and dose rate are highly correlated in the LSS. However, all survivors received most of their dose in the period of about 30 s or less, and so for all except the very lowest dose group (<5 mGy) survivors received their dose at high dose rate (Wakeford and Tawn, 2010). Therefore, analysis of LDEF in the LSS is effectively assessing curvature in the dose response at high dose rate.

## Scientific Evidence on Shape of Dose Response from Epidemiological studies

### Atomic Bomb Survivor Studies

1. For quite some time in the past, a linear relationship with dose described the shape of the dose response in the LSS rather well. This holds for all solid cancers combined, and for most individual cancer sites investigated (Little and Muirhead, 1996, 1998; Preston et al., 2007; UNSCEAR, 2008a; Ozasa et al., 2012), except for leukemia and non-melanoma skin cancer (Little and Charles, 1997; Ron et al., 1998; Preston et al., 2007). For example, the evidence for breast cancer, where there is reasonable power to study the risks at low doses, suggested that the data are most consistent with linearity (Preston et al., 2002). Earlier analyses indicated that when all solid cancers were analysed together, there was no evidence of significant departure from a linear dose-response in the latest LSS cancer incidence data, although there are suggestions of modest upward curvature in the latest LSS mortality data (Preston et al., 2007; Ozasa et al., 2012).
2. The study by Grant and co-workers represents the third solid cancer incidence report on the health effects among the Japanese atomic bomb survivors (Grant et al., 2017). The study was based on a follow-up time from 1958 to 2009 and included 105,44 individuals with 22,538 first primary solid cancer cases. When using a linear dose response model for all solid cancers combined, Grant and coworkers obtained a sex-averaged excess relative risk (ERR) per dose of 0.47 Gy-1 (95% CI 0.39. 0.55), which is consistent with what was reported in the second solid cancer incidence (Preston et al., 2007). When the evaluation was carried out separately for different sexes, significant differences were observed in the Grant et al. study: 0.33 Gy-1 (95% CI 0.25, 0.42) for males, and 0.60 Gy-1 (95% CI 0.49, 0.72) for females. Again, these results were not much different to the corresponding point estimates given in the Preston et al. report. However, when Grant et al. allowed for a linear-quadratic dose response model, significant curvature in the dose response curve was only observed for males. Grant et al. concluded that ‘*While these analyses revealed provocative results regarding the shape of the dose response, the most fundamental finding was that a single, acute whole-body exposure to ionizing radiation continued to increase solid cancer risks even after 50 years*.’, and further ‘*At this time, uncertainties in the shape of the dose response preclude definitive conclusions to confidently guide radiation protection policies.*’.
3. To analyse the findings described above further, Cologne and co-workers used the same data set and successively excluded individual or groups of cancer sites from all solid cancers, because of possible heterogeneity in the background rates of these sites (Cologne et al., 2019). Cologne et al. used two approaches: one in which they excluded certain cancer sites from analysis, another in which they jointly analysed all solid cancers combined but allowed for specific background parameters in the model for cancers with different background rates. Exclusion of individual cancer sites had little influence on the slope of the dose response when a linear model was used: For example, a linear ERR per Gy of 0.28 (CI 0.19, 0.38) was obtained for males when the five cancer sites most influential on the all-solid-cancer curvature parameter (i.e. brain/CNS, esophagus, bone/connective tissue, thyroid, and non-melanoma skin) were excluded. This result is close to the estimated linear ERR per Gy for males reported by Grant et al. for all solid cancers, 0.27 (95% CI 0.19, 0.37) (Grant et al., 2017). In contrast, in a linear-quadratic model the curvature decreased significantly for males when these cancer sites were excluded. Interestingly, curvature increased significantly when the three most influential cancer cites (i.e. breast, stomach, and thyroid) were excluded for females. Cologne et al. concluded that ‘*analysis based on all solid cancer as a single outcome is not the optimal method to assess radiation risk for solid cancer in the Life Span Study*’ and that ‘*joint analysis with suitable choices of cancer groups might be preferable by allowing for background-rate heterogeneity across sites while providing greater power to assess radiation risk than analyses of individual sites*’ (Cologne et al., 2019).
4. Walsh et al. noted that, although the results reported by Cologne et al. are important, they do not provide guidance on important aspects relevant for radiological protection including a) whether or not the linear-non-threshold model is justified, b) what the results mean in terms of DREF, c) how lifetime cancer risks after nuclear accidents should be deduced, d) and whether radiation risk effect modifiers such as sex need to be considered in radiological protection (Walsh and Schneider, 2020). They also noted that ‘*Only placing emphasis on results from outcomes of individual cancer types results in a substantial loss of power and diminished capabilities for inference*.’.
5. Along the lines set out by Cologne et al. (2019), results of a number of studies were published in which various cancer outcomes among the atomic bomb survivors were investigated separately. All these studies have in common that the data from the LSS follow-up from 1958 – 2009 on solid cancer incidence was used including 105,444 individuals for whom DS02R1 individual dose estimates were available. Cahoon et al. (2017) tested several dose-response models and found a significant linear lung cancer incidence in excess relative risk with weighted lung dose (where the neutron absorbed was multiplied by a factor of 10 to take into account increased relative biological effectiveness of neutrons as compared to gamma radiation, and then added to the gamma radiation absorbed dose). They assessed information on smoking status (never, past, current, unknown), average number of cigarettes per day, age started smoking, years smoked, and years since quitting. When fitting a model with linear and quadratic components in dose no evidence for non-linearity was found (Cahoon et al., 2017). Likewise, Brenner et al. did not find any departure from linearity in the dose response for the excess relative risk of breast cancer incidence (Brenner et al., 2018). In that study, factors such as age at menarche, number of full-term pregnancies, age at first full-term pregnancy, and age at menopause were taken into account. Utada et al. investigated the excess relative risk for uterine cancer among the cohort as a function of weighted uterus dose, taking into account factors such as number of full-term pregnancies, age at first pregnancy, age at menopause, body mass index, smoking habits, etc. They found a significant radiation-associated excess of uterus corpus cancer incidence without statistically significant departure from linearity. There was no significant radiation association for cervical cancer incidence (Utada et al., 2018). Colorectal cancer incidence was investigated by Sugiyama et al. (2020). Their analysis included data on smoking history, alcohol intake, meat consumption and body mass index. While they could not find any significant radiation effect for rectal cancer alone, they did find a significant linear dose response for total colon cancer incidence (including distal and proximal colon cancer), with no significant quadratic curvature (Sugiyama et al., 2020). Sadakane et al. (2019) analysed incidence of liver, biliary tract and pancreas cancer in the cohort, taking into account data on alcohol consumption, smoking and body mass index. They found a significant linear response for liver cancer as a function of weighted absorbed liver dose with no evidence for curvature. They did not find any radiation-induced effect for biliary tract cancer, but did find a non-significant increase for pancreatic cancer (Sadakane et al., 2019). Brenner et al (2020) assessed various types of central nervous system (CNS) tumours and found significant linear associations with radiation dose for glioma and meningioma, and borderline significant increase with increasing radiation dose for schwannoma. There were no statistically significant indications of quadratic curvature for any type of CNS tumour (Brenner et al., 2020). Prostate cancer incidence was analysed by Mabuchi et al. (2021). They found a significant linear dose response with no indications of non-linearity or of a statistically significant non-zero threshold.
6. French et al. analysed all solid cancer incidence using models fitted either to the proximal survivors, the proximal and distal survivors or both of these and the so-called not-in-city (NIC) group of survivors (French et al., 2017). The data was for the period 1958-2009, so identical to the analysis of Grant et al. (2017); the system of atomic bomb dosimetry used, DS02R1 was also identical to that of Grant et al. (2017). Fitting a linear-quadratic model, French et al. found similar effects of curvature in both proximal only, proximal+distal or proximal+distal+NIC groups. Unfortunately only p-values of the quadratic dose response curvature effect were given in the paper, so it is difficult to assess the quantitative impact of use of these groups for assessments of curvature. French et al. observed that models fitted using the NIC residents in the reference (zero dose) group yielded a relatively poor fit, unlike the other models fitted (French et al., 2017).
7. Brenner et al. (2022) analysed the mortality and incidence of all solid cancer in the Life Span Study (LSS) for the period 1958-2009 to compare the radiation dose-response shapes by sex, age at exposure and time since exposure, using similar methods and adjusting for smoking histories. They found consistent evidence of modest upward dose response curvature among males for both all cancer mortality and incidence. By contrast, upward curvature of a comparable magnitude among females was seen for all solid cancer mortality but not incidence. The sex difference in magnitude of dose response curvature was statistically significant for cancer incidence but not for cancer mortality. Dose response curvature was more evident in the more recent follow-up period and among survivors exposed to the atomic bomb during childhood (ages 0-19). The results of analyses in the 0-2 Gy range and restricted lower dose ranges generally supported inferences made about the sex-specific dose response shape over the entire range of doses for each outcome. Collectively, the findings strengthen evidence that the upward curvature in all solid cancer dose response in the LSS is neither specific to males nor to cancer incidence; its evidence appears to depend on the composition of sites comprising all solid cancer group and age at exposure or time since exposure. Of particular relevance to the present comparisons of the LDR and LSS risk estimates, the recent findings in the LSS that people exposed before age 20 exhibited significant departures from a linear dose-response for all solid cancer incidence and mortality, but no departures from linearity among those exposed in adulthood, should be noted.

### Recent Evidence of Radiation-Related Cancer Risk at or Below 100 mSv

1. Stewart et al. (1956) first identified excess cancer mortality among children who had received x-rays while in utero in a large case-control study in the UK, the so-called Oxford Survey of Childhood Cancers (OSCC). Although the findings of the study were initially highly controversial, the results contrasting with the absence of excess risk in the Japanese atomic bomb survivor in utero cohort. The reliance on interviews with mothers for obstetric exposure information was also regarded as a potential source of bias. The observance of similar excess risk in a slightly later cohort study in the US which did have medical record validation (MacMahon et al., 1962) suggested that the findings in the OSCC were probably not subject to bias. There has been considerable investigation of many other similar datasets, and the consensus seems to be that the risks observed in OSCC and these other studies likely represent a causal association (Doll and Wakeford, 1997; Wakeford and Little 2003), implying that maternal abdominal in utero exposure of 10-30 mGy is associated with cancer risk. The OSCC analysis has been recently updated (Wakeford and Bithell, 2021).
2. INWORKS has reported analysis of solid cancer mortality in a pooled analysis of nuclear workers in France, UK and USA. Significant trends were seen for all cancer with ERR Gy-1 = 0.53 (90% CI 0.30, 0.77), solid cancer with ERR Gy-1 = 0.52 (90% CI 0.27, 0.77) and solid cancer apart from lung cancer with ERR Gy-1 = 0.46 (90% CI 0.18, 0.76) (Richardson et al., 2023a). Analysis of solid tumours with dose range restricted to 0-200 mGy, 0-100 mGy and 0-50 mGy yielded significant excess risks, with ERR Gy-1 = 0.97 (90% CI 0.55, 1.39), 1.12 (90% CI 0.45, 1.80) and 1.38 (90% CI 0.20, 2.60), respectively, although for 0-20 mGy significance was lost. This analysis updates two other recent analyses of a slightly more limited follow-up in the INWORKS cohorts for solid cancer (Richardson et al., 2015), with site specific solid cancer analysis (Richardson et al., 2018).
3. Grant et al. analysed solid cancer incidence in the latest follow-up, over 1958-2009, in the LSS, using also slightly updated DS02R1 dosimetry (Grant et al., 2017). There was significant dose response over the full dose range as well as over the dose range 0-100 mGy, although not over any lower dose range (with upper limit of dose under 100 mGy). For males there was significant upward curvature (*p*=0.002) over the full dose range, but for females there was no such significant upward curvature (*p*=0.39). There was a significant difference (*p*=0.02) between the sexes in the dose response curvature parameter (ratio of quadratic to linear coefficient).
4. Lubin et al. performed a pooled analysis nine cohorts exposed in childhood with cumulative thyroid dose < 200 mGy (Lubin et al., 2017). They found significant dose response both over 0-200 mGy, with ERR Gy-1 = 11.1 (95% CI 56.6, 19.7) and 0-100 mGy, with ERR Gy-1 9.6 (95% CI 3.7, 17.0). There was no significant departure from linearity. This analysis was a subset of a larger pooling analysis of 12 childhood exposed cohorts (Veiga et al., 2016) without restriction of dose, which documented significant downward curvature in the dose response.
5. There have been a number of systematic reviews and meta-analysis of the low-dose data, in particular by Hauptmann et al. (2020), Little et al. (2022a,b). Hauptmann et al. analysed 26 studies with mean dose <100 mGy that appeared since the BEIR VII review, and found some evidence of excess risk for solid cancer, performing meta-analysis on the studies of adult solid cancer, yielding excess risk ERR Gy-1 = 0.29 (95% CI 0.11, 0.47) (Hauptmann et al., 2020). Little et al. (2022a,b) assessed groups exposed largely in childhood or *in utero* exposed to doses < 100 mGy and documented large excess risks of brain/CNS tumours, thyroid cancer (including nodules) and leukaemia.
6. A recent article summarized the epidemiological evidence of radiation-related cancer with emphasis on doses of low-LET ionising radiation of several tens and a few hundred mGy (or mSv). The article was not intended to be a systematic review, but discussed the results of major studies on radiation-exposed human cohorts including, among others, those discussed in the previous paragraphs. The authors concluded that there is ‘*growing evidence for doses below 100 mGy*’ that acute and protracted exposures to ionising radiation cause cancer (Rühm et al., 2022).

### Discussion of a Potential Threshold

1. There has been considerable scientific debate about the possibility of a threshold in dose below which no excess cancer risk is observed, or indeed for hormetic (beneficial) effects of low-dose radiation (Little et al., 2009; Tubiana et al., 2009; Doss et al., 2014). As noted above there is now accumulating epidemiological evidence of risk <100 mGy and even down to <20 mGy. As reviewed by Little et al. (2009) and Doss et al. (2014) there is also biological data suggesting excess risk at <100 mGy. Evidence for threshold effects has also been examined via model fitting using the LSS data. Little and Muirhead (1996, 1997, 1998, 2004) fitted linear-threshold and linear-quadratic-threshold models to the LSS incidence and mortality data (various solid cancer subtypes and leukemia), adjusting also for measurement error. There was no evidence of threshold departures from linearity or linear-quadratic curvature in the solid cancer data by subtype or overall; when using a linear-quadratic model, for the mortality data the central estimate of threshold is <0 Sv (95% CI <0, 0.15) (Little and Muirhead, 1998) while for cancer incidence the central estimate of threshold is 0.07 Sv (95% CI <0, 0.23) (Little and Muirhead, 2004). Pierce and Preston (2000) also fitted linear-threshold models to the LSS solid cancer incidence data, with an extra 7 years of follow-up, to the end of 1994, and estimated the threshold as 0 Sv (95% CI <0, 0.06); the somewhat tighter upper bound is perhaps because of the extra years of follow-up data and the use of a linear-threshold rather than a linear-quadratic-threshold model. There are certain technical difficulties associated with fitting of threshold model, since the asymptotic (*χ*2) distribution of the deviance difference statistic employed for significance tests is not guaranteed, because of lack of sufficient smoothness in the likelihood function (Schervish, 1995). However, this problem is circumvented by the likelihood-averaging techniques used (to account for the effects of dose error) by Little and Muirhead (1996, 1997, 1998, 2004).
2. Recently UNSCEAR has evaluated of the biological mechanisms relevant for low-dose and low-dose-rate radiation cancer risk inference (UNSCEAR, 2022c). They concluded that good justification remained for the use of a non-threshold model for risk inference given the robust knowledge on the role of mutation and chromosomal aberrations in carcinogenesis.

## Analysis of Curvature in LSS Mortality Data

### Rationale

1. In their analyses of the LSS mortality data, Ozasa et al. (2012) used colon absorbed dose for all solid cancers and for the remainder category (all solid cancers excluding breast, colon, lung, stomach). In contrast, for organ-specific analyses, the appropriate organ dose was used. Further, neutron absorbed dose was multiplied by a factor of 10, to account for an increased relative biological effectiveness of neutrons as compared to gamma radiation, and added to the gamma absorbed dose to calculate weighted organ dose. All doses were calculated using the DS02 dosimetry (Young and Kerr, 2005). A similar analysis was done here, with emphasis on assessment of curvature by cancer site and sex, also to assess the effects of restricting the dose range. This is motivated by the later analysis of the LSS incidence data of Grant et al. (2017), which found evidence of upward curvature in the solid cancer dose response for males but not for females.

### Methods

1. Because individual data were not available, all analyses used the publicly available stratified data. The stratification employed is very similar to that used by Ozasa et al. (2012), and is defined by time since exposure, age at exposure, attained age, city, sex, ground distance category, and (measurement-error adjusted) dose. Poisson disease models were used. The models that were used in this report were functions of the mean weighted organ dose, , averaged over the survivors in the stratum. A generalized relative risk model was used for solid cancers, where the expected number of cancer deaths in stratum with city , sex, , attained age, , age at exposure, , other stratifying variables, (ground distance category, Adult Health Study status, calendar time) and DS02 average weighted organ dose, , is (Eq. 5):

(5)

and where is the number of person years of follow-up in the stratum.

1. The background cancer death rate was assumed to be constant over each stratum defined by groups of city, sex, categorized attained age and categorized age at exposure, but was not otherwise parametrically specified. All doses are adjusted (via regression calibration (Carroll et al., 2006)) for dose error; the quadratic term in the dose response was additionally corrected (by multiplying by 1.12) to correct for the quadratic calibration approximation (specifically the discrepancy between and ). The model parameters were estimated using Poisson maximum-likelihood techniques (McCullagh and Nelder, 1989). In particular, the background cancer rate parameters were estimated in this way, which is equivalent to the fitting of a conditional binomial model, conditioning on the numbers of cancer deaths in each stratum defined by city, sex, categorized attained age and categorized age at exposure. Here we only use the linear-quadratic model (in which , are allowed to vary and is set to 0).

### Results

1. As can be seen from Table 5, there are generally only modest indications of curvature for any endpoint for the full dose range. For three endpoints (all solid cancer, colon cancer, stomach cancer) there are generally statistically non-significant (*p*>0.05) indications of upward curvature; these are strongest for colon cancer, for which the upward curvature is statistically significant (*p*<0.05), but there are also numerical instabilities in these non-linear dose-response fits, so that little weight should be attached to these. For the other solid cancer endpoints (female breast, liver, lung) there are statistically non-significant (*p*>0.05) indications of downward curvature in dose response.

Table 5. Fit of linear-quadratic model to Japanese LSS solid cancer mortality data of Ozasa et al*.* (2012), full dose range.

|  |  |  |  |
| --- | --- | --- | --- |
| Cancer type | Linear-quadratic model ERR Gy-1 (+95% CI) | | p-value (linear-quadratic vs linear) |
| Linear term | Quadratic/linear term |
| All solid | 0.233 (0.121, 0.380) | 0.105 (-0.087, 0.544) | 0.362 |
| Female breast | 1.155 (0.355, 2.425) | -0.102 (-0.256a, 0.200) | 0.330 |
| Colon | 0.055 (-0.254a, 0.364a) | 1.787 (-10.536a, 14.107a) | 0.024 |
| Liver | 0.380 (-0.066a, 0.987) | -0.093 (-0.462a, 0.275a) | 0.721 |
| Lung | 0.474 (0.155, 0.941) | -0.099 (-0.312, 0.376) | 0.480 |
| Stomach | 0.121 (-0.064a, 0.374) | 0.081 (-0.223a, 3.957) | 0.749 |

a Wald-based CI.

1. As depicted in Table 6 there are much stronger indications of upward curvature, for most endpoints over the 0-2 Gy dose range. However, only for all solid cancer there are statistically significant (*p*≤0.05) indications of upward curvature, and only for stomach cancer is there a (statistically non-significant (*p*>0.4)) indication of downward curvature in dose response. These results already suggest some dependence of the outcome on the dose range chosen for the analysis, due to the variability in the data which becomes obvious in the categorical presentation of the ERR values for solid cancer mortality (Ozasa et al., 2012). This will also affect LDEF estimates that are based on analyses of the dose response relationship.

Table 6. Fit of linear-quadratic model to Japanese LSS solid cancer mortality data of Ozasa et al*.* (2012), respective organ dose range < 2 Gy. Confidence intervals are based on the profile likelihood unless otherwise indicated.

|  |  |  |  |
| --- | --- | --- | --- |
| Cancer type | Linear-quadratic model ERR Gy-1 (+95% CI) | | p-value (linear-quadratic vs linear) |
| Linear term | Quadratic/linear term |
| All solid | 0.159 (0.025, 0.332) | 0.809 (0.080, 8.571) | 0.017 |
| Female breast | 0.584 (-0.285, 2.150) | 0.760 (-0.220, 3.040a) | 0.261 |
| Colon | 0.009 (-0.083a, 0.100a) | 2.594 (-28.705a, 33.893a) | 0.237 |
| Liver | 0.067 (-0.519a, 0.825) | 4.109 (-37.580a, 0.736) | 0.246 |
| Lung | 0.324 (-0.034, 0.829) | 0.330 (-0.242, 1.553a) | 0.430 |
| Stomach | 0.207 (-0.115a, 0.614) | -0.251 (-0.684a, 3.027) | 0.483 |

a Wald-based CI.

1. There is evidence in the LSS14 mortality data (Ozasa et al., 2012) of somewhat stronger curvature for males than for females, particularly for solid cancer in the dose range 0-2 Gy (*p*=0.027 for male curvature, *p*=0.176 for female curvature), although for colon cancer there is evidence of upward curvature for both sexes over the full dose range (*p*<0.05 for males and females) (Table 7). Nevertheless, even if not statistically significant over the 0-2 Gy dose range there is generally consistent upward curvature for most cancer endpoints and for both sexes, the only exception being female stomach cancer (Table 7).

Table 7. Solid cancer mortality risks fitted using linear-quadratic model by cancer site and dose range (using appropriate organ dose), fitted to LSS14 data of Ozasa et al. (2012). Using semi-parametric background model (with strata defined by age at exposure, attained age, city, sex). Unless otherwise specified profile confidence intervals are used.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Endpoint | Organ dose used | 0-2 Gy organ dose | | |  | | Unlimited (0-4 Gy) | | |
| linear coefficient  (Gy-1) | quadratic coefficient  (Gy-2) | *p*-valuea | |  | linear coefficient  (Gy-1) | quadratic coefficient  (Gy-2) | *p*-valuea |
| All solid cancer males | Colon | 0.032 (-0.265, 0.342) | 0.287 (0.033, 0.548) | 0.027 | |  | 0.267 (0.036, 0.508) | 0.028 (-0.107, 0.168) | 0.687 |
| All solid cancer females | Colon | 0.416 (0.086, 0.761) | 0.206 (-0.091, 0.510) | 0.176 | |  | 0.481 (0.214, 0.758) | 0.130 (-0.045, 0.311) | 0.147 |
| Colon cancer males | Colon | -0.442 (-1.569, 0.924) | 0.564 (-0.447, 1.688) | 0.283 | |  | -0.552 (-1.430, 0.525) | 0.671 (0.057, 1.363) | 0.032 |
| Colon cancer females | Colon | -0.661 (-1.773, 0.673) | 0.790 (-0.382, 2.011) | 0.186 | |  | -0.905 (-1.754, 0.085) | 1.084 (0.390, 1.879) | 0.002 |
| Liver cancer males | Liver | 0.141 (-0.586, 0.948) | 0.277 (-0.352, 0.933) | 0.393 | |  | 0.590 (0.057, 1.134b) | -0.163 (-0.418b, 0.133) | 0.271 |
| Liver cancer females | Liver | 0.117 (-0.696, 1.041) | 0.228 (-0.501, 1.021) | 0.548 | |  | 0.247 (-0.415, 0.997) | 0.133 (-0.267b, 0.581) | 0.532 |
| Lung cancer males | Lung | 0.180 (-0.518, 0.956) | 0.232 (-0.351, 0.838) | 0.440 | |  | 0.511 (0.000, 1.076) | -0.079 (-0.328b, 0.198) | 0.564 |
| Lung cancer females | Lung | 0.965 (-0.043, 2.127) | 0.191 (-0.674, 1.081) | 0.668 | |  | 1.261 (0.439, 2.187) | -0.116 (-0.565b, 0.376) | 0.632 |
| Stomach cancer males | Stomach | -0.087 (-0.565, 0.421) | 0.238 (-0.158, 0.662) | 0.245 | |  | 0.095 (-0.243, 0.459) | 0.020 (-0.156, 0.215) | 0.828 |
| Stomach cancer females | Stomach | 0.553 (-0.066, 1.229) | -0.124 (-0.659, 0.432) | 0.656 | |  | 0.305 (-0.151, 0.801) | 0.137 (-0.132, 0.433) | 0.329 |

a *p*-value of improvement in fit of linear-quadratic vs linear model

b Wald-based CI

## Update of UNSCEAR Approach where a DDREF is not used

### Methods

1. A similar approach as that used in the UNSCEAR report (UNSCEAR, 2008a; Little et al., 2008b) was applied recently (Little et al., 2020) to the most recent LSS mortality data (Ozasa et al., 2012). For most calculations solid cancer mortality risk (radiation-exposure induced deaths) was evaluated for a current UK population (Little et al., 2020). In the analyses described below, differences from the UNSCEAR approach are that in the new analyses a) risks were not only derived for solid cancer and leukaemia but also for additional individual cancer sites (i.e. lung, stomach, female breast cancer, all other solid cancers), b) LSS follow-up was extended from 2000 to 2003, and c) improved dose estimates for the atomic bomb survivors were based on DS02R1, similar to the dose estimates used in the cancer incidence analysis of (Grant et al., 2017). Furthermore, the new analyses used simpler ERR and EAR risk models than were used before involving linear-quadratic (rather than linear-quadratic-exponential) functions and allowing for effect modifiers of sex, age at exposure, and time since exposure, and using two different formulations of ERR and EAR risk modification, one which is identical to that used by Ozasa et al. (2012). As in the earlier papers, Bayesian Markov Chain Monte Carlo (MCMC) techniques were used to adjust for dose errors and their distributions, because such errors can have a significant influence on the shape of the dose-response relationship, and other uncertainties (NCRP, 2024). However, regression-calibration methods (Carroll et al., 2006) were also used, somewhat similar to those previously employed (UNSCEAR, 2008a; Little et al., 2008b). The standard measure of radiation exposure induced death (REID) is used, and further details are given by Little et al. (2008b), as also in UNSCEAR (2008a). REID is given by:

(6)

where is the death rate from cancer type at age for sex , is the all cause mortality rate and is the probability of a person of sex surviving to age given that they have survived to age (). This risk measure was employed by ICRP (2007) and by UNSCEAR (2008a). Risks were evaluated using baseline cancer mortality and overall mortality rates for a number of current world populations (UK (2017), France (2014), USA (2015), Russia (2013), Japan (2015), China (2000)). However, for the results given below we shall concentrate on risks evaluated using UK rates. IN all cases we evaluate REID to age 120, above which point the population in truncated.

1. For all endpoints a burn-in of half the total Monte Carlo samples were used; for most endpoints a total of 50,000 Monte Carlo samples were taken, with the exception of lung cancer (75,000 for the relative rate model) and breast cancer (150,000 for the relative rate model). The dose used is (a) weighted colon dose for all solid cancer and all solid cancers apart from lung, stomach and breast, (b) weighted lung dose for lung cancers, (c) weighted stomach dose for stomach cancer, and (d) weighted breast dose for breast cancer.

### Results

1. For example, for a UK population the solid cancer mortality risk (radiation-exposure induced deaths) at a test dose of 0.01 Gy was 3.57 per Gy × 100 (95% Bayesian credible interval (BCI) 0.70, 6.81), at a test dose of 0.1 Gy it was 3.88 per Gy × 100 (95% BCI 1.17, 6.97), and at a test dose of 1 Gy it was 6.59 per Gy × 100 (95% BCI 4.82, 8.46). These results are given in terms of colon weighted dose, and analysis was restricted to doses of less than or equal to 3 Gy (see Table 8). The results correspond, in the relative risk model, to a ratio of the quadratic to linear coefficient in a linear-quadratic dose response curve (*β/α*) of 1.04 (95% BCI 0.17, 6.14) Gy-1 implying a significant curvature for solid cancer versus weighted colon dose. Interestingly, for lung cancer, stomach cancer and female breast cancer no significant curvature was found, consistent with recent studies on cancer incidence among the atomic bomb survivor cohort (Cahoon et al., 2017; Brenner et al., 2018). The curvature was entirely concentrated in the remainder category of all solid cancers excluding lung, stomach and breast cancer. When weighted colon dose was restricted to less than or equal to 2 Gy, the curvature observed among solid cancer mortality remained, although it was much reduced if a dose range of 0-4 Gy was used (over which range there is appreciable downward curvature in the dose response at higher doses) - REID risks per unit dose were only elevated by ~10% at 1 Gy compared with 0.1 Gy, rather than the ~70% increase observed over the 0-3 Gy range (see Table 9). In general, the results obtained by Little et al. (2020) are broadly consistent with those reported earlier in UNSCEAR (2008a), Little et al. (2008b), which used models fitted over the 0-4 Gy range. For example, for a test dose of 0.1 Gy and solid cancer, the above results compare to those reported by UNSCEAR of 5.45 per Gy × 100 (3.06 – 7.99), and for a test dose of 1 Gy of 6.66 per Gy × 100 (5.29 – 8.09) (UNSCEAR, 2008a). The authors concluded that there was ‘*quite substantial dose-response curvature for most endpoints, in particular solid cancer …*’ and suggested that their results implied ‘*that the LDEF for cancer may be about 2*’ (Little et al., 2020).

Table 8. Population mortality risks (using 2017 mortality rates for England and Wales) predicted by optimal excess relative and excess absolute rate models, unadjusted weighted colon dose ≤ 3 Gy. (Reproduced from Little et al. (2020))

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Cancer mortality endpoint | Model | Test dose (Gy) | Radiation exposure-induced deaths / Gy (× 102) (95% BCI) | Years life lost / Gy (95% BCI) |
| All solid cancer | Relative rate | 0.01 | 3.57 (0.70, 6.81) | 0.50 (0.10, 0.94) |
| 0.1 | 3.88 (1.17, 6.97) | 0.55 (0.17, 0.96) |
| 1 | 6.59 (4.82, 8.46) | 0.96 (0.76, 1.18) |
| Absolute rate | 0.01 | 3.11 (-0.13, 6.51) | 0.43 (-0.02, 0.87) |
| 0.1 | 3.56 (0.54, 6.78) | 0.49 (0.08, 0.91) |
| 1 | 7.51 (5.61, 9.50) | 1.08 (0.85, 1.32) |
| Lung cancer | Relative rate | 0.01 | 2.57 (0.40, 5.09) | 0.32 (0.05, 0.62) |
| 0.1 | 2.61 (0.55, 5.02) | 0.33 (0.07, 0.61) |
| 1 | 2.99 (1.66, 4.53) | 0.38 (0.23, 0.55) |
| Absolute rate | 0.01 | 1.58 (-0.36, 4.07) | 0.15 (-0.04, 0.36) |
| 0.1 | 1.65 (-0.17, 4.03) | 0.16 (-0.02, 0.36) |
| 1 | 2.25 (0.86, 4.14) | 0.22 (0.09, 0.37) |
| Stomach cancer | Relative rate | 0.01 | 0.09 (-0.02, 0.26) | 0.01 (0.00, 0.03) |
| 0.1 | 0.09 (-0.01, 0.26) | 0.01 (0.00, 0.03) |
| 1 | 0.11 (0.03, 0.26) | 0.01 (0.01, 0.03) |
| Absolute rate | 0.01 | 0.54 (-0.33, 1.47) | 0.09 (-0.05, 0.23) |
| 0.1 | 0.58 (-0.23, 1.45) | 0.10 (-0.04, 0.23) |
| 1 | 0.90 (0.38, 1.58) | 0.15 (0.07, 0.24) |
| Breast cancer | Relative rate | 0.01 | 2.03 (0.49, 4.94) | 0.31 (0.09, 0.62) |
| 0.1 | 2.01 (0.53, 4.80) | 0.31 (0.10, 0.61) |
| 1 | 1.87 (0.72, 3.82) | 0.30 (0.16, 0.50) |
| Absolute rate | 0.01 | 0.91 (0.30, 1.76) | 0.14 (0.05, 0.24) |
| 0.1 | 0.90 (0.32, 1.73) | 0.14 (0.06, 0.23) |
| 1 | 0.87 (0.46, 1.50) | 0.14 (0.09, 0.20) |
| All solid cancer excluding lung, stomach, breast | Relative rate | 0.01 | 0.22 (-1.56, 2.23) | 0.03 (-0.25, 0.34) |
| 0.1 | 0.48 (-1.17, 2.38) | 0.08 (-0.19, 0.36) |
| 1 | 2.93 (1.76, 4.38) | 0.48 (0.32, 0.64) |
| Absolute rate | 0.01 | -0.52 (-2.75, 1.94) | -0.08 (-0.39, 0.27) |
| 0.1 | -0.13 (-2.21, 2.21) | -0.02 (-0.32, 0.30) |
| 1 | 3.57 (2.15, 5.22) | 0.53 (0.36, 0.71) |

1. A recent report assessed low dose extrapolation factors (LDEF) via fitting relative rate models that are linear or linear-quadratic in dose to the latest Japanese atomic bomb survivor solid cancer, leukemia and circulatory disease mortality data (followed from 1950 through 2003), also incidence data relating to solid cancer incidence over the period 1958-2009, using regression calibration techniques to adjust for errors in the latest Dosimetry System 2002 Revision 1 (DS02 or DS02R1) dose estimates (Little and Hamada, 2022). This study used the same underlying data as various previous analyses (Ozasa et al., 2012; Cahoon et al., 2017; Grant et al., 2017, 2021). These analyses should be contrasted with those of the earlier paper (Little et al., 2020a) which did not explicitly assess LDEF. There was modest evidence for upward curvature in dose response in the mortality data (Little and Hamada, 2022). For leukemia and for all solid cancer excluding lung, stomach and breast cancer there was significant curvature (*p*<0.05). The estimate of LDEF for all solid cancer was 1.273 (95% CI 0.913, 2.182), for all solid cancer excluding lung cancer, stomach cancer and breast cancer was 2.183 (95% CI 1.090, >100) and for leukaemia was 11.447 (95% CI 2.390, >100). For stomach cancer LDEF was modestly raised, 1.077 (95% CI 0.526, >100), while for lung cancer and female breast cancer the LDEF did not exceed 1. LDEF for solid cancer incidence was 1.186 (95% CI 0.942, 1.626) and for urinary tract cancer was 1.298 (95% CI <0, 7.723), although for lung cancer LDEF was not elevated, 0.842 (95% CI 0.344, >100) (Little and Hamada, 2022).
2. Comparison of the findings of Little and Hamada (2022) with those of Brenner et al. (2022) suggested that LDEFs were generally compatible, although tending to be higher in the analysis of Brenner et al. (2022). The derived LDEFs from Brenner et al. (2022) are generally above 1, and for the mortality data and male incidence data above 2, irrespective of whether the full dose range (0-4 Gy) or the restricted dose range (0-2 Gy) are employed; however, for the female incidence data the LDEF is lower, in the range 1.1-1.4. It is perhaps noteworthy that the estimates of LDEF are somewhat higher when the lower dose range (0-2 Gy) is used, both for incidence and mortality. This is consistent with what was observed by Little et al. (2020), and probably reflects a turnover in the dose response above 3 Gy. It was for this reason that Little et al. (2020) decided for most analyses to use 0-3 Gy data, as also in the analysis of Little and Hamada (2022). The curvature that can be seen in the higher dose groups may reflect dose errors, which could be more substantial in these groups of survivors. It may also reflect the effect of selection, since these higher doses are close to the human mean lethal dose (LD50) for acute gamma radiation doses, thought to be 3-5 Gy for healthy adults (Mole, 1984).
3. There are uncertainties associated with the dose response at low doses in the LSS. Ozasa et al. (2012) noted that the ‘*estimated ERRs under 0.3 Gy were nominally higher than the best-fitting linear slope or the LQ function for either 0–2 Gy or the full dose range*’ and they further observed that ‘*it was particularly notable that the ERR/Gy estimates for linear functions calculated for various low-dose ranges showed higher values for ranges less than 0.1 Gy compared to estimates obtained from higher dose ranges*’. However, these findings of higher ERRs and ERR Gy-1 were not observed in the later analysis for mortality and incidence in different periods and models, but the tendency of relatively low ERRs around 0.3-0.7 Gy still remained (Brenner et al., 2022). Ozasa et al. discussed about the latter finding to be ‘*The apparent upward curvature appears to be related to relatively lower than expected risks in the dose range 0.3 – 0.7 Gy, a finding without a current explanation.*’ and this question is still unsolved.

Table 9. Population mortality risks (using 2017 mortality rates for England and Wales) for all solid cancer predicted by optimal excess relative rate models, unadjusted+untruncated weighted colon dose ≤ 2 Gy, ≤ 3 Gy or ≤ 4 Gy, both sexes.a (Reproduced from Little et al. (2020))

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Unadjusted, untruncated colon dose limit used for analysis | Test dose (Gy) | Excess deaths / Gy (× 102) (95% BCI) | Radiation exposure-induced deaths / Gy (× 102) (95% BCI) | Years life lost / Gy (95% BCI) | Years life lost / radiation induced death (years) (95% BCI) |
| ≤ 2 Gy | 0.01 | 2.62 (-0.19, 5.68) | 3.17 (-0.24, 6.85) | 0.44 (-0.04, 0.93) | 14.18 (12.34, 16.23) |
| 0.1 | 2.95 (0.33, 5.82) | 3.57 (0.41, 7.01) | 0.50 (0.06, 0.95) | 14.20 (12.37, 16.24) |
| 1 | 5.80 (4.13, 7.68) | 7.03 (5.03, 9.28) | 1.02 (0.79, 1.27) | 14.67 (12.97, 16.62) |
| ≤ 3 Gy | 0.01 | 2.95 (0.58, 5.66) | 3.57 (0.70, 6.81) | 0.50 (0.10, 0.94) | 14.25 (12.63, 16.15) |
| 0.1 | 3.21 (0.97, 5.79) | 3.88 (1.17, 6.97) | 0.55 (0.17, 0.96) | 14.28 (12.66, 16.16) |
| 1 | 5.44 (3.96, 7.01) | 6.59 (4.82, 8.46) | 0.96 (0.76, 1.18) | 14.69 (13.18, 16.51) |
| ≤ 4 Gy | 0.01 | 5.08 (2.63, 7.90) | 6.14 (3.19, 9.52) | 0.86 (0.46, 1.28) | 14.07 (12.48, 15.92) |
| 0.1 | 5.13 (2.82, 7.79) | 6.20 (3.41, 9.40) | 0.87 (0.50, 1.26) | 14.10 (12.53, 15.94) |
| 1 | 5.54 (4.07, 7.15) | 6.72 (4.96, 8.64) | 0.97 (0.77, 1.19) | * 1. (13.04, 16.30) |

aA burn-in of half the total 50,000 Monte Carlo samples was used. The dose used is weighted colon dose.

## Conclusions

1. A number of recent studies including those performed by the Task Group have re-analysed the curvature in the data obtained from the LSS atomic bomb survivor data. The most recent LSS mortality and incidence analyses (Brenner et al., 2022) seem to show a tendency of upward curvature with some limitations discussed before.
2. Until quite recently, published studies have concluded that a linear relationship between risk and dose described the shape of the dose response in the LSS rather well. This conclusion held for all solid cancers combined, and for most individual cancer sites investigated (Little and Muirhead, 1996, 1998; Preston et al., 2007; UNSCEAR, 2008a; Ozasa et al., 2012), except for leukemia and non-melanoma skin cancer (Little and Charles, 1997; Ron et al., 1998; Preston et al., 2007). For example, the evidence for breast cancer, where there is reasonable power to study the risks at low doses, suggested that the data are most consistent with linearity (Preston et al., 2002).When all solid cancers were analysed together, there was no evidence of significant departure from a linear dose-response in the latest LSS cancer incidence data, although there is evidence of modest upward curvature in slightly more recent LSS mortality data (with follow-up to 2003 rather than 1998) (Preston et al., 2007; Ozasa et al., 2012).
3. A recent analysis of the LSS incidence data from atomic bomb survivors also found significant upward curvature, but strikingly only for males and not for females (Grant et al., 2017). This particular observation was further investigated by Cologne and co-workers (Cologne et al., 2019) who demonstrated that at least part of the observed curvature in solid cancer data could be explained due to heterogeneity in individual cancer background rates. Finally, the latest mortality and incidence data showed a tendency of upward curvature in some conditions (Brenner et al. 2022).
4. In this report the importance of studies to evaluate curvature among atomic bomb survivor mortality and incidence depending on cancer site is acknowledged. However, the indication of curvature and/or linearity reported in some of the studies on mortality and incidence dose response for males and females among atomic bomb survivors should still be interpreted with care (Cologne et al., 2020). The Task Group concludes that at present there is some evidence for non-linearity in the atomic bomb survivor data. In particular, the current scientific evidence on curvature in the data from the Japanese atomic bomb survivors may support an LDEF value of between 1 and 2 for all solid cancers combined, with some indication on variation between different cancer sites.

# STUDIES USING BIOLOGICALLY-MOTIVATED MECHANISTIC MODELS

## Introduction

1. As described in previous sections, epidemiological studies, although valuable in providing risk estimates after exposure to doses above about 50 mGy, provide less certain information on health risks for doses much below 50 mGy (Richardson et al., 2015; Lubin et al., 2017; Little et al., 2018b; Hauptmann et al., 2020; Little et al., 2022a,b; Richardson et al., 2023a). However, there are indications of excess leukaemia risk below 20 mGy in a pooled analysis of persons exposed in childhood (Little et al., 2018b) and excess solid cancer risk below 50 mGy in the INWORKS nuclear workers cohort (Richardson et al., 2023a).
2. It has been argued that the use of biologically-based mechanistic models that incorporate knowledge on the process of carcinogenesis along with appropriate quantitative data, could be used ‘*… for the important problem of low dosage extrapolation of risk due to a carcinogen, and synergy between two or more carcinogens, …*’ (Moolgavkar and Venzon, 1979), and that they might provide further insight on the shape of dose response curves at low doses obtained from epidemiological studies (e.g. (Boice, 2015; Preston, 2015)). This section reviews the potential of biologically-motivated mechanistic models to enhance the interpretation of epidemiological studies in terms of radiation-related cancer risk, in particular at low doses.
3. In the 1950s Nordling had postulated six or seven mutational cellular changes to be necessary for the development of cancer among humans (Nordling, 1953). This idea prompted Armitage and Doll to develop a mathematical formalism which they successfully applied to describe the observed cancer mortality among the population of England and Wales in 1950 and 1951 (Armitage and Doll, 1954).
4. In the following year, Platt proposed as an additional feature that a mutation in a healthy cell might result in faster divisions of the changed cells from which later malignant cells might develop (Platt, 1955). Based on this hypothesis, Armitage and Doll developed a two-stage model of carcinogenesis which included only two mutational steps and in which ‘… *the first stage is the production of a change of the type suggested by (Platt, 1955), that the faster rate of multiplication confers a selective advantage on the changed cells, such that the size of the affected clone relative to other normal clones continuously increases and that the appearance of clinical cancer follows the occurrence of a second, discrete event which constitutes the second stage*’ (Armitage and Doll, 1957). Those and other developments were supported for example by the observation that the occurrence of retinoblastoma in children could be explained by postulating two mutational events (Knudson, 1971).
5. A systematic study on the theoretical properties of models involving two mutational events was then performed by Moolgavkar and Venzon (1979). They assumed the first mutation to transform a healthy cell into an intermediate cell which is able to form a clone of intermediate cells. A second mutation then transforms an intermediate cell into a malignant cell which later might result in a malignant tumour. In the investigated models, healthy and intermediate cells were allowed to proliferate and differentiate.
6. These and many other studies led to what is nowadays called the Two-Stage Clonal Expansion (TSCE) model, a model that has been widely used to describe data from various epidemiological cohorts. In the TSCE model a pool of healthy (stem) cells, if exposed to ionising radiation, sustains mutational events forming so-called intermediate cells. This process which is often called ‘initiation’ is assumed to occur with rate *ν*. Compared to healthy cells these intermediate cells might show a proliferation advantage such that they are able to give rise to clones of intermediate cells. The net expansion rate *γ* of such clones is governed by the interplay of division of intermediate cells in the clone (with rate *α*), differentiation or inactivation of intermediate cells (with rate *β*), and loss of intermediate cells in the clone through a second possibly radiation-induced mutational step (with rate *µ*). A positive value of *γ* leads to a process called ‘clonal expansion’ or ‘promotion’. The rate *µ* describes the ‘transformation’ of an intermediate cell to a malignant cell which is assumed, after a certain lag time, to give rise to a malignant tumour that is either clinically diagnosed (incidence) or identified after death (mortality).
7. More recently, the simple TSCE model was developed further and more sophisticated models were developed, to study the influence of biological phenomena such as genomic instability on tumour development (Little and Wright, 2003; Little and Li, 2007; Little et al., 2008a; Eidemüller et al., 2015), or to account for a more detailed knowledge on development of certain solid cancers if available (Kaiser et al., 2014).
8. Generally, the performance of biologically-based mechanistic models such as the TSCE model to describe epidemiological data depends on the availability of the required biological parameters (rates of various processes involved such as mutation rates, cell division rates, etc.). Although knowledge on the biological processes involved in carcinogenesis is growing fast, this knowledge as in most cases is too limited to allow for a complete description of human carcinogenesis. As a consequence, when these models are used to describe the development of radiation risk as a function of time using epidemiological data, the remaining unknown parameters often serve as fit parameters. Consequently, it is often argued that if the numerical values of those parameters resulting from the fitting procedure of epidemiological data are biologically plausible, then the model was able to describe the data and could be useful for extrapolating to lower doses and dose rates (Rühm et al., 2017).
9. In the following paragraphs, studies are reviewed in which biologically-based mechanistic models such as the TSCE model or more sophisticated models were applied to human epidemiological cohorts that were exposed to ionising radiation. Emphasis is placed on exposure to low-LET radiation and high-LET radiation, to demonstrate the capabilities of such models. For the same reason, applications of those models to animal data are also summarized. A more detailed review on the application of these models to human data including high-LET exposure (due to incorporation of radon and radon progeny, plutonium, thorotrast, and radium) was recently published (Rühm et al., 2017) and the role of these models in the prediction of low-dose radiation effects was discussed in (NCRP, 2020). In all cases – it should be remembered that none of these models manages to apprehend all of the tissue level and whole organism level events (e.g. behaviour of the immune system, stress induced cell to cell communication, etc.) that support cancer development.

## Human Cohorts

### Atomic Bomb Survivors

1. Among the radiation-exposed human cohorts, the atomic bomb survivors in Japan were most extensively studied. Little (1996) used a generalised biologically-based mechanistic model including an arbitrary number of mutational steps to describe sex-specific total solid cancer mortality from the 1950 – 1985 follow-up. For solid cancers colon dose was used. For solid cancers they found that models with two or three mutations described the data similarly well.
2. Kai and coworkers used data on solid cancer incidence from the 1958 – 1987 follow-up of the atomic bomb survivors. They used the TSCE model and analysed stomach, colon, and lung cancer separately for males and females. With regard to the present report, the authors state that although they did not perform a systematic analysis of the shape of dose response curve, at least for the range of doses considered ‘… *the dose-response relationship appears to be consistent with linearity down to the lowest doses*’ (Kai et al., 1997).
3. In a similar approach, Heidenreich and coworkers used the TSCE-model and analysed incidence data from the atomic bomb survivors (follow-up 1958 – 1987) on all solid tumours. They found that the quality of fit using the applied mechanistic models was similar to that obtained when conventional age-attained and age-at-exposure models were used (Heidenreich et al., 1997).
4. Using the same data set (incidence data for all solid tumours among the atomic bomb survivors, follow up 1958 – 1987) and data restrictions, Heidenreich and co-workers applied several multi-stage models and analysed the occurrence of stomach, lung and colon tumours, as well as that of a combination of various cancer sites, as a function of age. The authors conclude that in general the models investigated ‘*describe cancer incidence among the A-bomb survivors equally well*’ (Heidenreich et al., 2002).
5. A detailed analysis of a longer follow-up of atomic bomb survivor incidence data on solid tumours (1958 – 1998) revealed that low-LET ionising radiation might not only act on initiation but also on promotion. Such an analysis was possible because radiation action on initiation and on promotion can result in different age and time patterns of resulting radiation risk. The authors report a somewhat higher evidence for radiation action on promotion than on initiation. In particular, the results suggest an almost linear action of radiation on initiation, and a supra-linear action of radiation on the net clonal expansion rate γ (Heidenreich et al., 2007).
6. Jacob and coworkers used the mortality data of the 1950 – 1997 (for stomach and liver cancer) and 1950-2000 (for all solid cancers combined) follow-up periods (Jacob et al., 2008). In this study, the TSCE model was used with the specific feature that cell inactivation after exposure to ionising radiation was considered based on experimental cell survival curves. Furthermore, low-dose hypersensitivity was alternatively modelled, again based on experimental cell inactivation data. The study showed that the overall dose response predicted by the TSCE model was typically linear when radiation action was only on the mutation rates. However, when cell data on low-dose hypersensitivity were considered there was a greater slope in the dose response at low doses than a pure linear shape would imply. The authors conclude that the lack of detailed knowledge on biological processes involved adds to the uncertainty in low-dose risk estimates.
7. Shuryak and co-workers developed a semi-empirical two-stage model of carcinogenesis. Their approach is characterized by the integration of what they called short- and long-term models of carcinogenesis. The short-term part models initiation, inactivation and repopulation (iir) and analyses normal and pre-malignant cells during radiation exposure and the following weeks of tissue recovery. The long-term part is similar to the TSCE model. The combined approach allowed both predictions of the number of pre-malignant cells during and shortly after exposure, until the development of cancer many years and even decades after exposure (Shuryak et al., 2009a). Applications of the model were discussed in Shuryak et al. (2009b). The combined model allowed for a description of radiation-induced cancer risks both for the atomic bomb survivors as well as for secondary cancers among radiotherapy patients. The model has been fitted to published risk coefficients for the atomic bomb survivors to explore cancer risks after exposure at middle ages, to assess implications of exposures due to radiological imaging and occupational reasons (Shuryak et al., 2010).
8. Kaiser and co-workers used the TSCE model to describe breast cancer incidence data of the 1958-1998 follow-up of atomic bomb survivors. In their analyses, the authors allowed radiation to act linearly in dose on initiation, promotion, or transformation, or on a combination of these processes, either directly (i.e. for a period of 1 week, on initiation or promotion) or in a life-long exposure (starting after one week when acute exposure ended, on initiation, promotion, or transformation). Based on multi-model inference, the authors identified three preferred scenarios among the 17 variants of exposure investigated with the TSCE model: a life-long action of radiation on clonal expansion, an acute radiation effect on initiation, and a life-long radiation action on initiation and transformation (Kaiser et al., 2012).
9. An extended biologically-based mechanistic model was developed by Kaiser and co-workers, to describe the incidence of colon cancer using the 1958-1998 follow-up of atomic bomb survivors (Kaiser et al., 2014). The model included various stages to account for several known precursor stages of colon cancer development and two pathways to describe microsatellite instability (MSI) and chromosomal instability (CIN) both known to play a role in colon cancer development. Radiation was allowed to act on the rate of second mutations in both pathways, and on the rate of inactivation of CIN cells influencing clonal expansion of these cells. The model allowed for a pathway-specific prediction of risk as a function of attained age, among males and females.

### Other cohorts – Low-LET Exposures

1. Using the TSCE model and various model extensions including up to ten sequential initiating mutational steps, Hazelton and co-workers investigated lung cancer incidence among a cohort of Canadian nuclear workers exposed to low-dose gamma radiation and tritium (follow-up period 1969 – 1988). These authors found a significant effect of the clonal expansion process, and reported the best likelihood for three initiation steps ahead of clonal expansion. In the study, radiation action was allowed to act on initiation, promotion and/or transformation, resulting in distinct time patterns of lifetime risk, and in a non-linear dose response in excess relative risk with somewhat lower values at higher doses. Based on likelihood tests, models allowing for radiation action on promotion and transformation performed best (Hazelton et al., 2006).
2. Eidemüller and co-workers used the TSCE model and allowed radiation to act on the various stages of the model either just linearly with dose rate during radiation exposure, or on a long term in a way that the affected initiation, promotion or transformation rates remain changed even when radiation exposure stopped. The model was applied to the extended Techa River Cohort. Follow-up of the solid cancer mortality data included the period 1950 – 2003, while that solid cancer incidence data included the period 1956 – 2003. The authors conclude that radiation action was best modelled assuming a life-long change in promotion rate of initiated cells, for both the mortality and incidence data (Eidemüller et al., 2010).
3. The Swedish hemangioma cohort (follow-up period 1958 – 2009) studied by Eidemüler and co-workers included 877 breast cancer cases. In the TSCE model, radiation was allowed to change the initiation rate proportional to dose, either just during radiation exposure or life-long. A more sophisticated model was also applied which allowed for healthy or initiated cells to undergo an event of destabilisation and in such way to enter the genomic instability pathway. Because of the young age of the investigated individuals, radiation was only allowed to act on the initiation rate and the destabilization rate of healthy cells. Models assuming a linear dose-response relationship with a life-long radiation action on initiation rate worked best. The study showed that allowing for a radiation-induced transition from healthy non-initiated cells to those with genomic instability significantly improved the fit of the data (Eidemüller et al., 2015).
4. Kaiser and co-workers investigated papillary thyroid cancer risk among about 13,000 members of the Ukrainian-American cohort who were exposed below age 19 years after the Chornobyl accident. Their model included two separate pathways: The first pathway allowed – for sporadic cancer development – for a multistage process including two mutational events followed by clonal expansion leading to thyroid cancer without CLIP2 overexpression. The second was based on the observation that thyroid cancer is associated with the overexpression of the CLIP2 gene. Consequently, this pathway was modelled by including two mutational steps that finally lead to thyroid cancer. In this pathway, both sporadic and radiation-induced cancers were assumed to be CLIP2-related. The study showed that the probability of finding the CLIP2 marker in tissue of papillary thyroid tumours as a function of dose is related to the radiation risk in the epidemiological cohort. The authors conclude that for the first time a mechanistic model to describe radiation-induced carcinogenesis was developed that included a radiation biomarker on a molecular level (Kaiser et al., 2016).

## Animal Data

1. Leenhouts and Chadwick analysed the formation of lung tumours in rats and mice by applying a modified two-stage model, in which they allowed initiated cells to show a net proliferation rate. The radiation response of the rate parameters in the model was motivated by observations that DNA double-strand breaks were induced by a linear dose and a quadratic dose component. Thus, in this study DNA damage was linked to lung tumour incidence. The authors showed that their model explained various radiobiological phenomena such as a) the fact that for short radiation exposure the dose-response relationship is governed by a single mutational step, b) the ‘reverse’ dose-rate effect where the combined processes of clonal expansion of intermediate cells, the changing radiation sensitivity with age, and radiation action on both mutational steps may play a role, c) the fact that depending on tumour type a relative or an absolute risk projection model is preferable, d) the age-dependence of radiation sensitivity throughout lifetime, e) the effects of continuous versus chronic exposures, and f) the fact that extrapolation of risks is not simple because it depends on the spontaneous mutation rate in the model (Leenhouts and Chadwick, 1994).

## Conclusion

1. Since the 1950s, biologically-based mechanistic models have been applied to various human and animal data, including different radiation qualities (x-rays, gamma radiation, alpha exposures e.g. from plutonium and radon), in a wide dose and dose-rate range.
2. Typically, in these models radiation can induce changes in the rates of initiation, promotion, and transformation. In most of the studies reported it is assumed that radiation action on these processes is linear with dose, resulting in rate changes either only during the exposure or possibly life-long. As a basic feature of such models, at very low doses they predict a linear increase of radiation risk with dose. However, even if radiation is assumed to induce changes in the rates of initiation, promotion, and transformation in a linear way, the overall radiation response at higher doses may be non-linear.
3. There are a number of arguments that tend to support the use of biologically-based mechanistic models. Among those are the biological plausibility of resulting parameter estimates, and their good performance compared with more conventional descriptive models. It is expected that use of such models will continuously benefit in the future from growing knowledge on human carcinogenesis and the basic molecular processes behind.
4. However, few studies included a systematic investigation of the implications on the shape of dose response or effects of varying dose rate. At present it is therefore not clear what extra information on LDEF and DREF is provided by these models. However, they have the potential to provide mechanistic insights into the effects of dose and dose rate.
5. The overall conclusion of this review is that current assumptions made in radiation protection including the linear-no-threshold model are not in contradiction to what is presently known on the process of cancer development.

# SUMMARY AND CONCLUSION

1. Since the discovery of x-rays by Roentgen in 1895 the biological effects of ionising radiation have been a matter of general interest. While initially there was the urgent need to protect humans against tissue reactions (deterministic effects) after high acute doses of ionising radiation, in later decades the need to protect against stochastic effects at lower doses or dose rates of ionising radiation such as cancer became also a major concern. Consequently, since its foundation in 1928 ICRP has continually reviewed the scientific evidence on the biological effects of ionising radiation and has regularly issued recommendations on its use with the aim to protect humans from any detrimental effects of ionising radiation without unduly limiting its beneficial use (e.g. ICRP, 1977, 1991, 2007).
2. After the atomic bomb explosions over Hiroshima and Nagasaki in Japan in 1945, epidemiological studies on the atomic bomb survivors became a major source of information for those working in the field of radiological protection, particularly with respect to (but not limited to) the stochastic effects including radiation-induced solid cancer and leukaemia. Statistically significant increasing trends with dose have been observed for all-cancer incidence among the atomic bomb survivors for doses in the range 0-100 mGy (Grant et al., 2017), but not over any lower dose range (for example 0-50 mGy), probably due to statistical limitations of the data. As such, extrapolation to low dose (i.e. application of LDEF) is not strictly necessary in the LSS data if risk estimates are derived over this low-dose range; however, the atomic bomb survivors were largely exposed to high dose rates, so that extrapolation to low dose rates (i.e. application of DREF) is still required. This extrapolation is complemented by information on radiation effects observed on the sub-cellular and cellular levels, and at the tissue and organism levels encompassing data from experimental animals and human cohorts other than the atomic bomb survivors.
3. Based on a concept developed by ICRP in *Publication 60* (1991), radiation-related cancer risk estimates deduced from studies on atomic bomb survivors are divided by a Dose and Dose Rate Effectiveness Factor (DDREF) using a numerical value of 2. This approach was developed as a means to extrapolate radiation risks from high doses and high dose rates to low doses and low dose rates more relevant for the radiological protection setting. Because the numerical value of DDREF has been controversial in recent years, ICRP has initiated a re-evaluation of DDREF. In the initial phase of this effort, it was decided to analyse scientific evidence on the biological effects of low doses and low dose rates of ionising radiation separately and to discuss the results of this analysis in terms of LDEF (Low Dose Effectiveness Factor) and DREF (Dose Rate Effectiveness Factor).
4. Radiobiological experiments on molecular systems for example to detect double strand breaks in the DNA) and cellular systems (for example to determine cell survival of various cell lines after radiation exposure and their DNA repair capacity) have offered much insight in the mechanisms of radiation action on molecular and cellular organisation levels. In the present report, the following mechanisms and cellular endpoints were reviewed because they were considered relevant for the process of carcinogenesis: DNA damage induction and repair, induction of gene mutations, induction of chromosome aberrations, and induction of cell cycle checkpoints and apoptosis.
5. Furthermore, the Commission acknowledges that there is convincing evidence of processes that could modulate carcinogenesis and therefore cancer risk differently at low- as opposed to high-doses and dose rates. These processes, which include ‘non-targeted’ effects, differential modulation of gene expression, cell migration/EMT, and differential modulation of the immune system, were also reviewed. It is concluded that the literature relating to these potentially risk modulating effects is not yet sufficient to allow firm conclusions to be drawn on their impact on the evaluation of DDREF.
6. In general terms cellular and molecular data allowed for numerical evaluations of both DREF and LDEF. For example, the value of 4 based on chromosomal aberration studies (both stable and unstable aberrations) is towards the higher end of values based on a wider range of endpoints. It is noted, however, that there is much time between induction of gene and chromosomal mutations and clinical presentation of cancer and, consequently, there are many processes likely to modulate the impact of these initial events on human carcinogenesis. This suggests that substantial caution is required to use cellular and molecular data in quantitative estimations of cancer risks.
7. Historically, many experiments have been performed to investigate the effects of ionising radiation on animal models including mice, rats, dogs, and others. As compared to molecular and cellular experiments, these experiments offer the advantage of studying radiation-induced biological effects in whole organisms, while as compared to epidemiological studies on humans these experiments offer the advantage of controlled exposure situations allowing for specific choice of radiation qualities, radiation doses and radiation dose rates. In this report, these historical studies along with a limited number of more recent animal studies were reviewed.
8. Recently, new databases were established in the United States and Europe to store and make broadly available the data obtained in historical animal experiments. The Task Group took this opportunity and, for the first time, pooled and analysed these data systematically in an effort to deduce information on low-dose vs high-dose effects (LDEF), and low-dose-rate vs high-dose-rate effects among animals (DREF). The results obtained from these studies as well as from more recent analyses suggest that after gamma ray exposure there is evidence of dose and dose-rate effects for biological outcomes including life shortening and various cancer types. Specifically, for all solid tumours combined recent pooled analyses of data from historical studies on experimental animals (mice) mostly suggest LDEF and DREF values close to 1, with considerable variation depending on tumour type, while a single study suggests a DREF value of about 3 and above. In contrast, for life-shortening pooled analyses suggest DREF values of about 2. The above noted caveats about the measure of life shortening should be noted. It is concluded that the current evidence from animal experiments implies that values of LDEF and DREF greater than about 3 and lower than 1 are unlikely. It is also noted that animal studies have suggested that many factors may influence low-dose radiation responses including genetic background, diet, overall health of the animal, and others.
9. As compared to molecular, cellular, and whole animal studies, epidemiological studies on human cohorts exposed to ionising radiation offer the advantage to provide information on the radiation-induced outcome of most interest in radiological protection, i.e. solid cancer or leukaemia in humans. The Commission has therefore sought, in addition to reviewing the current literature on the topic, to provide a comparison of available quantitative risk estimates from low-dose-rate studies as compared to those from the atomic bomb survivor studies, including studies of either occupational or environmental radiation exposures. Specifically, meta-analyses were performed where risk estimates deduced from 29 human cohorts exposed to low dose rates were compared with those from the atomic bomb survivors. For all solid cancers combined, these analyses resulted in DREF values of about 2, largely driven by the Mayak worker cohort. If the portion of the Mayak cohort with concomitant plutonium exposure was excluded, central estimates of DREF of about 1.5 were obtained, while exclusion of any other single cohort did not change the result substantially. Taking account of the appreciable statistical and methodological uncertainties involved in these estimates, the epidemiological evidence points toward DREF values in the range of about 1 to 3.
10. To further investigate the LDEF, a model with linear-quadratic dose response was fitted to current LSS solid cancer mortality and incidence data by the Task Group. The results obtained suggest some upward curvature in the dose response, implying LDEF values greater than 1 depending on dose range considered. A range of values was, however, observed for individual cancer sites, so that for breast cancer there is less evidence for an LDEF above 1. The mortality data suggest upward curvature for most cancer endpoints and sexes over the 0-2 Gy range, although only for male solid cancer was this curvature significant. The current scientific evidence on curvature in the mortality and incidence data from the Japanese atomic bomb survivors tend to support an LDEF value of greater than 1, for all solid cancers combined, with various factors influencing a single numerical value. However, indications of linearity or curvature for all solid cancers combined should be interpreted with care.
11. Epidemiological studies on post-natal exposures, are valuable in providing risk estimates after exposure to acute doses above about 100 mGy. More recently studies have also pointed towards cancer risks for doses below 100 mGy or for low dose rates. It has been argued that the use of biologically-based mechanistic models that incorporate knowledge on the process of carcinogenesis along with appropriate quantitative data, could be used for a better-informed dose and dose-rate extrapolation and that they might provide further insight on the shape of dose response curves at low doses obtained from epidemiological studies. Consequently, the Task Group has reviewed the scientific evidence from studies in which biologically-based mechanistic models were applied to data on cancer development in animals and humans exposed to ionising radiation. Such studies have the potential to provide mechanistic insights into the effects of dose and dose rate on the organism level. However, current knowledge on carcinogenesis and the mechanisms responsible is too limited to allow for a plausible quantitative mechanistic account of the process. Only a few studies included a systematic investigation of the implications on the shape of dose response or effects of varying dose rate. At present it is therefore not clear what extra information on LDEF and DREF is provided by these models. It is concluded that current assumptions made in radiological protection including the linear-no-threshold model are not in contradiction to what is presently known on the process of cancer development and on cancer risks at low doses and low dose rates in human populations.
12. In the evaluation of epidemiological studies growing evidence was found that acute and protracted exposures to ionising radiation do cause cancer below about 100 mGy, and that an inference of no cancer risk at relatively low doses is not warranted by the available data. Thus, the assumption of a radiation-related cancer risk at low doses (i.e. below about 100 mGy) is considered prudent given the current scientific evidence.
13. The overall conclusion of this report is that notwithstanding considerable uncertainties, based on current scientific evidence, an LDEF of much more than 3 is not supported, and much less than 1 likewise. Similarly, it is concluded that a DREF value much larger than 3 or less than 1 is also unlikely. These ranges of LDEF and DREF values appear largely consistent for the various sources of data reviewed in this report.

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ABBREVIATIONS

BEIR Biological Effects of Ionizing Radiation committee

DDREF Dose and dose rate effectiveness factor

DNA Deoxyribonucleic acid

DREF Dose rate effectiveness factor

DSB Double strand break

EAR Excess absolute risk

ERR Excess relative risk

ERA European Radiobiology Archive

FIA Free in air

FISH Fluorescence in situ hybridisation

HBRA High background radiation area

INWORKS International Nuclear Workers Study

LDEF Low dose effectiveness factor

LDR Low dose rate

LET Linear energy transfer

LNT Linear no-threshold

LSS Life Span Study

NASA National Aeronautics and Space Administration

NPP Nuclear power plant

NRRW National Registry for Radiation Workers

RBM Red bone marrow

TSCE Two stage clonal expansion

UNSCEAR United Nations Scientific Committee on the Effects of Atomic Radiation

ACKNOWLEDGEMENTS

The International Commission of Radiological Protection (ICRP), referred to as ‘the Commission’ below, introduced the dose and dose rate effectiveness factor (DDREF) with a numerical value of 2 in the ICRP60 Recommendations to be used in radiological protection when inferring health risks at low doses and low dose rates from risks at higher doses and dose rates. In 2007, the Commission confirmed this approach in the ICRP103 Recommendations. Based on similar scientific evidence, the US National Research Council proposed a value of 1.5 (95% confidence interval: 1.1 – 2.3) in 2006, while in the same year the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) abandoned the DDREF concept for scientific estimates of radiation risk at low doses and low dose rates, preferring to use linear quadratic functions instead of adjusted linear functions.

Thereafter, the discussion on the use of DDREF continued. For example, in 2013 the World Health Organisation (WHO) considered it prudent not use a DDREF when assessing the health consequences due to the radioactivity released during the Fukushima accident in Japan. In 2014 the German Radiation Protection Commission came to the conclusion that epidemiological evidence does not support a value for the dose rate effectiveness factor higher than 1.

Given this context, the Commission approved in April 2013 in Cambridge, UK, to form a Task Group on ‘Radiation Risk Inference at Low-dose and Low-dose-Rate Exposure for Radiological Protection Purposes: Use of Dose and Dose Rate Effectiveness Factors’ reporting to Committee 1, to develop guidance. The group was tasked; to review the currently available information on the estimation of risk coefficients; recommend whether it is desirable to continue to estimate risk at low doses by assessing the slope of the dose response at high doses and then apply a DDREF reduction factor; and recommend whether such coefficients are applicable to acute, protracted and prolonged exposure or need a particular correction.

The Task Group met five times physically, on 10-11 December 2013 at Helmholtz Center Munich, Germany; on 25 May 2015 at Kyoto University, Japan; on 11 November 2015 on the occasion of a MELODI workshop at Helmholtz Center Munich, Germany; on 6-7 October 2016 at RERF in Hiroshima, Japan; and on 25-26 May 2017 at IAEA in Vienna, Austria, with partial participation of the UNSCEAR secretariat. Furthermore, the Task Group benefited from discussions at a workshop with Japanese experts on ‘Dose and Dose-rate Effects Related to Radiation Effects’ on 22 May 2015 in Kyoto, Japan. Discussions were complemented by a number of digital meetings, particularly after the onset of the global COVID-19 pandemic early 2020.

The work of the Task Group included reviewing the current scientific literature on the use of DDREF; identifying gaps in knowledge that, if addressed could enhance the reliability of any values derived for the DDREF; adding to the scientific evidence on the topic by performing own scientific analyses; and publishing the results obtained in the peer-reviewed scientific literature prior to the preparation of this report, to continuously inform the scientific community on the work of the Task Group.

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\*Although formally not a Main Commission member since 1988, the ScientificSecretary is an integral part of the Main Commission

Finally, thank you very much to all organisations and individuals who took the time to provide comments on the draft of this publication during the consultation process.