Dose rate effects in radiation biology and radiation protection

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Abstract–Quantifications of biological effects (cancer, other diseases and cell damage) associated with exposure to ionising radiation have been major issues for ICRP since its foundation in 1928. While there is a wealth of information on the effects on human health for whole body doses above about 100 mGy, the effects associated with doses under 100mGy are still being intensively investigated and debated. The current radiation protection approach, proposed by ICRP for workers and the public, is largely based on risks obtained from high-dose and high-dose-rate studies, such as the Japanese Life Span Study on atomic bomb survivors. The risk coefficients obtained from these studies can then be reduced by the Dose and Dose Rate Effectiveness Factor (DDREF) to account for the assumed lower effectiveness of low-dose and low-dose-rate exposures. In the latest ICRP Recommendations, a value of 2 for the DDREF continues to be proposedwhile other international institutions suggest either to apply different values or to abandon the factor. This report summarizes the current status of discussions and highlights issues that are relevant to re-assessing the magnitude and application of DDREF.

Keywords: linear-no-threshold hypothesis; radiation risk; dose and dose rate effectiveness factor; low dose effectiveness factor; dose rate effectiveness factor; radiation protection

1. INTRODUCTION

1.1. Setting the scene

The International Commission on Radiological Protection (ICRP) is the leading organisation for developing recommendations on the protection of workers, the public and the environment, against exposures to ionising radiation. The radiation protection framework recommended by ICRP is based on more than a century of research on the biological effects of ionizing radiation, the scientific results of which are regularly reviewed by major international institutions, such as the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR).

In this regard, radiobiological studies at the molecular and cellular levels provide insights into the damage mechanisms that come into operation when cells or organisms are exposed to ionizing radiation. Such studies have well-defined conditions and can investigate the influence of numerous parameters (e.g., dose, dose rate, degree of fractionation, radiation quality, environment, cell type and line, position in the cell cycle, repair capacity) on the biological outcome. Indicators of cellular damage studied include, among others, identification of DNA damage (for example through detection of γH2AX-foci), induction of chromosome aberrations,

gene alterations, cell survival, and may also include non-targeted effects such as genomic instability, bystander effects, adaptive response, etc. Experimental studies on animals are another source of information. Animal studies enable direct investigations of biological effects again taking various parameters such as dose, dose rate and radiation quality, type of species (such as mice, rats, and dogs and sometimes incorporating human cell types such as in humanized mice models), etc. into account. The detrimental outcomes considered may include general effects such as life shortening, but also more specific outcomes such as cancer incidence or mortality, which are already close to those relevant for humans after exposure to radiation. Finally, epidemiological studies on human individuals exposed to ionizing radiation provide an important source of information for radiation protection. For obvious reasons, these epidemiological studies do not have the advantageous features of the controlled experimental conditions found in studies on molecules, cells, or animals. Instead, epidemiological studies must deal with exposure situations as they were in the past when the exposure happened (in epidemiological studies such as those on the A-bomb survivors, nuclear workers, uranium miners, the Techa river population, Chernobyl clean-up workers, medical cohorts) or as defined in epidemiological studies due to other reasons (e.g., in studies on CT exposures of patients where the exposure scenario is controlled but defined by getting the best image with the lowest dose).

Among the parameters included in the current ICRP system of radiological protection, the dose and dose rate effectiveness factor (DDREF) plays an important role. This is so because the risks of solid cancer and leukaemia incidence or mortality obtained from the Life Span Study (LSS) on the atomic bomb survivors , serve as a major input for ICRP in defining dose limits, dose constraints and reference levels for protection of workers and the public in planned, accidental and existing exposure situations. However, the LSS provides valuable statistically significant results on radiation-induced solid cancer and leukaemia only above whole body doses of about 100 mGy, from exposures that occurred during a relatively short time (say seconds up to minutes), and therefore involve high dose rates. Therefore, it was considered that some adjustments to the derived LSS risk coefficients had to be made, to make them applicable to the radiation protection setting where lower doses and dose rates are typical.

1.2. History

The requirement of a dose and dose rate adjustment was already noted in the first report of UNSCEAR published in 1958 where it was acknowledged that “effects of low radiation levels must be extrapolated from experience with high doses and dose rates”, and that “among other physical factors, distribution in time governs the effects of ionising radiation” (UNSCEAR 1958). For many years, however, data from the atomic bomb survivors did not show a statistical significance sufficient to quantify radiation-induced risk for cancer and leukaemia induction and mortality based on human data. It was only in 1977 that UNSCEAR first proposed a “reduction factor”, to compare effects from acute exposures to low-LET radiation with those from fractionated or protracted exposures. The proposed range, of 2-20 for this factor, was deduced from animal experiments (UNSCEAR 1977). Again based on animal data, the US National Council on Radiation Protection and Measurements (NCRP) coined the dose rate effectiveness factor (DREF) and proposed values between 2 and 10 (NCRP 1980). Finally, in 1991 ICRP introduced the DDREF and suggested a value of 2, to be applied for absorbed doses below 200 mGy, and for higher doses if the dose rate is less than 6 mGy per hour averaged over a few hours (ICRP 1991).

For many years the proposal of a DDREF value of 2 was generally accepted, and it was reaffirmed in 2007 when ICRP emphasised, in their most recent recommendations, that this value "should be retained for radiological protection purposes" (ICRP 2007). However, already around that time (in 2006) the Committee on the Biological Effects of Ionizing Radiation (BEIR VII) of the US National Academy of Sciences came to a somewhat lower point estimate of 1.5, based on a combination of information from animal and human data (NAS 2006), while UNSCEAR even suggested not to use DDREF at all but to rely instead on a linear-quadratic dose response relationship to analyse the data from the atomic bomb survivors (UNSCEAR 2006). Since then the trend has continued towards lower proposed values of DDREF. For example, the World Health Organisation (WHO) used a value of 1 in its recent report on the health effects after the Fukushima accident (WHO 2013), and the German Commission on Radiological Protection (SSK) stated recently that they no longer consider "justifications of the use of the DDREF in radiological protection as being sufficient" (SSK 2014). A more detailed review on the historical development of DDREF is given in (Rühm et al. 2015).

1.3. Methodological considerations

Although early radiation damage at the DNA level, such as the induction of double strand breaks visualized by γH2AX foci, often show a linear dependence on dose after acute exposure to low-LET radiation, more complex damage such as chromosome aberrations usually shows a linear-quadratic (LQ) dose response. The LQ model includes a term linear in dose with a proportional constant α and a term quadratic in dose with a proportional constant β. Cell survival curves after exposure to low-LET radiation can also be described by LQ models, as well as many results obtained in animal studies. These observations together with mechanistic arguments (double hit theory) led to the assumption that an LQ dose response model can generally be used to describe the induction of complex biological effects due to acute low-LET ionizing radiation. A pure linear extrapolation of experimental observations made at high doses would then result in an overestimation of the observed effect at low doses. Accordingly, the ratio of the slope of this linear extrapolation from dose D to dose zero, and the slope of the LQ dose response curve at low doses (dominated by the α-term) is defined as the low dose effectiveness factor (LDEF) (Eq. 1):

$$LDEF = \frac{\alpha D + \beta D^2}{\alpha D} = 1 + \frac{\beta}{\alpha} D \qquad \text{(Eq. 1)}$$

When a certain dose of low-LET ionizing radiation is delivered in a number of fractions rather than acutely within one short fraction, then the exposed cells might be able to repair the damage if there is sufficient time between two consecutive fractions. The dose response of the second fraction may then again start in a similar way as that of the first fraction, i.e., with the assumed linear slope in the LQ dose model. In the limit of chronic exposure (which can be considered as an infinite number of short fractions with no breaks in between), the resulting dose response curve is then linear with a slope corresponding to the α term in the LQ model. Consequently, the ratio of the slope of a linear extrapolation from dose D to zero dose using the LQ model for acute exposure ($(\alpha D + \beta D^2)/D$), and the slope of the dose response curve for chronic exposure (α) is defined as the dose rate effectiveness factor (DREF). In this limiting case, which implicitly assumes that the α term of the LQ model does not depend on dose rate, the DREF converges towards the LDEF.

Based on these and other considerations, ICRP had proposed to combine LDEF and DREF to one Dose and Dose Rate Effectiveness Factor DDREF (see above). It is noted, however, that there are indications that the α term in the LQ model may not necessarily be independent of dose rate, which would question the approach to use a combined DDREF. It is also noted that the general use of a simple LQ model can also be questioned. These and other controversial issues on DDREF were recently discussed on a workshop jointly organised by ICRP and the Janus group, and a summary of these discussions can be found in Rühm et al. 2015.

2. MOLECULAR AND CELLULAR BIOLOGICAL CONSIDERATIONS

Among radiogenic diseases, cancers and hereditary effects are currently considered of most importance, and these are included in the current ICRP approach to calculation of low dose radiation detriment. However, this approach may in the future have to extend to other conditions such as circulatory diseases, if the risk at low dose becomes well established. Current evidence (e.g. UNSCEAR 2010, 2012) places greatest emphasis on gene mutations and chromosomal aberrations arising from DNA damage as the main mechanism by which radiation exposure contributes to increasing the incidence of cancers and hereditary effects. One prediction, that follows from the proposition that gene and chromosomal mutations are the main contributor to radiation carcinogenesis, is that DNA repair genes, and particularly in the case of ionising radiation DNA double strand break repair genes, will modify radiation cancer risk. There is evidence that genes such as *Prkdc* and *Xrcc2*, involved in the non-homologous end joining and homologous recombination repair pathways respectively, modify radiation cancer risk in mouse models, and there is a degree of tissue specificity (eg Degg et al 2003, Haines et al 2010, 2015). Although DNA repair genes have not been commonly identified in screens for radiation cancer risk modifiers, some repair-related genes have been found to modify risk in humans, most notably in the case of *ATM* and radiogenic breast cancer (eg Bernstein et al 2010). It is appreciated, however, that other modulators may exist that might change the level of disease risk, but that these are not well defined or understood. It is such mechanistic considerations that are an important aspect contributing to judgements on the appropriate approach to low dose/low dose-rate risk extrapolation, and therefore considerations of DDREF. A clear understanding of the processes that contribute to radiogenic cancers and hereditary effects and their dose/dose-rate responsiveness, over wide ranges is therefore important in further development of the concept and use of DDREF.

The information relevant for risk estimation at doses less than those where direct human evidence is available, comes from studies on induction and repair of DNA double-strand breaks (DSBs), gene mutations, chromosomal aberrations, and thresholds for cell cycle checkpoint activation and apoptosis. The magnitude of the DDREF values derived from chromosome aberration studies is not large, generally indicating values around 4. 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 1 mGy/day), as they do at higher doses/dose rates. There are, however, pieces of evidence that may indicate that responses over a wide range of dose are non-linear. For example, some studies have been interpreted to suggest that the formation of protein foci around DSBs may be supra-linear at low doses (e.g. Beels et al. 2009, 2010; Neumaier et al. 2012). Furthermore, several studies indicate that DSB repair as monitored by foci of chromatin proteins is slower or incomplete following low dose exposures (e.g. Rothkamm and Löbrich 2003, Ojima et al. 2011, Grudzenski et al. 2010). Some cell cycle checkpoints have relatively

high thresholds for activation. The G2/M checkpoint, for example, is not activated at doses below 200 mGy (low LET exposure) and is estimated to require the presence of 10-20 DSBs for activation (Löbrich and Jeggo 2007). At the molecular level, there has been much interest in patterns of gene expression at high and low doses and dose rates, and their similarity or difference. While there can be differences in gene expression following exposure at high and low doses and dose rates (e.g. Ghandhi et al. 2015), some genes respond over all doses and dose rates, notably p53 responsive genes (Manning et al. 2013, 2014; Ghandhi et al. 2015). It is therefore important to develop an understanding of how gene expression alterations relate to disease, especially as modifications are usually assessed within hours or perhaps a few days following exposure. While these studies indicate that the magnitude of any DDREF value is endpoint-dependent, and developing a value for use in general radiation protection is problematic and highly dependent on judgements on the processes critical for the development of cancer and mutation following radiation exposure, one may conclude that cellular data tend to support the application of a DDREF to estimate risk at low doses.

One critical point is that much time elapses between the induction of gene mutations/chromosomal mutations, alteration of gene expression, etc, and the clinical presentation of cancer. Many processes are likely to affect and modulate the development of disease following the early induction of mutations or other cellular/molecular alterations. Rarely is it possible to link early post-irradiation events to disease, though this may be possible in some animal models (e.g. Verbiest et al. 2015).

In considering the cellular and molecular data relevant to low dose/dose rate risk extrapolation, it is concluded that there remain key challenges to identify the biological mechanisms that lead to disease following radiation exposure, to understand their dose and dose rate responsiveness and to identify the processes that may modulate the rate and frequency of progression to clinically manifest disease. All of these factors will be relevant to evaluation of DDREF from a mechanistic perspective.

3. EVIDENCE FROM ANIMAL STUDIES

When the US National Academy of Sciences prepared their BEIR VII report (NAS 2006), their analyses of animal data relied largely on the data set that had been produced at the Oak Ridge National Laboratory, US. However, that sort of analyses can now be based on much larger data sets because more recently databases for irradiated animal data (previously not used by the BEIR VII committee) have been set up in the US (Wang et al. 2010, Haley et al. 2011) and Europe (Gerber et al. 1996, Tapio et al. 2008, Birschwilks et al. 2011)..

For example, a recent analysis included data from 28,289 mice in 91 treatment groups from 16 studies. Inclusion criteria were: external radiation exposures to low-LET radiation (either X-rays or gamma rays), with a range of dose rates from 0.001 Gy/min to 4 Gy/min, a total dose up to 1.5 Gy, and at least three distinct treatment groups per stratum. In all cases, digitized data on treatment and lifespan was confirmed by crosschecking with primary literature. In performing this analysis it appeared that a) protracted exposures induce less risk for life shortening than acute exposures and to a larger extended than the value of 1.5 estimated by BEIR VII for DDREF would suggest, and b) the linear-quadratic dose response model that BEIR VII used did not fit the observed data. Instead both protracted and acute exposures appeared to have

approximately linear dose responses at total doses between 0 and 1.5 Gy, albeit with different slopes.

Next, the animal dataset was altered to include some additional datasets with exposures as high as 4 Gy which match the highest doses considered in some analyses of the LSS cohort data (Ozasa et al. 2012). Furthermore, for this work only those datasets where both acute and protracted radiation exposures occurred were selected, or else protracted exposures with different dose rates. Thus it happened that this second analysis included 11,528 mice in 115 treatment groups from 8 studies. Using this dataset and a linear model that closely mirrors that used to estimate risk from atomic bomb survivor data it turned out that a) protracted exposures induced about 2 fold less risk of life shortening than acute exposures. Specifically, DREF was estimated to be 2.1 with a 95% credible interval from 1.7 to 2.7, b) no evidence was found that DREF limited to a smaller total dose range (e.g. 0 to 3 Gy) would be significantly different. (Exclusion of animals or treatment groups that showed signs of tissue effects did not lead to significantly different outcomes of this analysis.), and c) life shortening associated with both acute and protracted exposures shows linear dependence on dose but the slopes of these curves are different. Nevertheless, it is important to emphasize that these linear models, even though they describe the data better than the linear quadratic model, are merely a convenient approximation.

Together, these results demonstrate the need for a systematic analysis of as many animal data sets as possible, with varying dose ranges, dose rate ranges, and for various sets of outcomes. Animals from different species should also be investigated in such analyses. The described results also demonstrate that the huge set of animal data that is now available will be a valuable source of information for the current re-evaluations of DDREF to be applied on human data from acute exposures such as those from the atomic bomb survivors.

4. EVIDENCE FROM EPIDEMIOLOGICAL STUDIES

Epidemiologic studies of cancer risks after low dose and/or low dose rate (LDLDR) radiation exposures complement the animal studies that compare effects of radiation exposures at high and low dose rates. Apart from studies on the atomic bomb survivors of Hiroshima and Nagasaki, Japan, which represent studies on high dose rate exposures (Ozasa et al. 2012, Hsu et al. 2014) (see also section 4.3), epidemiological studies characterized by exposure scenarios involving low dose-rate exposures such as, for example, the cohort of workers occupationally exposed to chronic radiation at the Mayak PA, the first Russian nuclear enterprise, and the Techa River cohort, which includes individuals exposed to radiation due to radioactive releases from the Mayak PA in the river, are also a very important source of information on the influence of radiation dose and dose rate on health effects. Both cohorts have a number of key strengths such as: large size of the cohorts; long follow-up periods; individual estimates of doses from external and internal exposure; heterogeneity by sex, age, and ethnicity; and known vital status and causes of death. Moreover, for the majority of Mayak PA workers (approximately 95 %) complete information on both incidence and mortality, initial health status and non-radiation factors such as smoking, alcohol consumption, body mass index, hypertension and others is available. For both cohorts, sufficient statistical power may be achieved to study incidence and mortality. In the framework of Russian-American and Russian-European collaborations improved dosimetry systems were developed (TRDS-2009 and MWDS-2009) for both cohorts aimed to provide as precise and reliable estimates of doses from external and internal radiation as possible. Results of epidemiological studies of these two cohorts performed during the last years

provide strong evidence for increased risks of solid cancers (Sokolnikov et al 2015; Schonfeld et al 2013), leukemia and non-cancer effects associated with both external and internal radiation exposures over prolonged periods delivered at a low dose rate

4.1. Major cohorts for epidemiologic LDLDR studies

In recent years, a number of LDLDR epidemiologic studies have provided risk estimates that can potentially be used to estimate the dose rate effectiveness factor (DREF) by comparing the quantitative risk estimates from LDLDR studies with matched LSS estimates of risk. Based on compilations from the literature, DREF is being evaluated from available LDLDR data for total solid cancer mortality, and for some major cancer subtypes such as breast, lung, colon, stomach and liver.

Since whole-body irradiation potentially can affect all organs, an analysis of total solid cancers (hereafter just "solid cancer") provides an integrated estimate of radiation risk. Because the total number of solid cancers will be much larger than that for any individual tumor site, it affords a risk assessment with greater statistical power and precision than assessments for individual organs.

For each type of cancer, a systematic literature search in the Pubmed-database in August 2015 was done, also using supplemental reference ascertainment methods, to find primary epidemiological studies with dose-response associations, covering the period January 1980 - June 2015. Search results were limited to cohort or nested case-control studies on cancer risks associated with ionizing radiation in environmental, occupational or emergency situations. The final selection of studies also filtered out overlapping data in individual and pooled studies as far as possible and used the most recent data available for each study. This comprehensive search for studies that had dose-response analyses of solid cancer (or of all cancer except leukaemia) was conducted to reduce/eliminate study-selection bias in the risk comparison. Ecological studies (e.g., (Tondel et al 2011)) or reports of only (or mostly) childhood cancers (e.g., Kendall et al 2013; Mathews et al 2013) were not included. For solid cancer mortality, 22 independent LDLDR studies with dose response-based risk estimates were identified to date, which represents about 960,000 individuals and over 17 million person-years of follow-up, a collective dose of 36,000 person-Sv and 33,000 solid cancer deaths. All except four studies had mean doses under 50 mSv, and most were worker studies, other than two studies based on environmental exposures (Techa River and Yangjiang, China; Schonfeld et al 2013; Tao et al 2012). Exposures were to low-LET radiation, except four had both external gamma exposures and significant high-LET internal exposures (Mayak and Rocky Flats plutonium workers; Sokolnikov et al 2015; Cardis et al 1995), and Port Hope and German uranium processing workers (Zablotska et al 2013; Kreuzer et al 2015)), requiring the authors to statistically factor out the internal exposure contributions to risk.

If one examines the 13 of the 22 dose response-based LDLDR studies that had at least 250 solid cancer deaths, it is notable that 11 out of the 13 studies had positive risk coefficients, though only four were statistically significant in the positive direction which is not surprising since individual LDLDR studies typically have low statistical power. A preliminary meta-analysis was performed of risk coefficients in the available studies in comparison to the A-bomb LSS risk coefficients for the subsets of LSS individuals with comparable composition by sex, ages at exposure and ages at observation. Once results of a combined study including nuclear

workers from France, UK and the US (Hamra et al 2015) for solid cancer are available, a more definitive analysis will be conducted.

Although an analysis of total solid cancer risk after LDLDR exposures provides a broad assessment of DREF, it may represent heterogeneous DREF's for various tumour sites. Radiation effects for tumour sites may differ because of biological diversity in genetic pathways, epigenetic influences, and tissue and metabolic co-factors. Various environmental or lifestyle risk factors may modify radiation risk for certain cancer types but not for others, e.g. smoking effects may modify the radiogenic risk of lung cancer and reproductive factors may modify radiogenic risk of breast cancer. The impact of those modifying factors might be dependent on dose. To get an overview of variations in low dose risk, LDLDR studies providing estimates for breast, lung, colon, stomach, and liver cancers were reviewed. Meta-analyses will be conducted for these sites to estimate DREFs and examine how much variation there is in DREF among tumour sites.

LDLDR epidemiologic studies have various limitations since they are all observational and not experimental. For individual LDLDR studies uncertainties and possibly bias may be contributed by such factors as dose uncertainties; incomplete cancer ascertainment; variations in health surveillance; and lack of information on lifestyle habits, occupational or socioeconomic status, and potential disease risk factors. The meta-analysis estimate of DREF from LDLDR studies is not very precise. It nevertheless provides the most direct evidence regarding the DREF for human radiation exposure, which is important because DREF represents an average for the human population that is highly heterogeneous with respect to innate susceptibility and exposure co-factors. Experimental studies typically do not mimic that heterogeneity. Ultimately judgments regarding DREF will need to integrate information about associated biological mechanisms, experimental studies of dose and dose-rate factors in controlled animal experiments, and the epidemiologic data.

4.2. Methodology for meta-analyses to deduce DREF values by comparing cancer risks associated with fractionated and acute doses of ionizing radiation

The purpose of the meta-analyses described here is to directly compare cancer risks associated with ionizing radiation, from two different non-medical radiation exposure modalities. Exposures considered are at low dose rates and low or moderate cumulative doses (mostly under 100 mGy mean cumulative organ dose) delivered at low-dose-rates or to doses covering a wider range than this (under 4 Gy organ dose) but delivered acutely. Whereas cancer risks associated with low or moderate doses from the fractionated exposure mode are the most relevant to modern radiation protection, there are well established radiation associated cancer risks for the acute exposure mode from the Life Span Study (LSS) on the cohort of the Hiroshima and Nagasaki A-bombs survivors. In order to quantify the overall differences in all solid cancer and site specific cancer risks (lung, breast, stomach, liver, colon) from these two exposure modalities, a meta-analysis has been initiated for each type of cancer, mostly considering cancer mortality and cancer incidence in separate meta-analyses.

For each of the studies in the final selection (see section 4.1), a set of information related to the radiation risks was extracted, i.e., type of dose reported (e.g., colon dose, skin dose, etc.), type of risk measure reported (e.g., usually the Excess Relative Risk (*ERR*) per unit dose – or some measure that could be converted to *ERR*), proportion of males, length of follow-up, age at first exposure, age at end of follow-up. With this information it was then possible to compute

"matching" cancer risks in sub-cohorts of the atomic bomb survivors with matching distributions according to sex, age at exposure, grouping of cancer types and follow-up time.

The ratio q_i of the *ERR* per unit dose from an individual study i, r_i, to the corresponding *ERR* from the atomic bomb survivors, r_{LSSi}, was then calculated as $q_i = r_i / r_{LSSi}$, and the combined variance V_i of q_i was obtained from Monte Carlo error propagation assuming Gaussian error types.

The pooled, inverse-variance weighted mean ratio Q of the q_i study to LSS estimates was then calculated from all individual q_i studies under the basic premise that the average of estimates provided by the pooled studies is closer to the truth than the estimates provided by any of the individual studies. Cochran's Q statistic (and corresponding p value) method was applied to test for between study heterogeneity and the DerSimonian-Laird method was applied for pooling heterogeneous groups of studies and for obtaining the overall variance on Q.

The study is ongoing and the final results obtained on total solid cancers and site-specific tumors will be published soon. A similar study is currently also being performed for leukemia.

4.3. Analysis of dose response among the atomic bomb surivors to deduce LDEF values

The dose response for most cancer sites in the Japanese atomic bomb survivors Life Span Study (LSS) cohort is well described by a linear dose response (Little and Muirhead 1996, 1998; Ozasa et al. 2012; Preston et al. 2007; UNSCEAR 2006). In the LSS, the major exceptional sites in this respect are leukemia and non-melanoma skin cancer (Little and Charles 1997; Preston et al. 2007; Ron et al. 1998). When all solid cancers are analysed together, there is 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 (Ozasa et al. 2012; Preston et al. 2007). The evidence for breast cancer, where there is reasonable power to study the risks at low doses, suggests that the data are most consistent with linearity (Preston et al. 2002).

Preliminary analysis has been conducted of the latest version of the solid cancer mortality dataset for the LSS cohort of A-bomb survivors (Ozasa et al. 2012). The organ dose used for all solid cancers and for the remainder category (all solid cancers excluding breast, colon, lung, stomach) was that to the colon, and the appropriate organ dose was used otherwise. In all cases a neutron relative biological effectiveness of 10 was assumed, as used by Ozasa *et al.* (Ozasa et al. 2012). All "nominal" organ doses were calculated using the latest dosimetry, the so-called DS02 dosimetry (Young and Kerr 2005). Individual data were not available, so that all analyses used the publicly available stratified data. The stratification employed is very similar to that used by Ozasa *et al.* (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 are used in this paper are functions of the mean organ dose, D, 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 i with city c, sex, s, attained age, a, age at exposure, e, other stratifying variables, v (ground distance category, Adult Health Study status, calendar time) and DS02 average organ dose, D, is (Eq. 3):

$$PY_i\lambda_i\left[1+(\alpha D+\beta D^2)\exp[\delta D+\gamma_1(e-30)+\gamma_2\ln(a/70)+\gamma_3 1_{sex=female}]\right] \qquad (3)$$

and where PY_i is the number of person years of follow-up in the stratum. The background cancer death rate λ_i 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 $E[D^2 \mid d]$ and $E[D \mid d]^2$). 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 α, β are allowed to vary and δ is set to 0).

As can be seen from Table 1 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 perhaps not too much 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. As can be seen from Table 2 there are much stronger indications of upward curvature, for most endpoints over the 0-2 Sv 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 1. 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/Sv (+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 (-0.256[a], 0.200)	0.330
Colon	0.055 (-0.254[a], 0.364[a])	1.787 (-10.536[a], 14.107[a])	0.024
Liver	0.380 (-0.066[a], 0.987)	-0.093 (-0.462[a], 0.275[a])	0.721
Lung	0.474 (0.155, 0.941)	-0.099 (-0.312, 0.376)	0.480
Stomach	0.121 (-0.064[a], 0.374)	0.081 (-0.223[a], 3.957)	0.749

[a]Wald-based CI;

Table 2. Fit of linear-quadratic model to Japanese LSS solid cancer mortality data of Ozasa *et al.* (2012), respective organ dose range < 2 Sv

Cancer type	Linear-quadratic model ERR/Sv (+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, 3.040[a])	0.261
Colon	0.009 (-0.083[a], 0.100[a])	2.594 (-28.705[a], 33.893[a])	0.237
Liver	0.067 (-0.519[a], 0.825)	4.109 (-37.580[a], 0.736)	0.246
Lung	0.324 (-0.034, 0.829)	0.330 (-0.242, 1.553[a])	0.430
Stomach	0.207 (-0.115[a], 0.614)	-0.251 (-0.684[a], 3.027)	0.483

[a]Wald-based CI.

5. OUTLOOK AND CONCLUSIONS

Since the early times of radiological protection the problem of how to extrapolate from high doses and dose rates where sound data on the health and biological effects of ionizing radiation exist, down to those low doses and dose rates which are relevant in radiological protection of workers and the public, has been a controversial issue. The current situation where a number of international bodies such as ICRP, UNSCEAR, NAS, WHO and SSK come to somewhat different conclusions with regard to the numerical value of the DDREF and its application, highlight the need to revisit the issue.

The deepening in our understanding of the radiobiological mechanisms of radiation action has revealed a number of processes with non-linear dose-response curves at low doses, and bystander effects where cells are affected although not hit by any ionizing particle complicate the situation. Currently it is difficult to judge how these processes contribute to carcinogenesis in humans, which takes place at a much higher level of organisation than the level of cellular and tissue organisation involving many unknown parameters, and which continues for many years or even decades after the initial radiation exposure.

In the past, experimental data on animal models from databases available then, served as a major input in deriving numerical values for DDREF. Through the current availability of newer and larger databases and tissue banks, more data are now available on historical animal experiments than in the past. It is recommended and supported by TG91 to use this new infrastructure with particular emphasis on investigating low dose and low dose rate effects in animals. Similar evaluation of data available for different animal species (mice, rats, dogs, etc.) might allow for the investigation of inter-species variability in low dose and low dose rate effects, thus helping to answer questions related to the extrapolation of results from animal models to humans.

The continuous follow-up of human cohorts exposed to ionising radiation allows for a continuous improvement in deduction of risk coefficients for the process of radiation-induced human carcinogenesis, the outcomes most closely related to those endpoints relevant for radiological protection of humans. It is recommended and planned by TG91 to support a meta-analysis of the most recent results of radio-epidemiological cohorts, comparing those exposed to high dose rates (e.g., atomic bomb survivors) and low dose rates (e.g., nuclear workers, medically exposed cohorts, Techa river population, Chernobyl clean-up workers, populations living in high background radiation areas) of ionizing radiation.

Some of the available results on radiation-induced biological effects and carcinogenesis in animals might suggest that dose effects and dose rate effects should be treated separately, meaning that values for LDEF and DREF should be independently deduced, before any decision on a combined factor is made. This may imply that, although ICRP in its most recent recommendations (ICRP 2007) does not recommend application of a DDREF on leukaemia data, the proposed new analysis should be also done for leukaemia even if the corresponding shape of the dose response curve follows an LQ behaviour. This has been already initiated by TG91 as well as an evaluation of the radiobiological evidence for treating dose and dose rate effects separately.

Finally it is noted that, while this paper focusses on the DDREF, the overall radiation protection concept recommended by ICRP includes a number of further issues that may need to be revisited: For example, calculation of detriment as proposed by ICRP in its most recent recommendations (ICRP 2007) includes numerical approaches to quantify the transfer of risk across populations, quality of life, years of life lost, etc. Additionally the numerical values recommended for radiation and tissue weighting factors, and whether or not one should include detriment from radiation-induced non-cancer diseases, need to be addressed. Therefore, in parallel to the current re-analysis of DDREF, these issues should also be revisited.

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