Radiat Environ Biophys
DOI 10.1007/s00411-015-0613-6

CONTROVERSIAL ISSUE

Dose and dose-rate effects of ionizing radiation: a discussion in the light of radiological protection

Werner Rühm[1] · Gayle E. Woloschak[2] · Roy E. Shore[3] · Tamara V. Azizova[4] · Bernd Grosche[5] · Ohtsura Niwa[6] · Suminori Akiba[7] · Tetsuya Ono[8] · Keiji Suzuki[9] · Toshiyasu Iwasaki[10] · Nobuhiko Ban[11] · Michiaki Kai[12] · Christopher H. Clement[13] · Simon Bouffler[14] · Hideki Toma[15] · Nobuyuki Hamada[13]

Received: 8 August 2015 / Accepted: 18 August 2015

Abstract The biological effects on humans of low-dose and low-dose-rate exposures to ionizing radiation have always been of major interest. The most recent concept as suggested by the International Commission on Radiological Protection (ICRP) is to extrapolate existing epidemiological data at high doses and dose rates down to low doses and low dose rates relevant to radiological protection, using the so-called dose and dose-rate effectiveness factor (DDREF). The present paper summarizes what was presented and discussed by experts from ICRP and Japan at a dedicated workshop on this topic held in May 2015 in Kyoto, Japan. This paper describes the historical development of the DDREF concept in light of emerging scientific evidence on dose and dose-rate effects, summarizes the conclusions recently drawn by a number of international organizations (e.g., BEIR VII, ICRP, SSK, UNSCEAR, and WHO), mentions current scientific efforts to obtain more data on low-dose and low-dose-rate effects at molecular, cellular, animal and human levels, and discusses future options that could be useful to improve and optimize the DDREF concept for the purpose of radiological protection.

Keywords Radiation risk · LNT model · DDREF · LDEF · DREF · ICRP

✉ Nobuyuki Hamada
hamada@icrp.org

[1] Institute of Radiation Protection, Helmholtz Zentrum München, German Research Center for Environmental Health, Ingolstädter Landstr. 1, 85764 Neuherberg, Germany

[2] Department of Radiation Oncology, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, USA

[3] Radiation Effects Research Foundation (RERF), 5-2 Hijiyama Park, Minami-ku, Hiroshima City 732-0815, Japan

[4] Southern Urals Biophysics Institute (SUBI), Ozyorskoe Shosse 19, Ozyorsk, Chelyabinsk Region, Russian Federation 456780

[5] Federal Office for Radiation Protection, Ingolstaedter Landstr. 1, 85764 Oberschleissheim, Germany

[6] Fukushima Medical University, Hikarigaoka 1, Fukushima 960-1295, Japan

[7] Department of Epidemiology and Preventive Medicine, Kagoshima University Graduate School of Medical and Dental Sciences, 8-35-1 Sakuragaoka, Kagoshima City, Japan

[8] Institute for Environmental Sciences, 1-7 Ienomae, Rokkasho, Aomori-ken 039-3212, Japan

[9] Department of Radiation Medical Sciences, Atomic Bomb Disease Institute, Nagasaki University, Nagasaki, Japan

[10] Radiation Safety Research Center, Nuclear Technology Research Laboratory, Central Research Institute of Electric Power Industry (CRIEPI), 2-11-1 Iwado-kita, Tokyo 201-8511, Japan

[11] Faculty of Nursing, Tokyo Healthcare University, 2-5-1 Higashigaoka, Meguro, Tokyo 152-8558, Japan

[12] Department of Environmental Health Science, Oita University of Nursing and Health Sciences, 2944-9 Megusuno, Oita 840-1201, Japan

[13] International Commission on Radiological Protection (ICRP), PO Box 1046, Station B, 280 Slater Street, Ottawa, ON K1P 5S9, Canada

[14] Centre for Radiation, Chemical and Environmental Hazards, Public Health England (PHE), Chilton, Didcot OX11 ORQ, UK

[15] JAPAN NUS Co., Ltd. (JANUS), 7-5-25 Nishi-Shinjuku, Shinjuku-Ku, Tokyo 160-0023, Japan

Published online: 05 September 2015

Introduction

In October 2012, the International Commission on Radiological Protection (ICRP) formally began discussions re-examining the basis for estimating risks due to exposure to low-dose and low-dose-rate exposure. These risks are the foundation of a key concept in radiological protection: the detriment-adjusted nominal risk coefficients, most recently published by ICRP in its 2007 Recommendations (ICRP 2007). In April 2013, these discussions led ICRP to establish Task Group 91 on Radiation Risk Inference at Low-dose and Low-dose Rate Exposure for Radiological Protection Purposes (ICRP 2013a).

Task Group 91 was given a mandate to review the currently available information on the estimation of risk coefficients, and prepare a position paper including recommendations for further action for consideration by ICRP. Specifically, the Task Group was asked to provide advice on '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 applying a dose and dose-rate effectiveness factor (DDREF)' and 'whether such coefficients are applicable to acute, protracted and prolonged exposure' (ICRP 2013b).

Task Group 91 is now in the process of preparing this position paper. Once concluded, ICRP will consider whether the method used to infer risk at low dose and low dose rates for radiological protection purposes should change. The result may be to maintain the status quo, to change the method of calculation and possibly the numerical value (now 2) of the DDREF currently recommended by ICRP, or to use a different method entirely to infer risk at low doses and dose rates. In turn, this may have an impact on the values of the detriment-adjusted nominal risk coefficients recommended by ICRP of around 5 % per Sv effective dose.

The work of Task Group 91 is focused first on issues related specifically to the DDREF. For this purpose, Task Group members and Japanese experts met in Kyoto, Japan, on May 22, 2015. This paper summarizes what was discussed and presented at this meeting in order to provide an overview of the key points in DDREF debate.

The dose and dose-rate effectiveness factor (W Rühm)

Definitions

The biological effects of low-dose and low-dose-rate exposures of humans to ionizing radiation have always been a major interest in the field of radiological protection. Various concepts have been suggested to extrapolate the risk of damage that could be quantified at high doses and dose rates down to levels of doses and dose rates that are typical for the radiological protection setting, and the terminology used in the literature is often confusing. In the present paper, the concepts of a low-dose effectiveness factor (LDEF) and a dose-rate effectiveness factor (DREF) are used. The LDEF is defined herein as the ratio of the slope of a linear extrapolation at a certain dose of a linear-quadratic (LQ) dose–response curve for acute exposure, and the slope of the linear component of this model. Thus, it is assumed that the LQ curve can be described by a linear component (α term) and a quadratic component (β term). In contrast, the DREF can be obtained, when an acute exposure (described by the LQ dose–response curve) is fractionated and the number of fractions becomes large to approach a chronic exposure. In this case, the numerical value of the DREF becomes close to that of the LDEF, provided that the slope of the linear term in the LQ dose–response curve does not depend on dose rate. When ICRP introduced the DDREF (ICRP 1991), it combined the concepts of DREF and LDEF.

It is rather difficult (and may always be somewhat arbitrary) to provide numerical estimates for what a low dose and a low dose rate are; nevertheless, it is necessary to set the dosimetric scene in which the current controversy on DDREF is debated. For example, in 2012, the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR 2012) defined low dose rates as being less than 0.1 mGy/min averaged over 1 h. This compares to a dose rate of about 2×10^{-4} mSv/min for workers exposed to dose at the level of the ICRP effective dose limit of 20 mSv/year, in a time period of 2000 working hours a year. In contrast, natural background radiation exposures to 1 mSv/year correspond to a dose rate of 2×10^{-6} mSv/min. As for low doses, the most recent mortality report on the Japanese atomic bomb (A-bomb) survivors (Ozasa et al. 2012) found a statistically significant radiation-induced excess relative risk (ERR) per weighted colon dose when data in the dose range of 0–200 mGy were combined. Accordingly, UNSCEAR (2012) defines low doses as doses below 100 mGy. Clearly, with respect to doses as well as dose rates, the numerical values typical for the radiological protection setting are often lower than what is relevant to experimental and epidemiological approaches.

Historical positions of various international organizations

Table 1 provides a historical overview on dose and dose-rate dependence of biological effects induced by ionizing radiation, including the development of the DDREF

Table 1 Selected statements and positions of various institutions important to understand the historical development of DDREF

Organization	Year	Scientific state-of-the-art	Position on shape of dose–response curve	Position on dose-rate effects	Numerical value	References
UNSCEAR	1958	Effects of low radiation levels must be extrapolated from experience with high doses and dose rates	Knowledge of the biological effects of low radiation levels is "meager." Understanding of the basic mechanisms is needed for assessing the damage produced at very low doses	Among other physical factors, distribution in time governs the effects of ionizing radiation	–	UNSCEAR (1958)
UNSCEAR	1962	There is still no clear dose response for leukemia among the LSS study. Usefulness of animal data is limited "by the difficulty of making valid extrapolations from one species to another, particularly to man from animals with a much shorter life span"	Based on theoretical considerations and experimental data from cells and animals, "proportionality between doses and corresponding incidence of tumors down to the lowest doses" is expected	Very little is known on radiation-induced effects "particularly following small doses of radiation received at low dose rates"	–	UNSCEAR (1962)
UNSCEAR	1964	Data on the incidence of leukemia among A-bomb survivors (in the dose range from 100 to 900 rads) suggest a linear dose response	Assumption of linearity "is the only one which allows the use of mean doses in estimating risks." This assumption is "likely to result in an overestimate of the degree of risk"	–	–	UNSCEAR (1964)
UNSCEAR	1969	New developments in cytogenetics allow assessment of radiation-induced chromosome aberrations in human cells. However, the "incidence of chromosome aberrations and that of tumors both increase with increasing dose, but the relationship between the two effects is complex"	Various dose–response relationships are found in vitro, for radiation-induced chromosome aberrations in human cells, but a quantitative evaluation turns out difficult, due to lack of standardization between laboratories	Assessment of radiation-induced chromosome aberrations in human cells as a function of dose rate is also possible.	–	UNSCEAR (1969)
UNSCEAR	1977	Animal experiments are considered important but "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"	"It is to be expected that low-LET radiation is likely to be less carcinogenic per unit absorbed dose at doses of a few rads than at levels of one of a few hundreds rads"	From animal data, reduction factors are reported when acute and fractionated or protracted doses of low-LET radiation are compared for a number of different endpoints	Reduction factor: 2–20	UNSCEAR (1977)

Table 1 continued

Organization	Year	Scientific state-of-the-art	Position on shape of dose–response curve	Position on dose-rate effects	Numerical value	References
NCRP	1980	Introduces a DREF based on data from animal models. It is felt that the deduced DREF values might represent somewhat higher values than what is evident from human exposures	–	A range for the DREF is provided, for an absorbed dose of less than 20 rad (0.2 Sv), or a dose rate of less than 5 rad per year (0.05 Sv/year)	DREF: 2–10	NCRP (1980)
UNSCEAR	1986	Point mutations and chromosome aberrations by low-LET X and γ radiation mostly show a linear-quadratic behavior with dose. 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	For animals, in most cases "dose–response relationships for X and γ rays tend to be curvilinear and concave upward at low doses." For cancer induction, however, "only fragmentary information supports the notion that similar quantitative relationships with the dose might apply"	For human tumors, 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	Reduction factor: 5	UNSCEAR (1986)
UNSCEAR	1988	The report notes that any reduction factor "*…certainly varies very widely with individual* (human) *tumor type and with dose-rate range*"	"The problems in deriving risk coefficients that are also applicable at low doses are the same as before"	"The problems in deriving risk coefficients … for low dose rates remain"	Reduction factor: 2–10	UNSCEAR (1988)
ICRP	1991	Introduces the so-called DDREF 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"	Suggests the DDREF to be used for absorbed doses below 0.2 Gy	Also suggests the DDREF to be used for absorbed doses above 0.2 Gy when the dose rate is less than 0.1 Gy per hour	DDREF: 2	ICRP (1991)
UNSCEAR	1993	Specifies DDREF in more detail and proposes a numerical value, based on radiobiological, animal and epidemiological data. Notes, however, that "epidemiology results do not exclude this value, but except for leukemia, they do not support it"	DDREF should be applied for doses below 0.2 Gy	DDREF should also be applied for higher doses, if the dose rate is less than 6 mGy per hour averaged over a few hours	DDREF: 2	UNSCEAR (1993)
UNSCEAR	1994	Notes that epidemiological studies on different human cohorts provide different quantitative results	–	Risk coefficients for all cancers and leukemia, among US and UK nuclear workers, are close to those from the A-bomb survivors, while a reduction factor 2.7 is found for Russian Mayak workers	–	UNSCEAR (1994)

Table 1 continued

Organization	Year	Scientific state-of-the-art	Position on shape of dose–response curve	Position on dose-rate effects	Numerical value	References
UNSCEAR	2000	Confirms the judgement in UNSCEAR 1993	–	Adds that "the effects of dose rate on cancer risks may differ among cancer types"	DDREF: < 3	UNSCEAR (2000)
UNSCEAR	2006	Emphasizes the unknown role of ionizing radiation on the immune system that "may be suppressive or stimulatory" Data from the A-bomb survivors "are largely consistent with linear or linear-quadratic risk-dose trends over a wide range of dose level"	Fits the data from the A-bomb survivors using a linear-quadratic model. In this way, the chosen approaches "implicitly take account of extrapolation of dose (if not dose rate), so that to some extent they take account of DDREF"	Extra adjustment for chronic exposure is not needed with this approach By comparing nuclear worker and A-bomb survivor data it is noted that "There is no strong evidence for a DDREF greater than 1"	No DDREF is applied, but approach consistent with a value for DDREF of 2	UNSCEAR (2006)
BEIR VII	2006	Bases its evaluation on animal and human data using a Bayesian approach	–	–	DDREF: 1.5 with a range of 1.1–2.3	NAS (2006)
ICRP	2007	The value proposed by ICRP 1991 "should be retained for radiological protection purposes"	–	–	DDREF: 2	ICRP (2007)
UNSCEAR	2010	Conclusion of UNSCEAR 2006 still holds	The dose–response relationship for mortality at low doses … may be described by both by a linear and a curvilinear function	–	No DDREF applied	UNSCEAR (2010)
WHO	2013	Decided to abandon DDREF in its Fukushima report	–	–	DDREF: 1	WHO (2013)
UNSCEAR	2013	Commented on the WHO decision to abandon DDREF	WHO decision consistent with results from A-bomb survivors, and with UNSCEAR's estimates of cancer risks after acute doses between 0.01 and 1.0 Sv	WHO decision consistent with a meta-analysis of low-dose-rate, moderate-dose exposures	–	UNSCEAR (2013)
SSK	2014	Studies on cell cultures do not provide a clear picture, and animal studies do not allow to determine a clear dose response at low doses or to determine dose-rate dependencies. Use of a DDREF in radiation protection is no more justified	Data on the A-bomb survivors do not allow a clear distinction between various types of dose–response relationship	A comparison of data from epidemiological studies involving low and high dose rates (Jacob et al. 2009) does not suggest any dose-rate effect	DDREF should be abolished (corresponding to a value of 1)	SSK (2014)

A-bomb Atomic Bomb, *BEIR VII* the 7th report of the Committee on the Biological Effects of Ionizing Radiation, *DREF* Dose-Rate Effectiveness Factor, *DDREF* Dose and Dose-Rate Effectiveness Factor, *ICRP* International Commission on Radiological Protection, *LET* Linear Energy Transfer, *LSS* Life Span Study, *NAS* National Academy of Science, *NCRP* National Council on Radiation Protection and Measurements, *SSK* German Commission on Radiological Protection, *UNSCEAR* United Nations Scientific Committee on the Effects of Atomic Radiation, *WHO* World Health Organization, 1 rad = 10 mGy

concept. In its first report, UNSCEAR (1958) mentioned the distribution of ionizing radiation in time as an important physical factor, and noted that "opinions as to the possible effects of low radiation levels must be based only on extrapolations from experience with high doses and dose rates."

In 1962, information from the A-bomb survivors was still limited, and UNSCEAR (1962) considered that animal experiments were important. However, their usefulness was judged limited "by the difficulty of making valid extrapolations … to man from animals …."

Two years later, UNSCEAR (1964) stated that "in general, the assumption of a linear dose–incidence relationship at low-dose levels is likely to result in an overestimate of the degree of risk."

In 1969, chromosome aberration data became available both in vivo and in vitro, and UNSCEAR (1969) noted that "the incidence of chromosome aberrations and that of tumors both increase with increasing dose, but the relationship between the two effects is complex."

First, numerical values on a potential reduction factor, i.e., values between 2 and 20, were suggested by UNSCEAR (1977) in 1977. These values were mainly based on animal data, but the Committee emphasized that estimates of harmful effects on man should use data from exposed human populations.

In 1980, the US National Council on Radiation Protection and Measurements (NCRP) introduced the first DREF, and noted that values between 2 and 10 were observed for a variety of endpoints in animal models (NCRP 1980).

Six years later, UNSCEAR (1986) also gave a first numerical estimate, and stated that "for human tumors, a linear extrapolation down to low doses and low dose rates would result in an overestimate of the real risk, possibly by a factor of 5." UNSCEAR (1988) added in 1988 that "… such a factor certainly varies very widely with individual (human) tumor type and with dose-rate range. However, an appropriate range to be applied … should lie between 2 and 10."

In 1991, ICRP (1991) introduced DDREF and proposed a numerical value of 2, acknowledging that the chosen value of 2 might be somewhat arbitrary, and it was felt that it may be conservative. Two years later, this view was adopted by UNSCEAR (1993), which took the same view and suggested a value of about 2 for DDREF based on radiobiological data and epidemiological data and emphasized the substantial uncertainties associated with this value. This was in part because epidemiological studies on different human cohorts provided different quantitative results for this factor (UNSCEAR 1994).

In 2000, UNSCEAR (2000) confirmed the conclusion of its 1993 report that "a reduction factor of less than 3 … still appears to be reasonable in general," whereas in 2006, UNCEAR (2006) used an alternative approach when the Life Span Study (LSS) data were fitted using a dose–response curve including a quadratic component. In this way, a DDREF was implicitly taken into account, and it was stated that "values of DDREF of about 2 are consistent with this approach."

In 2006, the 7th report of the Committee on the Biological Effects of Ionizing Radiation (BEIR VII) of the US National Academy of Science (NAS) applied the Bayesian analysis to animal and human data and came up with a range of values (1.1–2.3) and a point estimate of 1.5 for DDREF (NAS 2006). In contrast, 1 year later, ICRP (2007) recommended that a value of 2 be retained.

Recently, the World Health Organization (WHO) used a DDREF value of 1 in its 2013 Fukushima report (WHO 2013), on which UNSCEAR (2013) commented that "this is not incompatible with the Committee's estimates of cancer risks … and with (Ozasa et al. 2012), …." However, UNSCEAR (2013) acknowledged that "in contrast, experimental evidence indicates values of DDREF greater than one for high-dose exposures at low dose rate."

More recently, the German Commission on Radiological Protection (SSK) published a comprehensive report dedicated to various aspects of DDREF (SSK 2014). The report deals with basic scientific principles and other criteria relevant to radiological protection used to assess the DDREF. From the scientific viewpoint, radiobiological studies at molecular and cellular levels, animal studies, epidemiological studies and mechanistic models were discussed. Furthermore, the report discussed operational implementation criteria relevant to radiological protection requirement, including influence of uncertainties, implementation in real-life radiological protection, international involvement, consequences for stipulating limits, and risk communication. The report expresses the SSK's opinion that various scientific criteria indicate that a DDREF would not be introduced if it were not already in place. Based on current scientific findings, the SSK no longer considers justifications for the use of the DDREF in radiological protection as being sufficient. The SSK therefore recommends abolishing the DDREF or adjusting it to bring it into line with more recent findings. Due to its importance to risk evaluation and impact on radiological protection, however, in the case of adjusting the DDREF, the SSK recommends in parallel that all of the other parameters pertaining to the detriment be adapted to the latest scientific findings. An international agreement in these issues is urgently necessary. In this regard, ICRP plays a fundamental role (SSK 2014).

DDREF has been a moving target for decades. Task Group 91 is currently reviewing the historical development of DDREF, the positions of various international organizations on this issue, and the published molecular and

cellular data. Analyses of animal data and epidemiological data are ongoing.

Does DDREF correctly predict DREF? (O Niwa)

NCRP (1980) first defined a DREF based on the LQ dose–response equation. This was adapted by ICRP (1991) and further extended to the concept of DDREF. ICRP proposed the value of 2 to be applied when estimating the risk of low-dose or low-dose-rate (LDLDR) exposures, thus equating the risk of low dose and low dose rate. In a later publication, ICRP (2005) stated that the linear-no-threshold (LNT) model combined with DDREF serves as a prudent basis for radiological protection at low doses and low dose rates. In a trial to determine the value of the DDREF, the BEIR VII Committee applied the LQ model to the epidemiological data of A-bomb survivors, yielding the numerical value of 1.5 (NAS 2006). Furthermore, UNSCEAR (2006) assessed the low-dose risk value without using the DDREF, by applying the LQ equation to the epidemiological study of A-bomb survivors, yielding a risk value similar to that obtained by ICRP using the DDREF of 2.

All above exercises utilized the LQ equation as shown below. This can be used to estimate the risk of low-dose and low-dose-rate exposures, and to calculate a value of the DDREF. The LQ equation was used to describe radiation induction of chromosome aberration by Neary (1965), which was later extended by Kellerer and Rossi (1972). The equation is well accepted in the field of radiological sciences as a mechanistic model of radiation action. The equation is composed of two terms: linear term and the quadratic term. The LQ equation assumes that while the linear term is independent of dose rate, the quadratic term is dose rate sensitive. So, the dose response of a biological effect for high-dose-rate exposures (E_{H}) and low-dose-rate exposures (E_{L}) can be described as below, and the derivation of DDREF is also shown, where D is the dose.

$$E_{\mathrm{H}} = \alpha D + \beta D^2$$

$$E_{\mathrm{L}} = \alpha D$$

$$\mathrm{DDREF} = E_{\mathrm{H}}/E_{\mathrm{L}} = \left(\alpha D + \beta D^2\right)/\alpha D = 1 + \frac{\beta}{\alpha} D$$

As referred above, ICRP relies on the LNT model with the DDREF of 2. The LNT model means that the risk is linear to dose without curvature, and the DDREF value of 2 indicates that the linear term is dose rate sensitive. This approach differs from that using the original LQ equation.

In fact, numerous radiobiological data demonstrate the dose rate-dependent reduction in the linear term. One example can be found for radiation induction of chromosome aberration in vitro, where the linear term in the dose response was found to be lower when the dose rate was decreased from 1 Gy/min to 1 mGy/min (Loucas et al. 2004). In addition to the in vitro data, data from whole-body animal systems also indicate a strong dose rate-dependent reduction in the linear term. For example, the dose response for the hereditary effects of radiation on male mice was linear, but the slope decreased when the dose rate was decreased from 1 Gy/min to 10 mGy/min (Russell and Kelly 1982). The dose response in female mice varied with dose rate much more drastically in that the slope of the dose–response curve became zero at the dose rate below 0.01 mGy/min (Searle 1974).

DNA double-strand break (DSB) repair operates for hours to days after irradiation of cells, so that the range of the dose rate to consider would be a Gy per hour to week, i.e., in the range of 1 mGy/min to 100 mGy/min. It is important to note that in addition to DNA repair, another mechanism is likely to contribute at the tissue level to the dose rate-dependent linear term. This mechanism is the radiation response of tissue stem cells, the target of radiation carcinogenesis. Stem cells of certain tissues are under constant competition for their residence in the tissue stem cell niche. Stem cell competition has recently been proposed to operate as a quality assurance system to eliminate unhealthy tissue stem cells (ICRP 2015). Radiation-damaged stem cells are likely targets of such system. It is likely that this competitive elimination can best operate at a dose rate of a few mGy per month to year (roughly 0.01 to 0.001 mGy/h) for low linear energy transfer (LET) radiation, since under such conditions radiation-hit events are effectively always singular, and the hit stem cell is also singular, i.e., surrounded by non-hit healthy stem cells. Thus, this competitive elimination of stem cells at dose rates of a few mGy per month to year could contribute to the decrease in the slope of the linear term.

As discussed above, the linear term of the LQ dose response decreases by lowering the dose rate, and the mechanism for such decrease includes DNA repair and possibly preferential elimination of aberrant target cells by stem cell competition for the residence of tissue stem cell niche. Therefore, the DDREF assuming the dose rate-independent linear term is an erroneous concept and cannot properly represent the dose-rate effect of radiation.

Effects at molecular and cellular levels (S Bouffler)

Studies of ionizing radiation effects at molecular and cellular levels are essential to inform judgments on low-dose/low-dose-rate risk extrapolation. Identifying the processes that contribute to the diseases that occur after low-dose/-dose-rate exposures and their dose/dose-rate responsiveness over wide ranges is critical in this context. Among

radiogenic diseases, cancers and hereditary effects appear currently to be of most importance, and these are considered in the current ICRP approach to calculation of low-dose radiation detriment. However, this may have to extend to other conditions such as circulatory diseases if risk at low dose is established. Current evidence (e.g., UNSCEAR 2010, 2012) places greatest emphasis on gene mutations and chromosomal aberrations arising following DNA damage as the main mechanism by which radiation exposure contributes to increasing the incidence of cancers and hereditary effects. It is noted, however, that modulators may exist that might change the level of disease risk, but these are not well defined or understood.

The information relevant to risk extrapolation includes studies on induction and repair of DSBs, gene mutations, chromosomal aberrations, and thresholds for cell cycle checkpoint activation and apoptosis. At the present stage of preliminary analysis, one may conclude that multiple cellular datasets tend to support the application of a DDREF to estimate risk at low doses. The magnitude of the DDREF value is not large, with chromosomal studies 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 low dose rates (down to 20 mGy/day and 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 not necessarily 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 G_2/M checkpoint, for example, is not activated at doses of low-LET radiation below 200 mGy 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). As for the endpoints mentioned above, it is also therefore important to develop an understanding of how gene expression alterations relate to disease, especially as such modifications are usually assessed within hours or perhaps a few days following exposure.

This leads to what is perhaps the critical point; there is much time that elapses between the induction of gene mutations, chromosomal mutations, modulation of gene expression, etc., and the clinical presentation of cancer. Many processes are likely to modulate the development of disease following the early induction of mutations or other cellular or molecular alterations. In few situations 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).

It is concluded that there remain key challenges to identify the biological mechanisms leading 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 in evaluating DDREF from a mechanistic perspective. Clearly, there are currently only small insights into the complete picture.

An increase in animal mortality risk following low-LET radiation exposure is not linear-quadratic (G Woloschak)

Ionizing radiation exposure is a ubiquitous health risk, and the BEIR VII report estimates a 3–12 % absolute increase in the risk of fatal cancer development per Sv of exposure (NAS 2006). The BEIR VII Committee used A-bomb survivor data to evaluate DDREF for the LSS and animal data in order to estimate the relationship between dose, dose rate and risk. DDREF is thus applied to estimate the risk of low-dose exposures: the doses below 100 mSv, like most contemporary exposures, are considered 1.5-fold less of a risk per unit dose than the exposures of the A-bomb survivors (NAS 2006).

Uncertainty about the value of DDREF has recently been voiced by several studies. On one hand, Jacob et al. (2009) performed a meta-analysis of results from epidemiological studies, and found that individuals exposed to protracted radiation, and A-bomb survivors exposed to acute radiation, showed comparable increases in cancer risk per Sv. This result, albeit with substantial uncertainty, implies that acute and protracted exposures pose equal risk, i.e., DDREF is equal to 1. Ozasa et al. (2012) has made the same conclusion based directly on A-bomb survivor data. At low-dose exposures, the risk of carcinogenesis is sometimes equal to or greater than the risk suggested by a linear fit to the data. On the other hand, Hoel (2015) has argued that the DDREF estimate made by the BEIR VII Committee is too low, and that plausible alterations to the BEIR VII assumptions result in higher DDREF estimates closer to the value of 2.

One way to improve the estimate of DDREF is to increase the size of the dataset used to estimate it, which can be done most easily by increasing the pool of animal data. The BEIR VII Committee did not use many studies with extensive numbers of animals. Efforts by the International Radiobiology Archives (Gerber et al. 1996), the European Radiobiology Archives (Tapio et al. 2008; Birschwilks et al. 2011), and the Janus Tissue Archives (Haley et al. 2011; Wang et al. 2010) have made many of these datasets readily available on the internet.

Woloschak's group revisited the BEIR VII's DDREF analysis adding 15 animal studies that were not included in the original analysis. In the analyses performed, the dose range was 0–1.5 Gy (the same as BEIR VII cutoff), dose rates were from 0.001 to 4 Gy/min, number of fractions were 1–60 (most were acute), the interval between fractions was from 3 h to 1 week, and age at first exposure was from $\sim$4 days (in utero) to 580 days. It was found that the LQ model used by BEIR VII to estimate DDREF does not explain this data, and concluded that the LQ model should be modified or replaced in order to establish better radiological protection policy (Haley et al. 2015).

The LQ dose–response model employed in the BEIR VII report assumes that DDREF can be estimated from two types of exposure data: acute exposures, or comparisons between acute and chronic radiation exposures. According to the LQ model, both of these datasets should lead to the same DDREF estimate. Haley et al. (2015) found that this is not the case. More specifically, the value of DDREF estimated from the curvature observed in acute exposure data alone was significantly lower than the value of DDREF estimated from data that directly compared acute and chronic exposures. This suggests that a different model is required to estimate the risk of low-dose and low-dose-rate exposures. When the data for acute exposure were considered, BEIR VII's LQ model and each of the variations tested produced low estimates of DDREF. Central estimates ranged from 0.9 to 1.3. These estimates were never significantly greater than 1. BEIR VII's LQ model assumes that one can use high-dose/high-dose-rate exposures to extrapolate the effects of low-dose/low-dose-rate exposures: nevertheless, when acute data were used to extrapolate chronic exposures, calculated DDREF was close to 1 (Haley et al. 2015). By contrast, when the analysis was restricted to exposure data from strata including both acute and protracted exposures, DDREF estimates were consistently high. Central estimates were all infinite, which would imply that protracted exposure has no deleterious effects. All of the estimates were significantly greater than 1 and also significantly greater than the corresponding analyses of acute data.

This same contradiction is also apparent in the original BEIR VII analysis. Animal carcinogenesis and A-bomb survivor data only included acute exposures, leading to low DDREF estimates of 1.3 and 1.4. Animal mortality data, however, compared acute and protracted exposures, leading to the highest DDREF estimate of 2.0. While this difference was not statistically significant, it is in line with the current findings described above.

The described contradiction undermines the meaning of the BEIR VII DDREF estimate and calls to question any DDREF estimate based on an LQ model. The cumulative estimate of 1.5 depends arbitrarily on the weight given to acute exposure data versus data that compared acute and protracted exposures. By analyzing a larger dataset, the accuracy of BEIR VII's DDREF estimate should have been increased; instead, it was found that the type of data analyzed biases the estimate. Particularly, curvatures in the dose response following acute exposures do not suggest a DDREF correction, while comparisons of acute and protracted exposures do. A different dose–response model is needed to develop an estimate that is not biased by arbitrary factors in the data being analyzed.

It is concluded that there is compelling evidence in the analyzed animal data that protracted exposures are associated with less risk than acute exposures. A range of models suggest with 95 % confidence that DDREF form protracted exposures is between 2.0 and infinity. This result supports Hoel's analysis suggesting that BEIR VII's DDREF estimate is too low (Hoel 2015). It also contradicts findings by Jacob et al. (2009) that protracted exposures to radiation workers were as much of a health hazard as acute exposures to A-bomb survivors. However, the results of Haley et al. (2015) are based on the small number of studies that directly compared acute and protracted exposures and also met the BEIR VII inclusion criteria. Moreover, like BEIR VII, they do not specifically address differences in mean age at exposure between acutely exposed animals and those given protracted exposures, which, on average, were older when treated.

It is proposed that future estimates of the effects of protraction should be based on linear, rather than linear-quadratic, fits to data that include both acute and protracted exposures that account for mean age at exposure. This is not because the true dose response is necessarily linear, but because the true dose response cannot be known with certainty and linear fits provide simple models that approximate observed data. Estimating the risk of low-dose exposures is more challenging, because such risks are statistically difficult to measure. Woloschak's group encourages lively debate as to whether these risks are best estimated by protracted exposure risks as has historically been done.

Finally, it would be prudent to use as much data as possible to estimate the relative risks of protracted exposures. The amount of data could be increased by

considering a wider range of exposures (e.g., 0–3 Sv) including both human and animal data, considering both mortality and cancer incidence, and by adding more studies to existing animal archives.

Biological effects of chronic low-dose-rate irradiation in mice: a summary of the studies performed in the Institute for Environmental Sciences (IES) (T Ono)

Although humans are exposed daily to different kinds of low-dose radiation, little is known about the health effects of these low exposures. One of the approaches toward understanding the effects on humans would be to examine biological effects of low-dose radiation through experimental studies. The focus of IES is on chronic low-dose-rate exposures similar to those received by radiation workers and astronauts.

Using the mouse as a model, the aim is to elucidate any effect that could be induced by chronic low-dose-rate γ-irradiation. The exact dose rates chosen were 0.05 and 1 mGy/day, and the mouse exposure continued for 400 days starting from 8 weeks of age. Thus, the total accumulated doses were 20 and 400 mGy, which are comparable to the annual dose limit for radiation workers, and the dose which astronauts receive after spending 1 year in space, respectively. A third dose group, 20 mGy/day (total dose of 8000 mGy) is included to serve as a positive control. The chronic irradiation is interrupted for 2 h every day from 10:00 am to 12:00 am, in order to examine health conditions of each mouse as well as to supply new bedding, food, and water. Biological endpoints examined so far are life span (Tanaka et al. 2003), neoplasm incidence (Tanaka et al. 2007), anti-tumor immunity (investigated by subcutaneously injecting tumor cells into 15 chronically exposed mice per group, and evaluating tumor growth) (Takai et al. 2011), body weight change (Tanaka et al. 2007), chromosome aberration (Tanaka et al. 2009), gene mutation (Okudaira et al. 2010), mRNA levels (Taki et al. 2009; Uehara et al. 2010), protein levels (Nakajima et al. 2008), and trans-generational effects. It is important to note that the cause of death in about 90 % of the cases was cancer, so that it is difficult to tell whether or not radiation exposure affects the incidence of fatal cancer. Serial killing experiments were conducted where 60 mice were killed every 100 days after a start of chronic irradiation at 20 mGy/day. In some tissues, tumors appeared early in the exposed group. Several other tumors emerged at similar age, but the frequency was higher.

All of the endpoints mentioned revealed significant alterations after 8000 mGy, except for the neoplasm incidence in the offspring. After a total dose of 400 mGy, small but significant alterations were observed in life span, chromosome aberration, mRNA, and protein levels. All observed effects were significant on a 95 % level. A total dose of 20 mGy revealed no significant effects in all endpoints except for mRNA levels. The biological significance of the altered mRNA levels is not clear, however, because they are likely to disappear with time.

In conclusion, these results suggest that astronauts who stay in space for more than a year and receive more than 400 mSv could suffer from radiation-induced health effects. Chromosomal translocations induced by low-dose-rate radiation in splenic cells showed that the efficiency of induction is lower than that predicted from the acute exposure dose–response curve using the LQ model.

DNA damage and tissue response in tissues/organs exposed to low-dose and low-dose-rate γ-radiation in mice (K Suzuki)

Absorption of radiation energy in living cells gives rise to DNA damage of various kinds, among which DSBs are the most lethal and potentially carcinogenic. DSB induction and repair have been well studied after high-dose and high-dose-rate exposure. However, information is still limited on the effects of low-dose and low-dose-rate exposure. Therefore, accumulation of DSBs was assessed in various tissues and organs exposed to γ-rays at different dose and dose rates using an in vivo animal model.

B6C3F1 mice were irradiated with ^{137}Cs γ-rays at a low dose rate (LDR; 0.05 to 20 mGy/day), at a middle dose rate (MDR; 400 mGy/day), or at a high dose rate (HDR; 850 mGy/min) in collaboration with IES. After the completion of radiation exposure over several days, mice were killed, various tissues and organs were isolated, and tissue slices were obtained. DSBs were quantified indirectly by immunofluorescence using anti-p53 binding protein 1 (53BP1) antibody, together with the detection of proliferating cells using anti-Ki-67 antibody. It is noted that with 53BP1, the DNA damage response is evaluated, but not the DNA damage repair itself. For example, in differentiated tissues, 53BP1 foci are rarely detectable, while DSBs are induced by radiation exposure. Therefore, one should always be very cautious when using foci as the surrogate markers for DSBs. Moreover, in this experiment, 8-week-old mice were used. However, when 1-week-old mice were used, the distribution of 53BP1 foci was totally different. For example, most liver cells in 8-week-old mice did not respond. In contrast, not only cells in Glisson's capsules but also hepatocytes formed foci in 1-week-old mice. Damage repair response is thus age dependent, which should be taken into account in relation to DNA damage response in tissue stem cells.

53BP1 foci were detectable in the epithelial cells of all tissues and organs, but not in every part of them. For example, 53BP1 foci were detected in ciliated columnar cells in the bronchiolar regions, but were rarely detectable in the alveolar regions. In non-irradiated mice, the spontaneous frequency of 53BP1 foci was quite low, and HDR exposure (4 Gy) significantly increased the number of DSBs. Residual foci were observed even 10 days after HDR exposure, whereas the level of 53BP1 foci induced by MDR exposure for 10 days (4 Gy in total) was reduced to the control level by 7 days after the completion of exposure. It should be noted that MDR exposure, but not LDR exposure, accumulated DNA damage in tissues/organs.

The present study demonstrates that DNA damage accumulation might not be manifested if the DSB level does not exceed the ability of tissue repair response. Intriguingly, the frequency of Ki-67 was significantly increased in the bronchioles 3 days after HDR exposure at terminal bronchiolar regions, where the lung stem cells are assigned. It is concluded that such dose- and dose rate-dependent tissue responses should be taken into account for the estimation of cancer risks from the chronic low-dose and low-dose-rate radiation exposure.

The intestinal stem cell turnover (T Iwasaki)

The dose-rate effect of radiation-induced cancer is one of the most important issues in improving risk estimation for radiological protection. The current concept of radiological protection is based on the LNT model, which implies that risk would increase dependent on total dose but independent of dose rate. Some epidemiological data suggest the possibility that radiation-induced cancer risks would not increase at low dose rate (e.g., Nair et al. 2009), but this is still controversial and needs to be underpinned by biological mechanisms. Tissue stem cells have been discussed as the cells of origin for cancers, and understanding the behavior of tissue stem cells after ionizing radiation exposure can therefore contribute to the clarification of the mechanisms of radiation carcinogenesis.

In general, a constant number of stem cells are maintained in the tissue as stem cell pool. If an accumulated dose becomes sufficiently higher than an elemental dose (i.e., 1 mGy of γ-rays), high-dose-rate radiation would injure all of the tissue stem cells in the pool at the same time. Furthermore, in this situation, loss of stem cells would occur by radiation-induced cell death, or by aging and exhaustion as a consequence of DNA damage induction. The stem cell pool can therefore be replenished by proliferating damaged, radioresistant, and slow-cycling stem cells. This replenishment could be observed as an accelerated turnover of cycling stem cells. Thus, it can also contribute to accumulation of radiation damage in the stem cell pool.

When the dose rate is low enough, only a limited number of stem cells in the pool would be injured. Recently, cell competition between normal and cancer-initiated cells has been reported (Kajita and Fujita 2015). If the competition between radiation-damaged and surrounding normal cells occurred in case of low dose rate, damaged cells could be eliminated from the pool. If this tissue level maintenance system for genomic integrity exists, it may explain the low-dose-rate epidemiological data (e.g., Nair et al. 2009). This hypothesis was verified by a simple stochastic numerical model to simulate the recovery mechanisms of cycling stem cells, and it was found that even when the strength in competition was small, damage accumulation was suppressed, when the dose rate is lower than the turnover rate of cycling stem cells.

To evaluate turnover rates of stem cells and their radiation response, the conventional methods to observe loss of tissue stem cells, such as via apoptotic cell death, only provide snapshots of biological phenomena. However, long-term, cumulative effects of radiation, characteristic of low-dose-rate exposures, could not be estimated well. As an alternative method, the lineage tracing system has been used as a tool for chasing target cells in tissues. Here, *Lgr5-EGFP-IRES-Cre^{ERT2}* × *ROSA26-LSL-LacZ* mice were used, which express Cre^{ERT2} in EGFP-expressing Lgr5^{+} intestinal stem cells. In this model system, administration of tamoxifen results in translocation of Cre^{ERT2}-fused proteins into nuclei, and expression of the *LacZ* gene can be induced by Cre/loxP recombination. Once *LacZ* is expressed, Lgr5^{+} stem cells and their daughter cells continuously express β-galactosidase, allowing visualization of those cells in crypts. Loss of labeled crypts can indicate the replacement of cycling stem cells by replenishment from slow-cycling stem cells. It was found that colonic Lgr5^{+} stem cells are highly radiosensitive, and that the stem cell pool was replenished by non-labeled, probably slow-cycling, stem cells even after low-dose (1 Gy) irradiation (Otsuka et al. 2013). However, mice exposed to 1 Gy of low-dose-rate γ-irradiation (3 mGy/h) did not exhibit a significant acceleration of stem cell replenishment (Otsuka and Iwasaki 2015).

Under some dose-rate conditions of less than 30 Gy/h, clear dose-rate effects were found, and the trend suggests that there may be a dose-rate limit to induce replenishment, which is related to cancer progression. Under this "dose-rate limit," elimination of damaged stem cells by stem cell competition as well as induction of DNA repair and apoptotic cell death would be important to maintain genomic integrity. However, the validity of the concept of stem cell competition still has to be confirmed further. For

example, it should be investigated whether radiation could induce competition and whether even a single track of γ-irradiation could cause it. Low dose rate is defined as less than 0.1 mGy/min, to provide evidence-based estimates of the risks to human health (UNSCEAR 2010). The data presented here may also suggest that the range of low dose rate can be divided into at least two sub-ranges which have different significance in terms of accumulating radiation damage in tissues.

Cancer risk in epidemiologic studies of radiation exposure at low doses or low dose rates (R Shore)

The amount of risk at low radiation exposure levels is currently a major question in radiation risk assessment and radiological protection, prompted by concerns such as the adverse effects of Fukushima fallout, computed tomography examinations, and occupational radiation exposures. Radiological protection agencies are questioning how large a DDREF should be applied to the A-bomb risk coefficients in estimating risk after LDLDR exposures of low-LET radiations. DDREF is thought to represent two related factors: an LDEF for single acute exposures, and a DREF for exposures delivered as many small fractions or at low dose rates.

The LDEF can be examined in the LSS of the A-bomb survivors by determining whether there is evidence of upward curvature of the dose–response function that suggests a relative sparing effect at low doses. The LSS data have historically indicated only a linear effect. The most recent mortality report (Ozasa et al. 2012), however, reported upward curvature for solid cancer deaths over the range of 0–2 Gy, though the degree to which that curvature is due to a low-dose sparing effect indicative of an LDEF is uncertain. Note that the dosimetry for A-bomb survivors is currently being improved in terms of the accuracy of individual geographic locations and terrain shielding estimates, which may have some influence on the shape of the dose–response curve. The choice of the control population is another parameter that is important and might influence curvature in the LSS data. In general, in the analyses at Radiation Effects Research Foundation (RERF), all those within 10 km from the hypocenter were included in the baseline, along with a "not in city" subsample of individuals. The modest differences in tumor rates among the zero dose subgroups have been explored previously (Cologne and Preston 2001; Preston et al. 2007), and a composite of those subgroups has been used in recent papers (Preston et al. 2007; Ozasa et al. 2012).

In recent years, a number of LDLDR epidemiologic studies have provided risk estimates that can potentially be used to derive an estimate for DREF. Based on compilations from the literature, available LDLDR data for total solid cancer mortality, and for some major cancer subtypes such as breast, lung, colon, stomach, and liver, were summarized. The DREF will be examined by comparing the quantitative risk estimates from LDLDR studies with the LSS estimates.

Since whole-body irradiation can potentially affect all organs, an analysis of total solid cancers is informative and affords a risk assessment with greater statistical power and precision than assessments for individual organs. In examining the available data, an attempt was made to minimize data redundancy among reports inasmuch as possible. For solid cancer mortality, 24 independent LDLDR studies with dose–response-based risk estimates have been identified to date. They represent about 940,000 individuals and 15.7 million person-years of follow-up, with a collective dose of 35,600 person-Sv and over 25,000 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). Exposures were to low-LET radiation, except four that had both external γ exposures and significant high-LET internal exposures (Mayak and Rocky Flats plutonium workers, and Port Hope and German uranium processing workers), requiring the authors to statistically factor out the internal exposure contributions to risk.

If one examines the 19 of the 24 dose–response-based LDLDR studies that had at least 100 solid cancer deaths, it is notable that 13 out of the 19 studies had positive risk coefficients, though only five were statistically significant in the positive direction, which is not surprising since individual LDLDR studies typically have low statistical power. A meta-analysis will be performed of risk coefficients in the available studies in comparison with the A-bomb LSS risk coefficients for the subsets of LSS individuals with comparable composition by sex, ages at exposure, and ages at observation.

Although an analysis of total solid cancer risk after LDLDR exposures provides a broad assessment of DDREF, it may represent a mixture of discrepant DDREF's for various types of cancer. Radiation effects for various types of cancer may be modified diversely according to differences in tumor biology—pertaining to genetic pathways of varying complexity and redundancy, epigenetic influences, and tissue and metabolic cofactors. Various environmental or lifestyle risk factors may interact with certain cancer types but not with others, e.g., smoking effects may modify radiogenic lung cancer risk but not breast cancer risk. Risk transport to different populations appears to vary among cancer types as well. It is an open question as to whether such factors may impact risks differently at low doses or low dose rates for various cancer types. 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 are planned, but at this time, only descriptions of the individual studies are available.

Seven LDLDR studies of breast cancer were found that had 70 or more cancer cases. These were mainly incidence studies in view of the relatively low lethality of breast cancer, though two mortality studies were also included. Four of the studies were of fractionated or low-dose-rate medical exposure (X-ray examinations for scoliosis, fluoroscopic examinations during pneumothorax treatment for pulmonary tuberculosis, and radium applicators for skin hemangioma). Five of the six studies had positive risk coefficients, of which four were statistically significant. A consideration in interpreting the findings is that the medical exposure studies had fairly high dose rates, though they consisted of many small dose fractions spread out over a considerable time in the case of the scoliosis and two tuberculosis fluoroscopy studies.

Of 12 LDLDR studies of lung cancer mortality with 100 or more cases, 11 were radiation worker studies. Of these, six had positive risk coefficients; three were statistically significant in the positive direction and two in the negative direction. This suggests little evidence of an association for LDLDR studies, although it is possible that variation in smoking histories across the dose ranges might be confounding the risk estimates.

Only four LDLDR studies of stomach cancer had at least 100 deaths, and another three had 70–100 deaths. Five were worker studies, and two were environmental exposures (Techa River and Yangjiang, China). Six of the seven had positive risk coefficients, but none was statistically significant. The small numbers of LDLDR studies with 50 or more deaths from colon cancer (4 positive:4 negative risk coefficients) or liver cancer (4:2, respectively) did not provide material evidence of radiation effects for those endpoints.

It is concluded that, although meta-analyses of risk estimates for the LDLDR studies of radiation effects in comparison with LSS risk estimates are not yet available, an informal assessment of the results suggests that there is a positive effect for total solid cancer, and that there may be risk for breast cancer and stomach cancer. However, the data are unclear regarding risk for lung, colon, and liver cancer after LDLDR exposures to low-LET radiation, because of sparse data or possible confounding.

Results of epidemiological studies of the Mayak worker and Techa River cohorts (T Azizova)

One of the main objectives of radiation research is assessment of health effects of radiation exposure. Estimates of risks of incidence and mortality from cancer and non-cancer effects following radiation exposure are provided by epidemiological studies of various cohorts involving radiation-exposed individuals (as a result of nuclear accidents, occupational exposure, technogenic exposure, or medical exposure).

Epidemiological studies in the Mayak worker cohort, the cohort of workers of the first Russian nuclear enterprise, and the Techa River cohort, which includes individuals exposed to radiation due to radioactive releases in the river, are 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 Mayak worker cohort, complete information on both incidence and mortality is available, and regular data completeness and quality assurance checks are performed (diagnosis verification). Information on initial health status and non-radiation factors such as smoking, alcohol consumption, body mass index, hypertension and others is available for the majority of the Mayak worker cohort (approximately 93 %). For both cohorts, sufficient statistical power may be achieved to study incidence and mortality.

Efforts were made to obtain dose information that is as reliable as possible for both cohorts. For example, radiation exposures to the Techa River cohort members included external γ-ray exposure from river sediments and flood plain soil, and internal exposure from the consumption of water and milk contaminated primarily by strontium (^{89}Sr and ^{90}Sr) and cesium (^{137}Cs). The Techa River Dosimetry System (TRDS) was developed to support epidemiological studies of the Techa River cohort (Degteva et al. 2000, 2006, 2009; Shagina et al. 2012a, b). The TRDS uses the large number of measurements of long-lived radionuclides in the human body and in the environment, as well as measurements of external exposure rates at places where the Techa River cohort members lived.

External exposure was the major pathway for residents of villages located in the upper Techa region close to the site of the releases. The external dose rate peaked in 1951 and subsequently declined with time. Doses from external exposure markedly decreased with the distance along the Techa River. The major pathway of internal exposure of the Techa River cohort members was the intake of radionuclides through the consumption of river water and cow milk. Radionuclide intake decreased with the distance from the release site, and also depended on the availability of drinking water sources other than the contaminated river (such as wells) in the riverside villages (Tolstykh et al. 2006, 2011).

The intake estimates were derived from numerous data on tooth β-counts and whole-body counts for the Techa

River cohort members. Dose was unevenly distributed throughout the body due to the intake of strontium (^{89}Sr and ^{90}Sr), which resulted in elevated levels of absorbed dose to the bone marrow, bone surfaces, and the large intestine. Exposures to other tissues, mainly from external exposures and cesium (^{137}Cs) intake, were lower and relatively homogenous. Cesium is a major contributor to the red bone marrow dose. The proportion is estimated from 50 to 90 %, and depends on the distance from the site of radioactive releases into the Techa River. Cesium contribution to the dose to soft tissues is significantly lower, i.e., 15–20 % (Degteva et al. 2012).

With regard to the Mayak worker cohort, in contrast to the Techa River cohort, individual doses from external γ-rays measured by individual film badges are available for all workers (Vasilenko et al. 2007). Absorbed doses from internal α particles to organs were calculated based on individually measured α activity of plutonium in the urine samples (Khokhryakov et al. 2013).

Results of epidemiological studies of these two cohorts performed during the last years provide evidence for increased risks of cancer and non-cancer effects associated with both external and internal radiation exposures over prolonged periods delivered at a low dose rate. With regard to the Techa River cohort, there was a significant linear association of leukemia [excluding chronic lymphocytic leukemia (CLL)] mortality with absorbed dose from external γ-rays to the red bone marrow, suggesting an ERR per unit dose (at 100 mGy) of 0.22 [95 % confidence interval (CI): 0.08, 0.54]. In a model in which the ERR was allowed to vary with attained age, the ERR was estimated to increase in proportion to age to the power 0.45 (95 % CI: −1.1, 3.0), but this effect was not statistically significant ($p > 0.5$). There was no evidence of heterogeneity in the risk across four age-at-exposure groups (0–19, 20–29, 30–39, and 40 or more) ($p = 0.45$) (Krestinina et al. 2013). As regards the Mayak worker cohort, leukemia excluding CLL indicated a nonlinear dose–response relationship for external γ-ray exposure with exponential effect modifiers based on time since exposure and age at exposure. In this model, the central estimate of ERR/Gy is 0.54 (90 % CI: 0.18, 1.30) for 25 years of age at exposure 25 years since exposure (Kuznetsova et al. 2015).

As for solid cancer, there was a significant linear association of solid cancer mortality among members of the Techa River cohort with absorbed dose to the stomach with ERR/Gy 0.61 (95 % CI: 0.04, 1.27, $p < 0.03$). There were suggestions that the ERR/Gy increased with either older age at first exposure ($p = 0.05$) or older attained age ($p = 0.10$). When age at first exposure was used as an effect modifier, the ERR/Gy was estimated to increase by a factor of 2.2 (95 % CI: 1.0, 8.0) for each decade increase in age at first entry. With log-attained age as an effect modifier, the increase in the ERR/Gy with increasing age was estimated to be proportional to age to the power 5.1 (95 % CI: −0.7, 16.9). Estimates of the attained age effect on the ERR/Gy depended rather markedly on how the effects of attained age and oblast differences were addressed in the baseline rate model; this complicates the quantification and interpretation of this effect (Schonfeld et al. 2013).

The most frequent cancer type observed is stomach cancer, followed by lung cancer and breast cancer. During the last decades, the proportion of breast cancer has increased. However, due to a relatively low number of followed cases, only a preliminary ERR estimate for breast cancer was obtained in the Techa River cohort. In addition, it should be noted that multiple non-radiation factors may contribute to development of breast cancer, such as age and the number of childbirths (Ostroumova et al. 2008). As compared to stomach cancer, the proportion of intestinal cancer is significantly lower. It is noted, however, that risk analysis of a certain cancer site including intestinal cancer has low statistical power due to low number of cases.

In the Mayak worker cohort, there was also a significant linear association of mortality from solid cancers (excluding lung, liver, and bone cancers related to internal α particles) with absorbed colon dose from external γ-rays when adjusted for internal α dose, ERR/Gy = 0.12 (95 % CI: 0.03, 0.21, $p < 0.01$). There was no significant effect modification by sex or attained age. Exclusion of the adjustment for dose from internal α particles resulted in the increase in the risk estimate with ERR/Gy = 0.16 (95 % CI: 0.07, 0.26, $p < 0.001$) (Sokolnikov et al. 2015).

It is concluded that epidemiological studies in the Mayak worker cohort and the Techa River cohort are a very important source of information on the influence of radiation dose and dose rate on health effects, and may contribute toward a quantitative estimate of DDREF based on human data.

Epidemiological studies in high background radiation areas (S Akiba)

The coastal belt of Karunagappally Taluk in Karunagappally in Kerala State, India, is known for natural high background radiation (HBR) from thorium-containing monazite sand (Hosoda et al. 2015). In certain locations on the coast, the ambient dose rate is as high as 70 mGy per year. A cohort of all residents in Karunagappally Taluk was established in the 1990s to evaluate health effects of HBR (Nair et al. 2009). Radiation-related cancer incidence was analyzed using the data obtained from the follow-up of a radiation sub-cohort. Cumulative radiation doses, lagged

by 10 years for cancer excluding leukemia, were estimated for each individual, using outdoor and indoor doses of each household as well as sex- and age-specific house occupancy factors. Newly diagnosed cancer cases were identified through the Karunagappally Cancer Registry, which was established in 1990. Cancer incidence data obtained from this regional cancer registry are included in the Cancer Incidence in Five Continents, published by the International Agency for Research on Cancer (IARC) (Nair et al. 1997, 2002; Jayalekshmi and Rajan 2007). Following 69,958 residents for 10.5 years on average, 736,586 person-years of observation were accumulated, and 1379 cancer cases including 30 cases of leukemia were identified by 2005. The Poisson regression analysis of cohort data, stratified by sex, attained age, follow-up intervals, socio-demographic factors, and bidi smoking, showed no excess cancer risk from exposure to terrestrial γ-rays. The ERR/Gy of cancer excluding leukemia, assuming a linear dose–response relationship, was estimated to be -0.13 (95 % CI: -0.58, 0.46). In site-specific analysis of solid cancers, no cancer site was significantly related to cumulative radiation dose. Recently, cross-sectional studies on thyroid nodules, atherosclerosis, and lens opacities were completed.

Yangjiang area in Guandong Province, China, is known for its HBR area, where fine particles of monazite are washed down the mountains by rain, and accumulated in river basin and delta, giving rise to soil with high levels of radioactive nuclides, such as ^{232}Th and ^{238}U. Most residents in Yangjiang have lived there for six or more generations (High Background Radiation Research Group, China 1980). Ambient dose rates in the HBR and control areas were estimated to be 2.10 and 0.77 mGy per year, respectively. Individual dose from internal exposure has not been estimated, but doses to the lung from internal exposure through inhalation of radon and thoron progenies are estimated to be larger than those from external exposure (Kudo et al. 2015).

It is noted that the contribution of radon and its progeny and thoron progeny to lung dose were found significant in those two HBR studies. However, neither in the Yangjiang study nor in the Karunagappally study, lung cancer risk in the HBR areas was higher than that in the control areas. Thus, those two HBR studies presented no evidence indicating that radon and its progeny or thoron progeny contribute to lung cancer risk. Note that thoron gas is not considered to be related to lung cancer risk because of its short half-life.

In a China-US collaborative study conducted in the late 1980s, the frequency of stable-type chromosome aberrations in peripheral lymphocytes was found to be 0.29 (per 100 metaphases) in the HBR area and was 0.18 in the control area, for which the difference was statistically insignificant. On the other hand, the frequency of unstable-type chromosome aberrations in the HBR and control areas was 0.16 and 0.06, respectively, and the excess in the HBR area was statistically significant ($p = 0.04$) (Wang et al. 1990). Recent chromosome studies in Yangjiang showed that the cumulative HBR dose was significantly related to the frequency of unstable-type chromosome aberrations, but not to that of stable-type aberrations (Hayata et al. 2004). The major purpose of the China-US collaborative study was to examine thyroid nodule prevalence, and no excess thyroid nodules were found in HBR areas (Wang et al. 1990).

Cancer and non-cancer disease mortality rates were examined in the cohort of 31,604 men and women aged 30–74 years living in Yangjiang area during the period 1979–1998 examined (Tao et al. 2012). Cumulative doses from external exposure, lagged by 10 years for cancer excluding leukemia, were estimated for each individual based on hamlet-specific indoor and outdoor doses, and sex- and age-specific house occupancy factors. The follow-up study accumulated 736,942 person-years at risk, and ascertained 6005 deaths, including 956 cancer deaths (14 deaths of leukemia). Mean cumulative radiation doses among the HBR and control area residents were 84.8 and 21.6 mGy, respectively. The ERR/Gy of cancer excluding leukemia was estimated to be -1.01 (95 % CI: -2.53, 0.95). In site-specific analysis, liver cancer mortality was inversely related to the cumulative dose ($p = 0.002$). Since mortality of non-cancer liver disease tended to increase with cumulative radiation dose ($p = 0.061$), misdiagnosis between liver cirrhosis and liver cancer was suspected. When liver cancer and leukemia were excluded from all cancers, the ERR/Gy was 0.19 (95 % CI: -1.87, 3.04).

On the basis of studies of A-bomb survivors, the dose–response relationship between solid cancer risk and radiation exposure is considered to be linear. However, whether the ERR per dose associated with chronic exposure is lower than that of acute exposure remains unclear. It is concluded that the Karunagappally cohort study appears to provide a good chance to address this question, while the Yangjiang cohort study does not seem to have a sufficient statistical power for such a cancer risk comparison.

It should be noted, however, a comparison of the radiation-related cancer risk among A-bomb survivors with those obtained from studies on chronic exposure is not straightforward. In the cancer incidence study in the LSS cohort (Preston et al. 2007), for example, the ERR/Gy for solid cancer was 0.47 for those exposed at age 30 and attained the age of 70. This is the value based on the assumption that the sex ratio in the population is 1:1. For male subjects, the corresponding ERR/Gy is 0.35. Although adjustment (more exactly, standardization) for

sex is straightforward, age at exposure and attained age are more complicated to handle. In the LSS, the ERR per Gy decreased by about 17 % per decade increase in age at exposure (90 % CI: 7 %, 25 %), and the ERR decreased in proportion to attained age to the power 1.65 (90 % CI: 2.1, 1.2).

These modification coefficients are mutually independent. In the case of HBR area residents, age at first exposure is zero. However, since the exposure takes place over a long period of time, it does not seem to be a good idea to use age at first exposure as age at exposure. Therefore, a complicated calculation is desirable, taking into account the age-at-exposure structure of the HBR area population, using a risk model obtained from the LSS. A possible approach to obtain a single estimate is to calculate a weighted sum of coefficients for age-at-exposure subgroups (taking into account other factors, including attained age). However, the ERR estimate obtained from such a calculation can be approximated by an ERR estimate at a weighted sum (e.g., average) of age at exposure if the modifying effect is small enough.

In the IARC 15-country study of nuclear workers, the ERR estimate at the age at exposure of 35 was calculated, using the risk model obtained from the LSS. It should be noted, however, that a more complicated approach is necessary if the magnitude or direction of age-at-risk dependence of ERR/Gy in the population to be compared is different from that in the LSS. Another problem is the attained age.

For illustrating the problem of using an average attained age, an extreme example seems useful. Consider a male cohort consisting of two sub-cohorts with different attained age structures. Both sub-cohorts consist of exposed and unexposed cohort members. Suppose that the follow-up of a young sub-cohort accumulated 5 million person-years, and the average attained age for this sub-group is 35 years. Also suppose that 4 million person-years are accumulated by the follow-up of the other sub-cohort with the average attained age of 70. In this case, the average attained age for all the cohort members in this study is approximately 45 years. However, if the younger sub-cohort does not have any cancer cases during the follow-up regardless of exposure status, and all cancer cases are found only among the older sub-cohort, then the young sub-group does not make any contribution to ERR estimation; the ERR/Gy estimate is determined only by the older subgroup. In this case, it does not seem a good idea to compare the ERR/Gy estimate obtained from this study with that of male A-bomb survivors using attained age: needless to say, age at exposure should also be taken into account in this comparison, but it was ignored for the sake of simplicity.

Discussion

The above-mentioned issues already indicate a number of questions that remain open and probably need to be addressed in future studies. Some of these questions are raised below in an effort to stimulate and structure the current debate on DDREF.

Should DREF and LDEF be separated or combined as DDREF?

The DREF is a correction factor for low-dose-rate exposure, while the LDEF corrects for low-dose exposure. As was outlined above in more detail, based on an LQ dose–response curve, the numerical values of DREF and LDEF are similar at low doses and low dose rates if the α term of the curve does not depend on dose rate. If this assumption is not correct, DREF and LDEF should first be investigated separately before one decides whether to combine them in one factor. While such a debate is based on scientific arguments, one should also keep in mind that ICRP introduced the DDREF for radiological protection purposes. The system of radiological protection must be practicable and therefore reasonably simple, while an introduction of two different factors might complicate the situation. Nevertheless, it is important to understand the scientific aspects to make the best possible decisions on the radiological protection aspects.

Should a DREF also be applied to leukemia?

It is generally accepted that the incidence of leukemia other than CLL or adult T cell leukemia (ATL) among A-bomb survivors can be described by an LQ dose–response curve (Hsu et al. 2013), and that the curvature observed suggests a significant reduction in effect at low doses. Consequently, any low-dose effects are already described by the linear term of the curve, and application of an LDEF is not necessary in this case. For this reason, ICRP has decided not to apply the DDREF to leukemia in its system of radiological protection (ICRP 2007). It is noted again, however, that this approach implicitly assumes that the α term in the LQ dose–response curve does not depend on dose rate. In contrast, for example, if the α term in an LQ model depends on dose rate, as was argued above, then one should consider this possibility also for leukemia, and a DREF could be applied in addition to the LQ curvature. As a consequence, the risk for leukemia in the radiological protection setting (characterized by low doses and low dose rates) may be less than currently assumed.

An aspect that complicates the discussion on leukemia might be that dose dependence is not the same for the

induction of different types of leukemia. For example, it is the incidence of acute myeloid leukemia (AML) in the LSS that drives the LQ dose response observed for leukemia other than CLL and ATL, while the data on acute lymphoblastic leukemia (ALL) and chronic myeloid leukemia (CML) among A-bomb survivors suggest a linear dose response (Hsu et al. 2013). This suggests that biological aspects should also be considered for leukemia. Moreover, the results of different leukemia studies must be compared to care, because the development of leukemia is highly time dependent, and the risk is highest in the first 10 years after exposure (Hsu et al. 2013).

Nonetheless, it may be argued that leukemia is one of the cancer types in which low-dose-rate exposure is important and could be studied. In this context, the available datasets of 7000 dogs (Carnes and Fritz 1991, 1993) have never been analyzed for leukemia induction at low dose rates, and it may be valuable to initiate such analyses in the future. Regarding human epidemiological studies, there are a number of low-dose and low-dose-rate studies, for example, on nuclear workers (Daniels et al. 2013; Leuraud et al. 2015), or on populations exposed to natural levels of ionizing radiation (Kendall et al. 2013; Spycher et al. 2015), which could be used, and their results could be compared to those obtained from A-bomb survivors.

As aforementioned, however, if the situation turns out to be scientifically complicated, there will be a need for some simplification, to translate the scientific findings into approaches that are usable for radiological protection purposes.

How robust are the scientific results obtained from human epidemiological studies at low doses and low dose rates?

Robustness concerns pooled analyses versus meta-analyses, and many believe that pooled analyses are more reliable. However, one should keep in mind that confirmed risk factors are different from cancer to cancer, and from country to country, and that when different studies are compared, one is limited to factors with commonly available data in these studies. There are many known factors that contribute to induction of solid cancers or leukemia, and their influence on risk estimates deduced from epidemiological studies must be carefully studied. For example, smoking is important for the induction of lung cancer, while chronic alcohol consumption is important for liver cancer. Indeed, adjustment for smoking and particularly alcohol consumption altered risk estimates in the Japanese worker study (Akiba and Mizuno 2012). However, this is not necessarily true in other studies. For instance, the IARC 15-country study did not find substantial confounding by smoking (and no alcohol data were available); the main potential confounders in that study were duration of employment and socioeconomic status (Cardis et al. 2007). Adjustment for duration of employment (Vrijheid et al. 2007a, b) was important, because those who were employed for a short time might have a lifestyle different from those employed for a longer time, meaning, for example, that short-term workers may tend to consume more alcohol and tobacco than long-term workers. Therefore, alcohol and tobacco consumptions are again important factors. So, investigators of occupational studies should adjust for duration of employment if needed. For these reasons, it is preferable to identify the relevant factors for each epidemiological study separately before conducting a combined analysis.

However, combining epidemiological studies can be helpful. After exposure to low doses of ionizing radiation, the probability of induction of effects such as chromosome aberrations at the cellular level or cancer and leukemia induction at the organism level is rather low. It is therefore difficult to quantify any such effects with high precision at these low-dose levels. With regard to epidemiological studies, for example, the number of investigated individuals in an exposed cohort is critical, and pooling several exposed cohorts using individual raw data is usually beneficial for statistical reasons. This was already demonstrated in studies on the cancer risk of nuclear workers due to occupational exposures (Cardis et al. 2005) or on lung cancer risk of populations due to indoor radon exposure (Darby et al. 2005). It is highly desirable that individual raw data be made available from all large epidemiological studies, to allow for more of such combined pooled studies. If such data are not available, however, meta-analyses can still be performed where the risk estimates deduced from single studies are combined to obtain an average risk value. In such studies, it is important to avoid analyses where one study dominates the overall result, making the deduced mean value less robust. In a meta-study by Jacob et al. (2009), results from various studies were analyzed separately and compared to results from A-bomb survivors (matched for age distribution, and sex) before weighted averages were calculated. The robustness of the combined results was then tested by leaving out each single study, in an effort to quantify the influence of any single study on the combined result.

In this context, it might also be important to note that even within a low-dose-rate epidemiological study, there could be some differences in dose rates that might be difficult to quantify. For example, in a nuclear worker study, there could be workers exposed at a low dose rate and those at a high dose rate. It may well be that those who work closer to the reactor core at higher dose rates are mostly contractors whose lifestyle could be different from those who work farther away from the reactor core at lower dose rates who may be mostly permanent employees.

Animal studies: how variable are other factors besides radiation?

When BEIR VII published their estimate on DDREF, the committee used as a major input grouped animal data that had been produced at the US Oak Ridge National Laboratory, and data from this single source of information greatly influenced the DDREF value. If more animal studies could be included in such an analysis, the robustness of the BEIR VII estimate of DDREF could be tested and enhanced. It is important to note that since publication of the BEIR VII report in 2006, the US Janus Tissue Archives (Haley et al. 2011; Wang et al. 2010) and the European Radiobiology Archives (Tapio et al. 2008; Birschwilks et al. 2011) collected individual data on many additional animal experiments. These archives have incorporated data from past studies. To allow the archiving of recent animal and human studies, a web-based repository named STORE for data and a pointer to biomaterial has been developed (http://www.storedb.org or http://rbstore.eu). Moreover, there is currently a large animal experiment ongoing at IES. In the context of cooperation, IES could be an important counterpart from Japan, although the IES dose rate data may still require some additional time until they will become available. In any case, nowadays there are many more animal data available for analysis than there were at the time when BEIR VII published their report on DDREF, and it is argued here that as much data as possible should now be used to address the influence of ionizing radiation and other factors on various biological outcomes. Any animal study may have specific problems, but by using large datasets (e.g., 200,000 animals), one may be able to address at least some of these problems, especially for dose-rate studies.

Are animal data applicable to humans?

The difficulty to extrapolate from mice to humans has been acknowledged for a long time. For example, in the US Argonne National Laboratory (ANL) animal dataset available for life shortening, some mice got exposed at an older age, and despite chronic exposure, their life span did not change considerably compared to non-exposed mice. This was especially true for 6-month-old mice. In contrast, humans at younger ages are more sensitive to radiation than at older ages, but some sensitivity remains at older ages as well (Preston et al. 2007; Hsu et al. 2013). Thus, proper mathematical models are needed to correct for this effect.

It is noted, however, that if dose-rate effects observed among mice and dogs could be compared in a reasonable way, then one would get at least a rough idea on interspecies differences. This could also help to judge the validity of any extrapolation from animal data to humans. The ANL datasets involving about 21,000 dogs could contribute to investigating this problem. It is therefore emphasized here again that there is a need to better use the tissue archives that have recently become available, and that the opportunity to do so now is thanks to recent and ongoing efforts to preserve these data.

Which endpoints are relevant in radiobiological studies?

In general, DNA damage is considered important, but currently, it is not really clear which specific DNA damage is relevant to the DDREF issue. There is no clear molecular endpoint identified specific for carcinogenesis, in particular because other parameters such as ethnicity or the immune system may also play an important role in carcinogenesis. It is thus concluded that further studies are needed to identify the radiobiological endpoints relevant to the present discussion on DDREF. Additionally, there is a growing awareness from cancer research in general that cancer development requires consideration of the microenvironmental and tissue context in which cancer cells develop as well as the primary target cells and cancer cells themselves.

How to integrate information (especially animal vs. human data)?

Regarding how to integrate information, statistical progress is currently being made. For example, the BEIR VII methodology of using state-of-the-art Bayesian models to integrate data is considered as an important step forward compared to earlier approaches. There may be further improvements in statistical capabilities. In addition, much larger datasets are now available, and machine learning-based approaches and neural networks may help interpret the available data. As these methods evolve, they may support some of the analyses needed for DDREF. It is noted, however, that although modern statistical techniques may be powerful, the need to reconcile human and animal data remains before applying these techniques. Use of archived tissue samples could open the way for an in-depth comparison between animals and humans.

Conclusions

Extrapolation of biological effects observed at high doses and high dose rates to low doses and low dose rates of ionizing radiation typical for radiological protection settings has become a central issue. Since the discovery of X-rays by Röntgen in 1895, the scientific evidence on this issue has continually been reviewed. In particular,

UNSCEAR has published a series of reports since 1958, which have been used by ICRP, in their efforts to protect workers, patients, and the public from the adverse effects of ionizing radiation without unduly limiting its beneficial uses.

Because scientific knowledge on the effects of ionizing radiation at molecular, cellular, tissue, and organism levels is continually increasing, a number of international bodies such as BEIR, SSK, UNSCEAR, and WHO have reviewed the scientific literature on this issue during the last decade. In particular, the concept of DDREF and its numerical estimate were critically analyzed, and depending on organization, different conclusions were reached.

The present paper has discussed the concept of DDREF. The DDREF concept as suggested by ICRP combines dose and dose-rate effects for radiological protection purposes, with the rationale being to keep radiological protection simple and practical. Given the discussion above, there is the need to reassess this approach. In particular, the suggestion is made that dose and dose-rate effects should be considered separately, at all levels of biological effect, keeping, for example, in mind that the linear term in an LQ dose–response curve might depend on dose rate. This does not exclude, however, that in the end, for the sake of simplification, ICRP will continue to use a combined single factor to describe extrapolation of risks from high doses and dose rates to low doses and dose rates typical for most radiological protection scenarios. However, the assessment must be made in light of the best scientific evidence.

As for endpoints at molecular and cellular levels, it is still unclear which endpoint is most relevant to the DDREF discussion, and more research is needed to identify markers that are indicators for carcinogenesis. However, molecular and cellular studies are indispensable for investigating the mechanisms behind radiation action. Many new biological phenomena, such as genomic instability, bystander effects, adaptive response (Hamada et al. 2011; Morgan and Sowa 2015), have been discovered during the last two decades, some showing different dose–response behavior at low doses. This highlights the complicated action of ionizing radiation. At present, it is still unclear to what extent such effects are of relevance to human disease and therefore for radiological protection. A significant challenge is presented by the lapse of time between the induction of effects at molecular and cellular levels, and the development of stochastic effects on the organism level such as cancer or leukemia, and furthermore there may be other and still unknown processes which also influence cancer development, the role of the immune system just being one example.

Animal experiments may offer some potential in this regard, because radiation-induced effects such as life shortening or tumor incidence manifest at the organism level, and on a timescale of several months or years. Nevertheless, the question of how to transfer results obtained in experimental animals to humans has been an issue for decades, and is still difficult to answer. It is important to note that, in contrast to earlier times, it is now much easier to analyze data jointly from many more animal studies that were performed in the past, due to the existence of newly established databases and tissue archives in the USA and Europe. Combined analysis of these data may offer the possibility of investigating radiation-induced effects (in particular in terms of dose and dose rate) with better statistical precision than before, thus providing results that are more robust, or to investigate inter-species differences among different animal models that would allow judgment of the uncertainties involved when results from animal experiments are extrapolated to humans.

Finally, there are a number of human cohorts with individuals who were exposed to ionizing radiation in the past, such as the A-bomb survivors, the population living downstream along the Techa River, various nuclear worker cohorts from all over the world, individuals who were exposed for medical reasons, and populations living in HBR areas. These studies are ongoing, and they regularly produce updates of the observed health effects with increasing follow-up period. It is now time to look at these new results and combine them in pooled studies or meta-analyses, albeit with care. The outcome of these studies is closest to what one is interested in radiological protection. It is also clear, however, that the results that can be obtained at dose and dose rate relevant to radiological protection will be difficult to quantify with high precision, because the probability of occurrence of stochastic effects such as the incidence of cancer or leukemia at those low doses and dose rates is low, and spontaneous incidence of cancer in the human population is high.

Acknowledgments The present paper is based on presentations held at and discussions stimulated during a one-day workshop on DDREF jointly organized by ICRP and JANUS, on May 22, 2015, in Kyoto, Japan. RS and WR acknowledge the contribution of Dr. Linda Walsh (Bundesamt für Strahlenschutz, Germany) toward the planned meta-analysis of epidemiological studies. RERF, Hiroshima and Nagasaki, Japan, is a public interest foundation funded by the Japanese Ministry of Health, Labour and Welfare (MHLW) and the US Department of Energy (USDOE). RERF research is also funded in part through USDOE award DE-HS0000031 to the NAS. This publication is associated with RERF Research Protocol 1-75. The views of the authors do not necessarily reflect those of the two governments. The study at IES is performed under contract with the Aomori Prefectural Government, Japan.

References

Akiba S, Mizuno S (2012) The third analysis of cancer mortality among Japanese nuclear workers, 1991–2002: estimation of excess relative risk per radiation dose. J Radiol Prot 32:73–83

Beels L, Bacher K, De Wolf D, Werbrouck J, Thierens H (2009) γ-H2AX foci as a biomarker for patient X-ray exposure in paediatric cardiac catheterization: are we underestimating radiation risks? Circulation 120:1903–1909

Beels L, Werbrouck J, Thierens H (2010) Dose response and repair kinetics of γ-H2AX foci induced by in vitro irradiation of whole blood and T-lymphocytes with X- and γ-radiation. Int J Radiat Biol 86:760–768

Birschwilks M, Gruenberger M, Adelmann C, Tapio S, Gerber G, Schofield PN, Grosche B (2011) The European radiobiological archives: online access to data from radiobiological experiments. Radiat Res 175:526–531

Cardis E, Vrijheid M, Blettner M, Gilbert E, Hakama M, Hill C, Howe G, Kaldor J, Muirhead CR, Schubauer-Berigan M, Yoshimura T, Bermann F, Cowper G, Fix J, Hacker C, Heinmiller B, Marshall M, Thierry-Chef I, Utterback D, Ahn YO, Amoros E, Ashmore P, Auvinen A, Bae JM, Solano JB, Biau A, Combalot E, Deboodt P, Diez Sacristan A, Eklof M, Engels H, Engholm G, Gulis G, Habib R, Holan K, Hyvonen H, Kerekes A, Kurtinaitis J, Malker H, Martuzzi M, Mastauskas A, Monnet A, Moser M, Pearce MS, Richardson DB, Rodriguez-Artalejo F, Rogel A, Tardy H, Telle-Lamberton M, Turai I, Usel M, Veress K (2005) Risk of cancer after low doses of ionising radiation: retrospective cohort study in 15 countries. BMJ 331:77

Cardis E, Vrijheid M, Blettner M, Gilbert E, Hakama M, Hill C, Howe G, Kaldor J, Muirhead CR, Schubauer-Berigan M, Yoshimura T, Bermann F, Cowper G, Fix J, Hacker C, Heinmiller B, Marshall M, Thierry-Chef I, Utterback D, Ahn YO, Amoros E, Ashmore P, Auvinen A, Bae JM, Bernar J, Biau A, Combalot E, Deboodt P, Diez Sacristan A, Eklöf M, Engels H, Engholm G, Gulis G, Habib RR, Holan K, Hyvonen H, Kerekes A, Kurtinaitis J, Malker H, Martuzzi M, Mastauskas A, Monnet A, Moser M, Pearce MS, Richardson DB, Rodriguez-Artalejo F, Rogel A, Tardy H, Telle-Lamberton M, Turai I, Usel M, Veress K (2007) The 15-country collaborative study of cancer risk among radiation workers in the nuclear industry: estimates of radiation-related cancer risks. Radiat Res 167:396–416

Carnes BA, Fritz TE (1991) Responses of the beagle to protracted irradiation. I. Effect of total dose and dose rate. Radiat Res 128:125–132

Carnes BA, Fritz TE (1993) Continuous irradiation of beagles with γ rays. Radiat Res 136:103–110

Cologne J, Preston DL (2001) Impact of comparison group on cohort dose response regression: an example using risk estimation in atomic-bomb survivors. Health Phys 80:491–496

Daniels RD, Bertke S, Waters KM, Schubauer-Berigan MK (2013) Risk of leukaemia mortality from exposure to ionising radiation in US nuclear workers: a pooled case-control study. Occup Environ Med 70:41–48

Darby S, Hill D, Auvinen A, Barros-Dios JM, Baysson H, Bochicchio F, Deo H, Falk R, Forastiere F, Hakama M, Heid I, Kreienbrock L, Kreuzer M, Lagarde F, Mäkeläinen I, Muirhead C, Oberaigner W, Pershagen G, Ruano-Ravina A, Ruosteenoja E, Rosario AS, Tirmarche M, Tomásek L, Whitley E, Wichmann HE, Doll R (2005) Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. BMJ 330:223

Degteva MO, Kozheurov VP, Tolstykh EI, Vorobiova MI, Anspaugh LR, Napier BA, Kovtun AN (2000) The Techa River dosimetry system: methods for the reconstruction of internal dose. Health Phys 79:24–35

Degteva MO, Vorobiova MI, Tolstykh EI, Shagina NB, Shishkina EA, Anspaugh LR, Napier BA, Bougrov NG, Shved VA, Tokareva EE (2006) Development of an improved dose reconstruction system for the Techa River population affected by the operation of the Mayak Production Association. Radiat Res 166:255–270

Degteva MO, Shagina NB, Tolstykh EI, Vorobiova MI, Anspaugh LR, Napier BA (2009) Individual dose calculations with use of the Revised Techa River Dosimetry System TRDS-2009D. Final Report for Milestone 22. Chelyabinsk, Russia and Sault Lake City, Utah: Urals Research Center for Radiation Medicine and University of Utah

Degteva MO, Shagina NB, Vorobiova MI, Anspaugh LR, Napier BA (2012) Reevaluation of waterborne releases of radioactive materials from the Mayak Production Association into the Techa River in 1949-1951. Health Phys 102:25–38

Gerber G, Watson C, Sugahara T, Okada S (1996) International radiobiology archives of long-term animal studies I. Descriptions of participating institutions and studies. Retrieved from http://www.ustur.wsu.edu/NRA/pdf/IRA.pdf

Ghandhi SA, Smilenov LB, Elliston CD, Chowdhury M, Amundson SA (2015) Radiation dose-rate effects on gene expression for human biodosimetry. BMC Med Genomics 8:22

Grudzenski S, Raths A, Conrad S, Rube CE, Lobrich M (2010) Inducible response required for repair of low dose radiation damage in human fibroblasts. Proc Natl Acad Sci USA 107:14205–14210

Haley B, Wang Q, Wanzer B, Vogt S, Finney L, Yang PL, Paunesku T, Woloschak G (2011) Past and future work on radiobiology mega-studies: a case study at Argonne National Laboratory. Health Phys 100:613–621

Haley B, Paunesku T, Grdina D, Woloschak G (2015) Animal mortality risk increase following low-LET radiation exposure is not linear-quadratic. PLOS ONE (submitted in June 2015)

Hamada N, Maeda M, Otsuka K, Tomita M (2011) Signaling pathways underpinning the manifestations of ionizing radiation-induced bystander effects. Curr Mol Pharmacol 4:79–95

Hayata I, Wang C, Zhang W, Chen D, Minamihisamatsu M, Morishima H, Wei L, Sugahara T (2004) Effect of high level natural radiation on chromosomes of residents in southern China. Cytogenet Genome Res 104:237–239

High Background Radiation Research Group, China (1980) Health survey in high background radiation area in China. Science 209:877–880

Hoel DG (2015) Comments on the DDREF estimate of the BEIR VII Committee. Health Phys 108:351–356

Hosoda M, Tokonami S, Omori Y, Sahoo SK, Akiba S, Sorimachi A, Ishikawa T, Nair RR, Jayalekshmi PA, Sebastian P, Iwaoka K, Akata N, Kudo H (2015) Estimation of external dose by car-borne survey in kerala, India. PLOS ONE 10:e0124433

Hsu W-L, Preston DL, Soda M, Sugiyama H, Funamoto S, Kodama K, Kimura A, Kamada N, Dohy H, Tomonaga M, Iwanaga M, Miyazaki Y, Cullings HM, Suyama A, Ozasa K, Shore RE, Mabuchi K (2013) The Incidence of Leukemia, Lymphoma and Multiple Myeloma among Atomic Bomb Survivors: 1950–2001. Radiat Res 179:361–382

ICRP (1991) 1990 Recommendations of the International Commission on Radiological Protection. ICRP Publication 60. Ann ICRP 21(1–3)

ICRP (2005) Low-dose extrapolation of radiation-related cancer risk. ICRP Publication 99. Ann ICRP 35(4)

ICRP (2007) The 2007 Recommendations of the International Commission on Radiological Protection. ICRP Publication 103. Ann ICRP 7(2–4)

ICRP (2013a) ICRP Main Commission Meeting. April 15 to 18, 2013—Cambridge, UK. http://www.icrp.org/docs/Summary%20of%20April%202013%20Main%20Commission%20Meeting%20in%20Cambridge%20UK.pdf

ICRP (2013b) Task Group 91. Radiation risk inference at low-dose and low-dose rate exposure for radiological protection purposes. http://www.icrp.org/icrp_group.asp?id=83

ICRP (2015) Stem Cell Biology with Respect to Carcinogenesis Aspects of Radiological Protection. ICRP Publication 131. Ann ICRP 44(3–4)

Jacob P, Rühm W, Walsh L, Blettner M, Hammer G, Zeeb H (2009) Is cancer risk of radiation workers larger than expected? Occup Environ Med 66:789–796

Jayalekshmi P, Rajan B (2007) Cancer incidence in Karunagapally 1998–2002, Kerala, India. In: Cuardo MP, Edwards B, Shin HR, Storm H, Ferlay J, Heanue M, Boyle P, eds. Cancer incidence in five continents, vol IX. Lyon: International Agency for Research on Cancer; IARC Publication 160

Kajita M, Fujita Y (2015) EDAC: Epithelial defence against cancer-cell competition between normal and transformed epithelial cells in mammals. J Biochem 158:15–23

Kellerer AM, Rossi HH (1972) The theory of dual radiation action. Curr Top Radiat Res Q 8:85–158

Kendall GM, Little MP, Wakeford R, Bunch KJ, Miles JC, Vincent TJ, Meara JR, Murphy MF (2013) A record-based case-control study of natural background radiation and the incidence of childhood leukaemia and other cancers in Great Britain during 1980-2006. Leukemia 27:3–9

Khokhryakov VV, Khokhryakov VF, Suslova KG, Vostrotin VV, Vvedensky VE, Sokolova AB, Krahenbuhl MP, Birchall A, Miller SC, Schadilov AE, Ephimov AV (2013) Mayak Workers Dosimetry System 2008 (MWDS-2008): assessment of internal α-dose from measurement results of plutonium activity in urine. Health Phys 104:366–378

Krestinina LY, Davis FG, Schonfeld S, Preston DL, Degteva M, Epifanova S, Akleev AV (2013) Leukemia incidence in the Techa River Cohort: 1953–2007. Br J Cancer 109:2886–2893

Kudo H, Tokonami S, Omori Y, Ishikawa T, Iwaoka K, Sahoo SK, Akata N, Hosoda M, Wanabongse P, Pornnumpa C, Sun Q, Li X, Akiba S (2015) Comparative dosimetry for radon and thoron in high background radiation areas in China. Radiat Prot Dosimetry. doi:10.1093/rpd/ncv235

Kuznetsova IS, Labutina EV, Hunter N, Haylock R (2015) Radiation risks of leukemia, lymphoma and multiple myeloma incidence among workers at the Mayak PA: 1948–2004. PLOS ONE (submitted in February 2015)

Leuraud K, Richardson DB, Cardis E, Daniels RD, Gillies M, O'Hagan JA, Hamra GB, Haylock R, Laurier D, Moissonnier M, Schubauer-Berigan MK, Thierry-Chef I, Kesminiene A (2015) Ionising radiation and risk of death from leukaemia and lymphoma in radiation-monitored workers (INWORKS): an international cohort study. Lancet Haematol 2:e276–e281

Löbrich M, Jeggo P (2007) The impact of a negligent G_2/M checkpoint on genomic instability and cancer induction. Nat Rev Cancer 7:861–869

Loucas BD, Eberle R, Bailey SM, Cornforth MN (2004) Influence of dose rate on the induction of simple and complex chromosome exchanges by γ rays. Radiat Res 162:339–349

Manning G, Kabacik Finnon P, Bouffler S, Badie C (2013) High and low dose responses of transcriptional biomarkers in ex vivo X-irradiated human blood. Int J Radiat Biol 89:512–522

Manning G, Taylor K, Finnon P, Lemon JA, Boreham DR, Badie C (2014) Quantifying murine bone marrow and blood radiation dose response following ^{18}F-FDG PET with DNA damage biomarkers. Mutat Res 770:29–36

Morgan WF, Sowa MB (2015) Non-targeted effects induced by ionizing radiation: mechanisms and potential impact on radiation induced health effects. Cancer Lett 356:17–21

Nair MK, Amma S, Mani KS (1997) India, Karunagappally 1990–1994. In: Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J, eds. Cancer incidence in five continents, vol VII. Lyon: International Agency for Research on Cancer; IARC Publication 143:350–353

Nair MK, Gangadharan P, Jayalakshmi P, Mani KS (2002) Cancer incidence in Karunagappally 1993–1997, Kerala, India. In: Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB, eds. Cancer incidence in five continents, vol VIII. Lyon: International Agency for Research on Cancer; IARC Publication 155:240–241

Nair RR, Rajan B, Akiba S, Jayalekshmi P, Nair MK, Gangadharan P, Koga T, Morishima H, Makamura S, Sugahara T (2009) Background radiation and cancer incidence in Kerala, India-Karanagappally cohort study. Health Phys 96:55–66

Nakajima T, Taki K, Wang B, Ono T, Matsumoto T, Oghiso Y, Tanaka K, Ichinohe K, Nakamura S, Tanaka S, Nenoi M (2008) Induction of rhodanese, a detoxification enzyme, in livers from mice after long-term irradiation with low-dose-rate γ-rays. J Radiat Res 49:661–666

NAS (2006) Health risks from exposure to low levels of ionizing radiation (BEIR VII Phase 2). National Academy Press, Washington

NCRP (1980) Influence of dose and its distribution in time on dose-response relationships for low-LET radiations, NCRP Report No. 64. Issued April 1, 1980. Bethesda, Maryland

Neary GJ (1965) Chromosome aberrations and the theory of RBE. General considerations. Int J Radiat Biol 9:477–502

Neumaier T, Swenson J, Pham C, Polyzos A, Lo AT, Yang P, Dyball J, Asaithamby A, Chen DJ, Bissell MJ, Thalhammer S, Costes SV (2012) Evidence for formation of DNA repair centers and dose-response nonlinearity in human cells. Proc Natl Acad Sci USA 109:443–448

Ojima M, Furutani A, Ban N, Kai M (2011) Persistence of DNA double strand breaks in normal human cells induced by radiation-induced bystander effect. Radiat Res 175:90–96

Okudaira N, Uehara Y, Fujikawa K, Kagawa N, Ootsuyama A, Norimura T, Saeki K, Nohmi T, Matsumura K, Matsumoto T, Oghiso Y, Tanaka K, Ichinohe K, Nakamura S, Tanaka S, Ono T (2010) Radiation dose-rate effect on mutation induction in spleen and liver of gpt delta mice. Radiat Res 173:138–147

Ostroumova E, Preston DL, Ron E, Krestinina LY, Davis FG, Kossenko M, Akleyev AV (2008) Breast cancer incidence following low-dose rate environmental exposure: Techa River Cohort, 1956–2004. Br J Cancer 99:1940–1945

Otsuka K, Iwasaki T (2015) Effects of dose rates on radiation-induced replenishment of intestinal stem cells determined by Lgr5 lineage tracing. J Radiat Res 56:615–622

Otsuka K, Hamada N, Magae J, Matsumoto H, Hoshi Y, Iwasaki T (2013) Ionizing radiation leads to the replacement and de novo production of colonic Lgr5$^+$ stem cells. Radiat Res 179:637–646

Ozasa K, Shimizu Y, Suyama A, Kasagi F, Soda M, Grant EJ, Sakata R, Sugiyama H, Kodama K (2012) Studies of the mortality of atomic bomb survivors, report 14, 1950–2003: an overview of cancer and noncancer diseases. Radiat Res 177:229–243

Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, Mabuchi K, Kodama K (2007) Solid cancer incidence in atomic bomb survivors: 1958-1998. Radiat Res 168:1–64

Rothkamm K, Löbrich M (2003) Evidence for a lack of DNA double strand break repair in human cells exposed to very low x-ray doses. Proc Natl Acad Sci USA 100:5057–5062

Russell WL, Kelly EM (1982) Mutation frequencies in male mice and the estimation of genetic hazards of radiation in men. Proc Natl Acad Sci USA 79:542–544

Schonfeld SJ, Krestinina LY, Epifanova S, Degteva MO, Akleyev AV, Preston DL (2013) Solid cancer mortality in the Techa River cohort (1950–2007). Radiat Res 179:183–189

Searle AG (1974) Mutation induction in mice. Adv Radiat Biol 4:131–207

Shagina NB, Vorobiova MI, Degteva MO, Peremyslova LM, Shishkina EA, Anspaugh LR, Napier BA (2012a) Reconstruction of the contamination of the Techa River in 1949-1951 as a result of releases from the "MAYAK" Production Association. Radiat Environ Biophys 51:349–366

Shagina NB, Tolstakh EI, Degteva MO, Vorobiova MI, Anspaugh LR, Napier BA (2012b) Re-evaluation of radionuclide intakes for Techa River residents on the basis of revised source-term parameters. Health Phys 103:S96–S97

Sokolnikov ME, Preston DL, Gilbert ES, Schonfeld SJ, Koshurnikova NA (2015) Radiation effects on mortality from solid cancers other than lung, liver and bone cancer in the Mayak Worker cohort: 1948–2008. PLoS ONE 10:e0117784

Spycher BD, Lupatsch JE, Zwahlen M, Röösli M, Niggli F, Grotzer MA, Rischewski J, Egger M, Kuehni CE, Swiss Pediatric Oncology Group, Swiss National Cohort Study (2015) Background ionizing radiation and the risk of childhood cancer: a census-based nationwide cohort study. Environ Health Perspect 123:622–628

SSK (2014) Dose- and dose-rate-effectiveness factor (DDREF), Recommendation by the German Commission on Radiological Protection with scientific grounds, http://www.ssk.de/SharedDocs/Beratungsergebnisse_E/2014/DDREF_e.html?nn=2876278

Takai D, Todate A, Yanai T, Ichinohe K, Oghiso Y (2011) Enhanced transplantability of a cell line from a murine ovary granulosa cell tumour in syngeneic B6C3F$_1$ mice continuously irradiated with low dose-rate γ-rays. Int J Radiat Biol 87:729–735

Taki K, Wang B, Nakajima T, Wu Y, Ono T, Uehara Y, Matsumoto T, Oghiso Y, Tanaka K, Ichinohe K, Nakamura S, Tanaka S, Magae J, Kakimoto A, Nenoi M (2009) Microarray analysis of differentially expressed genes in the kidneys and testes of mice after long-term irradiation with low-dose-rate γ-rays. J Radiat Res 50:241–252

Tanaka S, Tanaka BI 3rd, Sasagawa S, Ichinohe K, Takabatake T, Matsushita S, Matsumoto T, Otsu H, Sato F (2003) No lengthening of life span in mice continuously exposed to γ rays at very low dose rates. Radiat Res 160:376–379

Tanaka BI 3rd, Tanaka S, Ichinohe K, Matsushita S, Matsumoto T, Otsu H, Oghiso Y, Sato F (2007) Cause of death and neoplasia in mice continuously exposed to very low dose rates of γ rays. Radiat Res 167:417–437

Tanaka K, Kohda A, Sato K, Toyokawa T, Ichinohe K, Ohtaki M, Oghiso Y (2009) Dose rate effectiveness for unstable-type chromosome aberrations detected in mice after continuous irradiation with low-dose-rate γ-rays. Radiat Res 171:290–301

Tao Z, Akiba S, Zha Y, Sun Q, Zou J, Li J, Liu Y, Yuan Y, Tokonami S, Morishima H, Koga T, Nakamura S, Sugahara T, Wei L (2012) Cancer and non-cancer mortality among Inhabitants in the high background radiation area of Yangjiang, China (1979–1998). Health Phys 102:173–181

Tapio S, Schofield PN, Adelmann C, Atkinson MJ, Bard JL, Bijwaard H, Birschwilks M, Dubus P, Fiette L, Gerber G, Gruenberger M, Quintanilla-Martinez L, Rozell B, Saigusa S, Warren M, Watson CR, Grosche B (2008) Progress in updating the European Radiobiology Archives. Int J Radiat Biol 84:930–936

Tolstykh EI, Degteva MO, Vorobiova MI, Peremyslova LM, Shagina NB, Anspaugh LR, Napier BA (2006) Reconstruction of long-lived radionuclide intakes for Techa Riverside residents. Part 2. Cesium-137. Radiat Safety Problems Mayak Production Association Scientific Journal) Special issue 1:68–79 (in Russian, the English abstract is available separately in the issue)

Tolstykh EI, Degteva MO, Peremyslova LM, Shagina NB, Shishkina EA, Krivoshchapov VA, Anspaugh LR, Napier BA (2011) Reconstruction of long-lived radionuclide intakes for Techa Riverside residents: Strotium-90. Health Phys 101:28–47

Uehara Y, Ito Y, Taki K, Nenoi M, Ichinohe K, Nakamura S, Tanaka S, Ogisho Y, Tanaka K, Matsumoto T, Paunesku T, Wolschak GE, Ono T (2010) Gene expression profiles in mouse liver after long-term low-dose-rate irradiation with γ-rays. Radiat Res 174:611–617

UNSCEAR (1958) Report of the United Nations Scientific Committee on the Effects of Atomic Radiation General Assembly official records: Thirteenth session Supplement No. 17 (A/3838), http://www.unscear.org/unscear/en/publications/1958.html

UNSCEAR (1962) Report of the United Nations Scientific Committee on the Effects of Atomic Radiation, http://www.unscear.org/unscear/en/publications/1962.html

UNSCEAR (1964) Report of the United Nations Scientific Committee on the Effects of Atomic Radiation General Assembly official records: Nineteenth session Supplement No. 14 (A/5814), http://www.unscear.org/unscear/en/publications/1964.html

UNSCEAR (1969) Report of the United Nations Scientific Committee on the Effects of Atomic Radiation, http://www.unscear.org/unscear/en/publications/1969.html

UNSCEAR (1977) Sources and effects of ionizing radiation, United Nations Scientific Committee on the Effects of Atomic Radiation 1977 Report to the General Assembly, with Annexes, http://www.unscear.org/unscear/en/publications/1977.html

UNSCEAR (1986) Genetic and somatic effects of ionizing radiation, United Nations Scientific Committee on the Effects of Atomic Radiation 1986 Report to the General Assembly, with Annexes General Assembly Official Records: Forty-first session, Supplement No. 16 (A/41/16), http://www.unscear.org/unscear/en/publications/1986.html

UNSCEAR (1988) Sources, effects and risks of ionizing radiation, United Nations Scientific Committee on the Effects of Atomic Radiation 1988 Report to the General Assembly, with Annexes, http://www.unscear.org/unscear/en/publications/1986.html

UNSCEAR (1993) Sources and effects of ionizing radiation, United Nations Scientific Committee on the Effects of Atomic Radiation UNSCEAR 1993 Report to the General Assembly, with Scientific Annexes, http://www.unscear.org/unscear/en/publications/1993.html

UNSCEAR (1994) Sources and effects of ionizing radiation, United Nations Scientific Committee on the Effects of Atomic Radiation UNSCEAR 1994 Report to the General Assembly, with Scientific Annexes, http://www.unscear.org/unscear/en/publications/1994.html

UNSCEAR (2000) Sources and effects of ionizing radiation, United Nations Scientific Committee on the Effects of Atomic Radiation UNSCEAR 2000 Report to the General Assembly, with Scientific Annexes, http://www.unscear.org/unscear/en/publications/2000_2.html

UNSCEAR (2006) Effects of ionizing radiation, United Nations Scientific Committee on the Effects of Atomic Radiation UNSCEAR 2006 Report to the General Assembly, with Scientific Annexes, http://www.unscear.org/unscear/en/publications/2006_1.html

UNSCEAR (2010) Summary of low-dose radiation effects on health, http://www.unscear.org/docs/reports/2010/UNSCEAR_2010_Report_M.pdf

UNSCEAR (2012) United Nations Scientific Committee on the Effects of Atomic Radiation UNSCEAR 2012 Report to the General Assembly, with Scientific Annexes, http://www.unscear.org/unscear/en/publications/2012.html

UNSCEAR (2013) Sources, effects and risks of ionizing radiation, United Nations Scientific Committee on the Effects of Atomic Radiation UNSCEAR 2013 Report to the General Assembly, with Scientific Annexes, http://www.unscear.org/unscear/en/publications/2013_1.html

Vasilenko EK, Khokhryakov VF, Miller SC, Fix JJ, Eckerman K, Choe DO, Gorelov M, Khokhryakov VV, Knyasev V, Krahenbuhl MP, Scherpelz RI, Smetanin M, Suslova K, Vostrotin V (2007) Mayak worker dosimetry study: an overview. Health Phys 93:190–206

Verbiest T, Bouffler S, Nutt SL, Badie C (2015) PU.1 downregulation in murine radiation-induced acute myeloid leukaemia (AML): from molecular mechanism to human AML. Carinogenesis 36:413–419

Vrijheid M, Cardis E, Blettner M, Gilbert E, Hakama M, Hill C, Howe G, Kaldor J, Muirhead CR, Schubauer-Berigan M, Yoshimura T, Ahn YO, Ashmore P, Auvinen A, Bae JM, Engels H, Gulis G, Habib RR, Hosoda Y, Kurtinaitis J, Malker H, Moser M, Rodriguez-Artalejo F, Rogel A, Tardy H, Telle-Lamberton M, Turai I, Usel M, Veress K (2007a) The 15-Country Collaborative Study of Cancer Risk Among Radiation Workers in the Nuclear Industry: design, epidemiological methods and descriptive results. Radiat Res 167:361–379

Vrijheid M, Cardis E, Ashmore P, Auvinen A, Bae JM, Engels H, Gilbert E, Gulis G, Habib R, Howe G, Kurtinaitis J, Malker H, Muirhead C, Richardson D, Rodriguez-Artalejo F, Rogel A, Schubauer-Berigan M, Tardy H, Telle-Lamberton M, Usel M, Veress K (2007b) Mortality from diseases other than cancer following low doses of ionizing radiation: results from the 15-Country Study of nuclear industry workers. Int J Epidemiol 36:1126–1135

Wang ZY, Boice JD Jr, Wei LX, Beebe GW, Zha YR, Kaplan MM, Tao ZF, Mazon HR 3rd, Zhang SZ, Schneider AB, Tan B, Wesseler TA, Chen D, Ershow AG, Kleinerman RA, Littlefield LG, Preston D (1990) Thyroid nodularity and chromosome aberrations among women in areas of high background radiation in China. J Natl Cancer Inst 82:478–485

Wang Q, Paunesku T, Woloschak G (2010) Tissue and data archives from irradiation experiments conducted at Argonne National Laboratory over a period of four decades. Radiat Environ Biophys 49:317–324

WHO (2013) Health risk assessment from the nuclear accident after the 2011 Great East Japan earthquake and tsunami based on a preliminary dose estimation. World Health Organization, Geneva